Translating Science

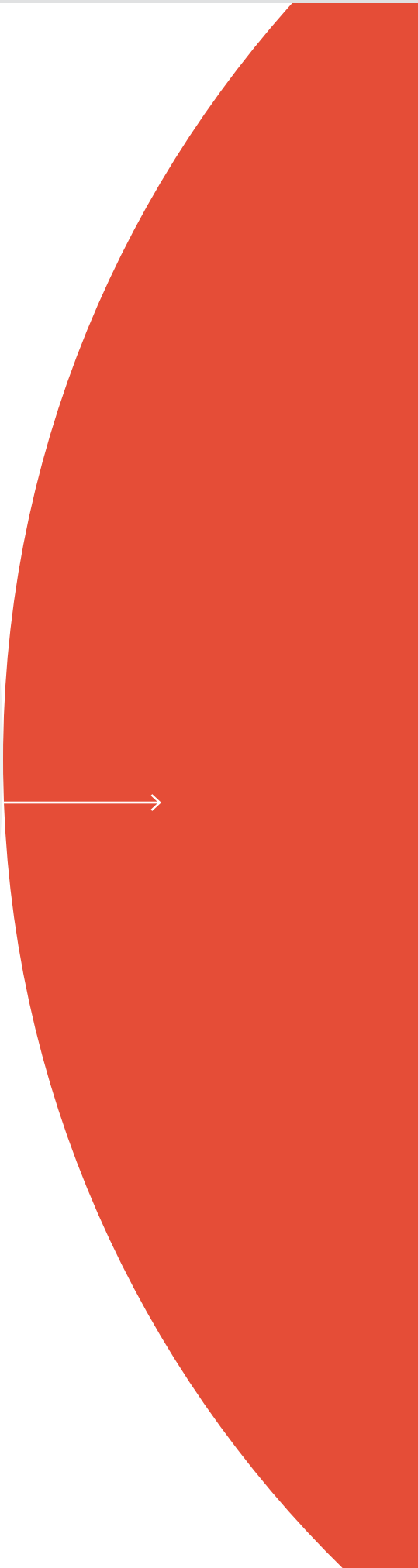
Transforming Lives

2021 ANNUAL REPORT

PTC THERAPEUTICS™

OUR PROMISE

Rare diseases, real strides to treat them—this is why we're here. No matter how uncommon the disorder, the life-limiting effects are a daily reality for those affected. When Stu Peltz founded PTC over 20 years ago, he had this unique insight. That's why we're creating life-changing treatments every day.



IN OUR DNA

With every setback and advance, we continue to push forward every day because this is not simply a job to us, it's a calling.

THE FAMILY APPROACH

We are not simply there for you on the rare disease journey, but we are with you, because we know that family gets its strength from one another. We're in this together.

RARE RESOLVE FOR RARE DISEASE

Our people choose to work here because they believe in the moments that we build—in the labs and for our patients.

THE SCIENCE OF PROGRESS

We use data and groundbreaking science in our search for progress—progress in rare-disease treatments, of course, but also in the day-to-day lives of those affected.

The progress we have made across all our fronts in the past several years is a testament to PTC's culture and its people. People are our most important asset and we prove that everyday.

STUART W. PELTZ, PH.D.
Chief Executive Officer

A MESSAGE TO OUR SHAREHOLDERS

For nearly 25 years, we have advanced innovative therapies for rare diseases—going from ideas to discovery, from discovery to development, and finally from development to commercialization and distribution to patients across the globe. These efforts have propelled PTC towards an enduring, innovative biopharmaceutical company with substantial revenues that help us reinvest in our research to develop new treatments for patients. Our goal is to develop transformative new therapies every 2-3 years. We continue to populate our pipeline with programs such that at steady state we will have enough shots to achieve this goal. Importantly, we will continue to utilize our groundbreaking science to continue to innovate and bring novel products to help patients.

I am proud to report that 2021 was the most successful year in our company's history to date. In 2021, we saw PTC revenues grow 41% year-over-year, with total net revenue of $538.6 million. The increased revenue was driven primarily by our Duchenne muscular dystrophy franchise consisting of Translarna™ (ataluren) and Emflaza®(deflazacort). Of note, revenue for Emflaza increased approximately 35% year-over-year which was driven by continued new prescriptions, continued high compliance, and more favorable access. Translarna revenues increased more than 31% year-over-year. These results were driven by treatment of new patients, continued high compliance, and geographic expansion. Our goal is to bring Translarna to nonsense mutation Duchenne muscular dystrophy patients globally, and we see continued geographic expansion in regions like Asia Pacific, Central and Eastern Europe, Middle East, North Africa and Latin America to further grow the business.

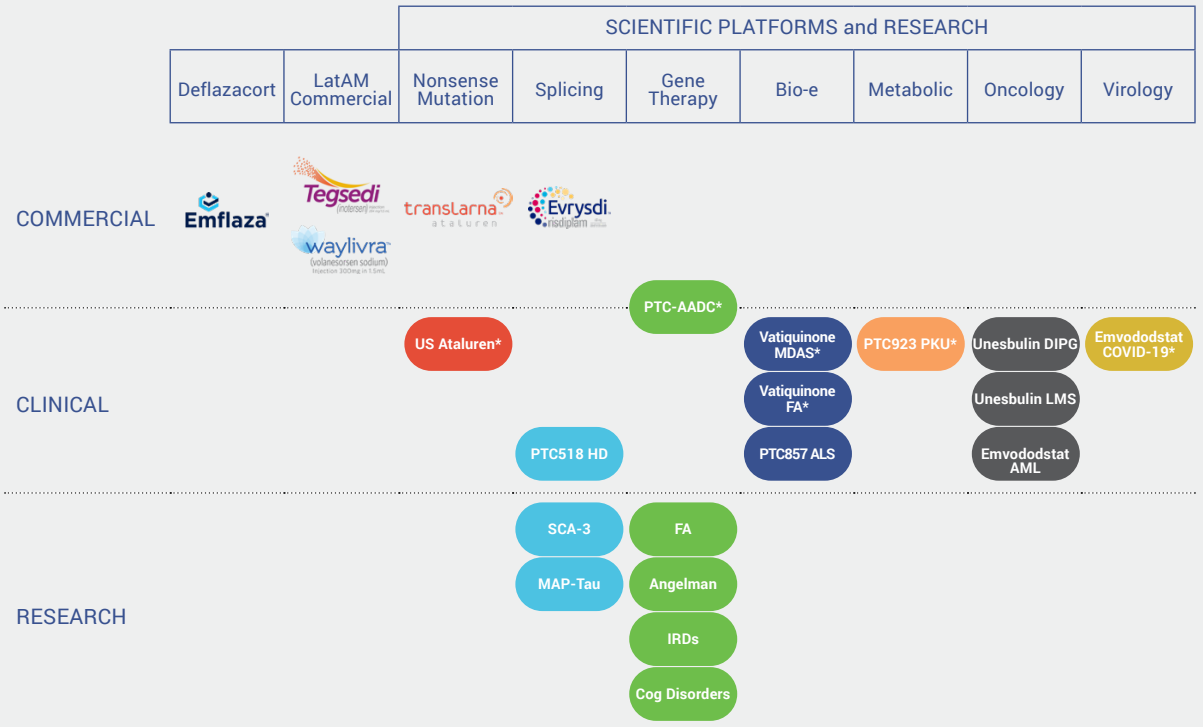
Along with our Duchenne franchise, Evrysdi®—a landmark product for the treatment of Spinal Muscular Atrophy (SMA)—has shown remarkable growth in 2021, just over a year after launch. Developed in conjunction with Roche and the SMA Foundation, Evrysdi is now approved in over 75 countries, capturing over 20% of the SMA market and becoming the most prescribed disease modifying therapy for SMA in the United States. We also saw continued growth outside the United States, and I am pleased to report that 2021 revenues for Evrysdi exceeded $500 million. This triggered a milestone payment to PTC from Roche bringing the total milestone payments PTC received from Roche in 2021 to be $55M. In addition to milestone payments, PTC received $54.6 million in 2021 in royalty payments.

Our commercial success also includes Waylivra® (volanesorsen) and Tegsedi® (inotersen), both of which received Category 1 classification in 2021 from CMED in Brazil. This allows for pricing in Brazil in line with international markets. Tegsedi and Waylivra are now well-positioned for continued growth.

We are also excited about the potential approval in Europe of our first gene therapy product for the treatment of Aromatic L-Amino Acid Decarboxylase, or AADC deficiency. We recently completed Scientific Advisory Group and Oral Explanation meetings with the Committee for Advanced Therapies and we now expect them to provide an opinion to the EMA's Committee for Medicinal Products for Human Use in May 2022. If approved, PTC-AADC would be the first marketed gene therapy administered directly into the brain.

We are equally excited about the progress across our clinical pipeline, with five registration-directed studies ongoing. By the end of 2022 we anticipate that we will have initiated three additional registration-directed studies. Our registration-directed PTC923 APHENITY trial for PKU, which is expected to be completed by the end of this year, is an example of one of these ongoing

A Diversified Platform Drives Our Strong Portfolio



AADC, aromatic L-amino acid decarboxylase deficiency; AML; acute myeloid leukemia; COVID-19, coronavirus disease 2019; DIPG, diffuse intrinsic pontine glioma; FA, Friedreich ataxia; ALS, amyotrophic lateral sclerosis; HD, Huntington's disease; IRD, inherited retinal disorders; LMS, leiomyosarcoma; MDAS, mitochondrial disease associated seizures; PKU, phenylketonuria; SCA-3, spinocerebellar ataxia type 3.

**Potential registrational studies*

Our goal is to develop transformative new therapies every 2-3 years. We will continue to utilize our groundbreaking science to continue to innovate and bring novel products to help patients.

trials. There is high importance for new treatments for PKU patients as there is a substantial unmet medical need. In addition, with newborn screening, well-defined centers of excellence, and a clear path to registration we're extremely excited about this program.

We're also moving forward with the next compound from our splicing platform, PTC518 for the treatment of Huntington's disease. We recently announced the initiation of a Phase 2 study in Huntington's disease patients. A Phase I healthy volunteer study was completed in 2021 and demonstrated that PTC518 reduced HTT mRNA and protein levels to the target level of 30-50% reduction. PTC518 was also measured in the CSF, demonstrating that it crosses the blood-brain barrier and has minimal efflux.

Another exciting event for us was the opening of our new gene therapy manufacturing facility in Hopewell, New Jersey. This state-of-the-art biologics facility is one of the largest facilities of its kind in New Jersey and one of only a handful of gene-therapy manufacturing operations in the northeastern United States. Not only will this facility provide us with the immediate ability to control the quality and efficiency of our gene therapy manufacturing—particularly important at a time when supply-chain issues have erupted across industries and borders, it also allows us to leverage our excess capacity and expertise to create revenue by providing manufacturing services for other biotechnology companies. Our new facility exemplifies our entrepreneurial spirit that is the foundation of PTC's success for more than two decades.

Indeed, the progress we have made across all fronts in the past several years is a testament to PTC's culture and its people—and to our ability to retain and enhance that culture even as we have grown. People are our most important asset, and we prove that every day. We strive to create a culture based on trust, respect, and inclusion, and to act as "One PTC"—a team that is passionate and focused about our purpose to bring new therapies to patients. Our clear strategy and emphasis on innovation allows us to rapidly build our pipeline of potential products.

We have now grown to over 1,200 employees with 20 offices around the globe, making diversity a natural element of our culture. We continue to foster our diverse and talented group of professionals and develop them so that they can continue to grow and tackle new responsibilities. In 2021, our Equality, Diversity and Inclusion (ED&I) initiatives undertook a series of new efforts to bring opportunities to women, minorities and other underrepresented groups through efforts in education, mentorship, and career flexibility. These are part of our core principles that we deeply believe in.

Caring about the Environment, Social and Governance issues has also been part of PTC's fabric since its founding in 1998. We always continue to improve these efforts that we believe are vitally important to our continued success. We focus our efforts on five areas—our patients, our people, our community, our values and the environment:

- Much of our operating expenses each year are reinvested in research and development to find new, innovative treatments for patients with high unmet needs. We have also distributed well over 20,000 free genetic tests to support accurate diagnosis for rare disease patients and partnered with more than 200 patient advocacy groups to support patients and families across the globe.

- We have made improvements throughout the course of the year to ensure that our governance is to the highest legal and ethical standards and have a new compliance app that is on every one of our employees mobile phone.

- We focused on areas like energy, waste and sustainability to ensure that, even as we work to enhance the lives of some of the most vulnerable populations, we are doing so in the most environmentally efficient manner possible. We have steadily increased our use of electricity from green sources and replaced our reliance on hazardous waste stream with new scientific approaches.

- We continually engage our employees with opportunities to advance their careers on both personal and professional levels. We provide employee educational opportunities and unique "PTC University" educational sessions covering topics from scientific discovery to personal wellness, mentoring programs and strength-based coaching.

- Our robust Talent Pipeline Program (TPP) provides recent graduates with real-world experience in biotech and related professions, with a focus on colleges that have historically served minority and other underrepresented communities. We also work with local high schools in underprivileged areas to support careers in the life sciences.

Most importantly, we provide a work environment with purpose: for nearly 25 years, we have been on a mission to provide innovative, life-changing therapies to patients with rare diseases. We are deeply engaged with patients and their families. We firmly believe that PTC is more than a company; it is a cause. As long as we remain focused on this mission, benefits will flow to investors, employees, partners, patients and all our other stakeholders. We remain committed to staying steadfast in our commitment to this principle, even as we grow and provide value to all our stakeholders.

PTC Therapeutics' 25th anniversary will be in 2023. As we approach that historic milestone, I have never been more confident in our company's position, nor so optimistic as to our future.

Sincerely,

Stuart W. Peltz, Ph.D.

Five Registration-Directed Clinical Trials Drives Near-Term Value

Emvododstat	US Ataluren	Vatiquinone	PTC923	Vatiquinone
Covid-19	Nonsense Mutation Duchenne (nmDMD)	Mitochondrial Disease Associated Seizures (MDAS)	Phenylketonuria (PKU)	Friedreich Ataxia (FA)
FITE19	Study 041	MIT-E	aphenity	MOVE-FA
Data Expected				
1H 2022	mid-2022	4Q 2022	YE 2022	2Q 2023

We are excited about the progress across our clinical pipeline. By the end of 2022 we anticipate that we will have initiated three additional registration-directed studies.

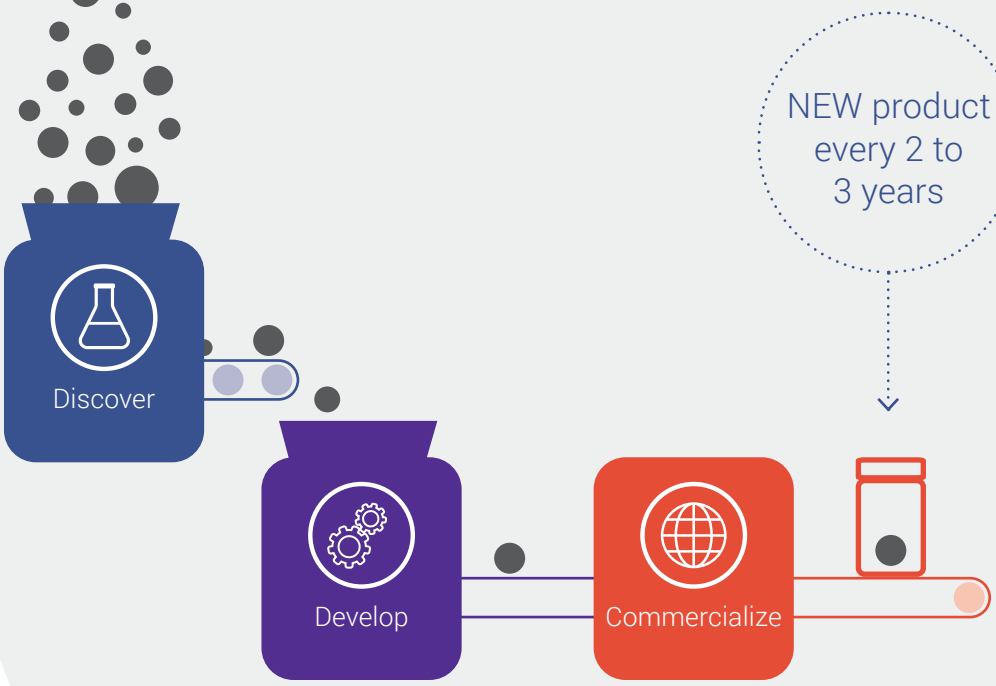
Significant Execution & Value Creation In 2021

- **Completed Phase 1** healthy volunteer trial of PTC518
- **Completed Phase 1** healthy volunteer trial of PTC857
- **Completed enrollment** of vatiquinone MOVE-FA registration-directed trial
- **Initiation** of registration-directed APHENITY **Phase 3 trial** for PTC923 in PKU
- **Completion** of **Phase 1b** unesbulin LMS trial
- **Completion** of **Phase 1b** unesbulin DIPG trial

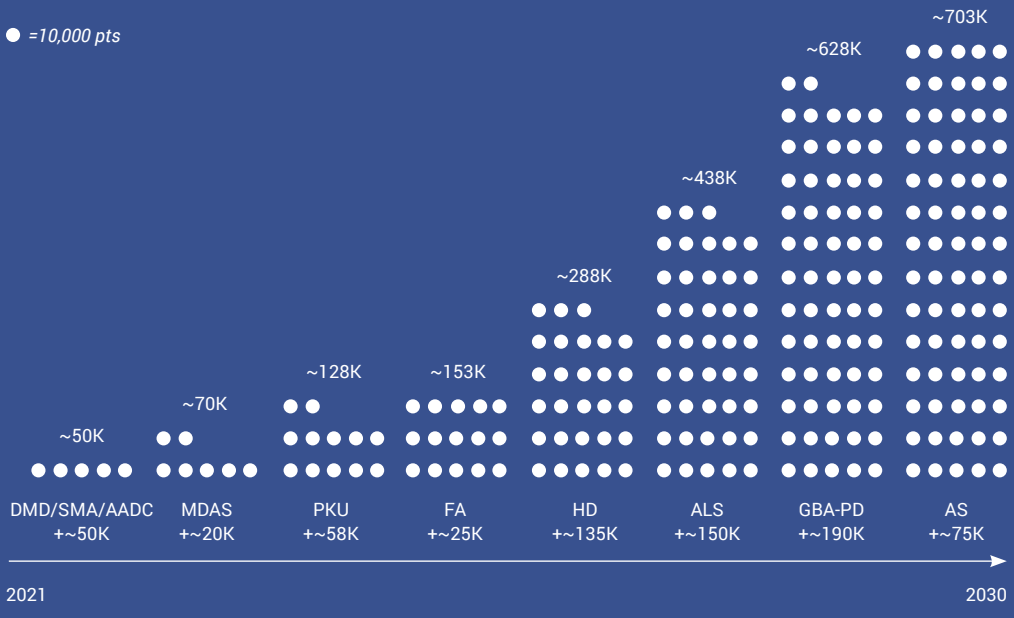
- **Evrysdi®** now approved in over **75 countries** including the EU and Japan
- **Waylivra® approved** in Brazil for treatment of FCS
- **Translarna™ label expansion** in Brazil to include patients 2 years of age and up
- **2 Rare** Pediatric Disorder Designations
- **6 Orphan** Drug Designations

- **DMD franchise continues to grow** with new patients in existing geographies and **geographic expansion** for Translarna and new patients and increased compliance for Emflaza®
- Evrysdi is **most prescribed SMA product** and reached **~20% market share** in the US
- Tegsedi® **Category 1 pricing** in Brazil
- Waylivra **Category 1 pricing** in Brazil

Building a Pipeline to Produce a Therapy Every Three Years



Multiple Platforms Provide Opportunity to Target Over 700,000 Patients by 2030



Estimated Global Prevalence

Enduring Innovation Drives Value Creation

COMMERCIAL

2021

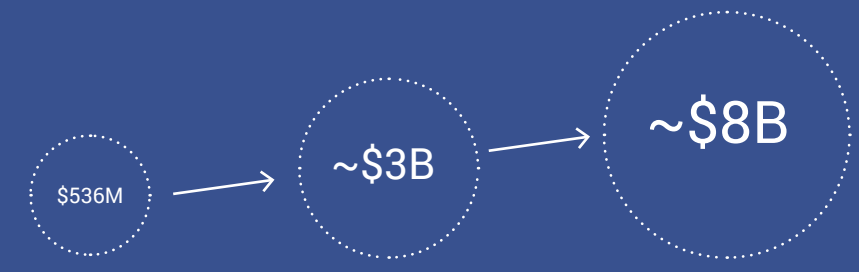
Evrysdi, Emflaza, translarna, Tegsedi, waylivra

2026

Key Drivers: Evrysdi®, PTC-AADC, Tegsedi®, Waylivra®, Translarna™, Vatiquinone, PTC923, Unesbulin

2030

Key Drivers: Evrysdi®, PTC-AADC, Tegsedi®, Waylivra®, Vatiquinone, PTC923, Unesbulin, PTC518, PTC857



Unaudited total revenue

Potential future revenues

CLINICAL

Vatiquinone | PTC923 | PTC518 | PTC857 | Unesbulin | Emvododstat | GT-FA | GT-AS | Research

PTC has a Growing Global Footprint

Founded in 1998

Footprint in > 50 Countries

20 Offices Worldwide

Over 1,200 Employees

Our Commitment to the Rare Disease Community

PTC was founded in 1998 by a scientist with a desire to serve patients with rare diseases and unmet medical needs. Over the course of our history, we have grown to a team of more than a thousand employees and developed new innovative therapies. However, we've always maintained our foundational commitment to our patients and their caregivers. Here is a collection of inspirational stories we've amassed along our journey partnering with the brave, strong people of the rare disease community.

For Anne, It's Personal

Anne Bruns is a patient advocate at PTC, but she's also a rare disease mom. Her story is one of resilience; and she brings this heroic force to her work helping patients in our clinical trial programs.

Anne, along with our Patient Engagement Liaison team continuously seek ways to connect with new patients and caregivers to help share their stories with others who are looking for inspiration and hope along their rare disease journey.

CLICK HERE to learn more.

Celebrating #DuchenneCan

Since its launch in early 2021, #DuchenneCan has brought together stories of individuals in the community whose abilities, strengths, and determination have inspired personal growth and progress, positive change in the community and amplified the voice of Duchenne globally.

CLICK HERE to read the stories.

Developing a Therapy for SMA

PTC partnered with Roche and the SMA Foundation to develop a small molecule treatment for spinal muscular atrophy (SMA). After many years of research and development, we experienced a collective success that could not have been possible without camaraderie with our partners, patients and patient advocates.

CLICK HERE to learn more about how we developed our SMA therapy.

Working to Reduce Seizures

Developing treatments for rare diseases can be difficult, but no less rewarding than developing therapies for diseases that affect millions. At the end of the day, PTC is working to bring more precious moments to people – we're people working for people.

The MIT-E Study team exemplifies this approach when it comes to helping patients with mitochondrial disease associated seizures.

CLICK HERE to read more about their story.

Racing to Treat Huntington's Disease

Our scientists talk about feeling "honored" to do their work at PTC – honored because they recognize the struggles endured by members of the rare disease community, and because those brave people have placed their trust in our team.

Anu Bhattacharyya, Ph.D. and clinical project leader Brian Beers have kept patients top of mind when transitioning Huntington's Disease (HD) research into clinical development.

LEARN MORE about their story here.

Promoting AADC Awareness

In 2020, PTC supported patient advocacy partner the AADC Family Network by sponsoring the first AADC Deficiency Awareness Day (October 23). We repeated these efforts in 2021. We are truly heartened by the tremendous feats of courage shown by founder and AADC parent Kelly Heger, her heroic family, and her daughter Jillian, who is living with AADC deficiency.

CLICK HERE to learn more about this historic day.

ESG

As a growing global company with a footprint in 50 countries, our mission remains focused on bringing more moments to our patients living with rare diseases and their loved ones. Our approach to corporate social responsibility is rooted in our commitment to patient advocacy, access to medicines, and advancing science.

Who We Are
We strive to provide access to best-in-class treatments for patients living with rare diseases. This mission underpins our focus on the discovery, development and global commercialization of clinically differentiated medicines that provide benefits to patients with rare disorders.

Our Patients
From our robust Products and Pipeline, to our commitment to patient advocacy to our growing investment in research and development, we know that we are more than just a company; we work for a cause.

People of PTC
We are a dynamic, global network of empowered, high-performing teams that achieve extraordinary results. We partner to bring out the best in ourselves and maximize talent.

Our Culture & Community
We are dedicated and committed to enriching the PTC culture. We aspire to enhance the employee experience and empower our employees to make a difference within internal and external communities.

Ethics & Compliance
PTC conducts activities in accordance with applicable laws and regulations and is committed to acting honestly, ethically, and fairly.

Our Environment
As a science-based company, we understand the impact people and companies have on the environment. We, as well as our employees, care about the world we live in and have a stead-fast commitment to maintaining the environment.

Glossary

AADC: AADC Deficiency (AADC-d) is a rare central nervous system disorder arising from reductions in the enzyme aromatic L-amino acid decarboxylase (AADC) that result from mutations in the dopa decarboxylase (DDC) gene. This reduction leads to deficits in the neurotransmitters dopamine, norepinephrine, epinephrine, serotonin and melatonin. AADC Deficiency causes severe developmental delays, the inability to develop any motor strength and control (global muscular hypotonia/dystonia) resulting in breathing, feeding, and swallowing problems, frequent hospitalizations, and the need for life-long care. Patients with severe forms often die in the first decade of life due to profound motor dysfunction, autonomic abnormalities, and secondary complications such as choking, hypoxia, and pneumonia. No treatment options other than palliative care currently exist for many AADC patients.

ALS: Amyotrophic Lateral Sclerosis (ALS) is a progressive neurodegenerative disease that affects nerve cells in the brain and spinal cord. Motor neurons reach from the brain to the spinal cord and from the spinal cord to the muscles throughout the body. The progressive degeneration of the motor neurons in ALS eventually leads to their demise. When the motor neurons die, the ability of the brain to initiate and control muscle movement is lost. When voluntary muscle action is progressively affected, people may lose the ability to speak, eat, move and breathe. There is no cure for this fatal disease.

AML: Acute myeloid leukemia (AML) is a cancer characterized by the rapid growth of abnormal cells that build up in the bone marrow and blood and interfere with normal blood cells. Symptoms may include feeling tired, shortness of breath, easy bruising and bleeding and increased risk of infection. Occasionally, spread may occur to the brain, skin or gums. AML progresses rapidly and is typically fatal within weeks or months if left untreated.

AS: Angelman Syndrome (AS) is a severe neurological development disorder characterized by profound developmental delays, problems with motor coordination (ataxia) and balance, and epilepsy. Individuals with AS do not develop functional speech, have seizures and sleeping difficulties. AS is caused by a problem with UBE3a gene and affects all races and both genders equally. People living with AS require life-long care, intense therapies to help develop functional skills and improve their quality of life, and close medical supervision involving multiple interventions. AS may be misdiagnosed since other syndromes have similar characteristics. There are currently no approved treatments for AS.

DIPG: Diffuse interstitial pontine glioma (DIPG) is a rare, rapidly fatal pediatric brain tumor. Patients are usually diagnosed between 5-6 years of age. 98% of patients die within two years of diagnosis.

DMD: Duchenne muscular dystrophy (DMD) is the most common and one of the most severe types of muscular dystrophy. DMD occurs when a mutation in the dystrophin gene prevents the cell from making a functional dystrophin protein. Dystrophin is a muscle membrane associated protein and is critical to the structural and membrane stability of muscle fibers in the skeletal, diaphragm and heart. The absence of normally functioning dystrophin results in muscle fragility, such that muscle injury occurs when muscles contract or stretch during normal use. As muscle damage progresses, connective tissue and fat replace muscle fibers, resulting in inexorable muscle weakness. Patients with DMD typically lose walking ability by their early teens, require ventilation support in their late teens and, eventually, die due to heart and lung failure. The average age of death for DMD patients is in their mid-twenties.

FA: Friedreich ataxia (FA) is an inherited neuromuscular disorder most commonly caused by a single genetic defect in the FXN gene that leads to reduced production of frataxin, a mitochondrial protein that is important for cellular metabolism and energy production. FA results in a physically debilitating, life-shortening condition and is the most common hereditary ataxia. Symptoms of FA include progressive loss of coordination and muscle strength, which lead to the full-time use of a wheelchair; scoliosis (which often requires surgical intervention); diabetes mellitus; hearing and vision impairment; serious heart conditions; and premature death. Current FA therapies are primarily focused on symptom relief, and there are no FDA-approved drugs to treat the cause of FA.

FCS: Familial Chylomicronemia Syndrome (FCS) is an ultra-rare disease caused by impaired function of the enzyme lipoprotein lipase (LPL) and characterized by severe hypertriglyceridemia (>880mg/dL) and a risk of unpredictable and potentially fatal acute pancreatitis. Because of limited LPL function, people with FCS cannot breakdown chylomicrons, lipoprotein particles that are 90% triglycerides. FCS patients are also at risk of chronic complications due to permanent organ damage. They can experience daily symptoms including abdominal pain, generalized fatigue and impaired cognitions that affect their ability to work. People with FCS report major emotional and psychosocial effects including anxiety, social withdrawal, depression and brain fog. There is no effective therapy for FCS currently available.

hATTR: hereditary transthyretin (hATTR) amyloidosis is a progressive, systemic and fatal inherited disease caused by the abnormal formation of the TTR protein and aggregation of TTR amyloid deposits in various tissues and organs throughout the body, including in peripheral nerves, heart, intestinal tract, eyes, kidneys, central nervous system, thyroid and bone marrow. The progressive accumulation of TTR amyloid deposits in these tissues and organs leads to sensory, motor and autonomic dysfunction often having debilitating effects on multiple aspects of a patient's life. Ultimately, hATTR amyloidosis results in death within three to 15 years of symptom onset. Therapeutic options for the treatment of patients with hATTR amyloidosis are limited.

HD: Huntington's Disease (HD) is a rare genetic disorder that is caused by a CAG repeat expansion in the HTT gene. The mutated HTT protein leads to severe neuron degeneration predominately in the striatum and the cerebral cortex. Currently, there are no approved disease-modifying treatments.

IRDs: Inherited retinal disorders are a group of rare eye disorders caused by an inherited gene mutation and can result in vision loss or blindness. Some people with inherited retinal diseases experience a gradual loss of vision, eventually leading to complete blindness. Others may be born with or experience vision loss in infancy or early childhood.

LMS: Leiomyosarcomas (LMS) are malignant tumors of muscle tissue. They are rare tumors with a high rate of relapse. Median overall survival is 14 months.

MDAS: Mitochondrial Disease Associated Seizures (MDAS) are part of a group of conditions called, metabolic disorders. The organs with the most mitochondria in them are the brain, nerves, muscles and liver and because of this, neurological disorders, including epilepsy, occur quite commonly in mitochondrial disorders. Most of the epilepsy caused by a mitochondrial disorder starts in childhood and usually in the first two years of life. Most mitochondrial disorders are progressive meaning the symptoms and the seizures will worsen over time. How quickly the progression happens will depend on the particular type of mitochondrial disorder. The seizures in most mitochondrial disorders are usually very difficult to control. Unfortunately, for most mitochondrial disorders there is no specific treatment, such as diet or surgery, which can stop the seizures or stop the disorder from progressing.

PKU: Phenylketonuria (PKU) is a rare inherited metabolic disorder and is caused by a defect in the gene that helps create the enzyme needed to break down phenylalanine. Without treatment, phenylalanine can build up to harmful levels in the body, causing mental retardation, cognitive disabilities, seizures and other serious problems. The majority of patients do not initially respond or are not well controlled by the standard of care.

SCA-3: Spinocerebellar ataxia type 3 (SCA-3) is a rare, inherited, ataxia (lack of muscular control) affecting the central nervous system and characterized by the slow degeneration of particular areas of the brain called the hindbrain. Patients may eventually become crippled and/or paralyzed but their intellect remains intact.

SMA: Spinal Muscular Atrophy (SMA) is a genetic disease caused by mutation or deletion of the SMN1 (survival of motor neuron) gene. In its most severe forms, is associated with a high rate of childhood mortality. SMA is characterized by progressive loss of motor neurons, muscle weakness, and atrophy. The disease affects mainly proximal muscles including intercostal muscles (chest muscles), and patients often die due to respiratory complications.

Form 10-k ⟶

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 10-K

(Mark One)

☑ **ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

For the fiscal year ended: December 31, 2021

or

☐ **TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

Commission file number: 001-35969

Delaware	**04-3416587**
(State or other jurisdiction of incorporation or organization)	(I.R.S. Employer Identification No.)
100 Corporate Court **South Plainfield, NJ**	**07080**
(Address of principal executive offices)	(Zip Code)

(908) 222-7000

(Registrant's telephone number, including area code)

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	Trading Symbol (s)	Name of each exchange on which registered
Common Stock, $0.001 par value per share	PTCT	Nasdaq Global Select Market

Securities registered pursuant to Section 12(g) of the Act: **None**

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes ☑ No ☐

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Act. Yes ☐ No ☑

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes ☑ No ☐

Indicate by check mark whether the registrant has submitted electronically every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T (§232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit such files). Yes ☑ No ☐

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, a smaller reporting company, or an emerging growth company. See the definitions of "large accelerated filer," "accelerated filer," "smaller reporting company," and "emerging growth company" in Rule 12b-2 of the Exchange Act.

Large accelerated filer	☑	Accelerated filer	☐
Non-accelerated filer	☐	Smaller reporting company	☐
		Emerging growth company	☐

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

Indicate by check mark whether the registrant has filed a report on and attestation to its management's assessment of the effectiveness of its internal control over financial reporting under Section 404(b) of the Sarbanes-Oxley Act (15 U.S.C. 7262(b)) by the registered public accounting firm that prepared or issued its audit report. ☑

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Exchange Act). Yes ☐ No ☑

The aggregate market value of the Common Stock held by non-affiliates of the registrant, based upon the last sale price of the Common Stock reported on the Nasdaq Global Select Market on June 30, 2021, the last business day of the registrant's most recently completed second fiscal quarter, was $2,191,128,010. For purposes of this calculation, shares of Common Stock held by directors and officers have been treated as shares held by affiliates.

As of February 18, 2022, the registrant had 71,362,471 shares of Common Stock, $0.001 par value per share, outstanding.

DOCUMENTS INCORPORATED BY REFERENCE

Part III of this Annual Report incorporates by reference information from the definitive Proxy Statement for the registrant's 2022 Annual Meeting of Shareholders which is expected to be filed with the Securities and Exchange Commission not later than 120 days after the registrant's fiscal year ended December 31, 2021.

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TABLE OF CONTENTS
PTC Therapeutics, Inc.

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FORWARD-LOOKING STATEMENTS

This Annual Report on Form10-K contains forward-looking statements that involve substantial risks and uncertainties. All statements, other than statements of historical facts, contained in this Annual Report on Form 10-K, including statements regarding our strategy, future operations, future financial position, future revenues, projected costs, prospects, plans and objectives of management, are forward-looking statements. The words "anticipate," "believe," "estimate," "expect," "intend," "may," "might," "plan," "predict," "project," "target," "potential," "will," "would," "could," "should," "continue," and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words.

The forward-looking statements in this Annual Report on Form 10-K include, among other things, statements about:

- our expectations with respect to the COVID-19 pandemic and related response measures and their effects on our business, operations, clinical trials, potential regulatory submissions and approvals, our collaborators, contract research organizations, suppliers and manufacturers;

- our ability to negotiate, secure and maintain adequate pricing, coverage and reimbursement terms and processes on a timely basis, or at all, with third-party payors for our products or product candidates that we commercialize or may commercialize in the future;

- expectations with respect to our gene therapy platform, including any potential regulatory submissions and potential approvals, including those related to our gene therapy for the treatment of Aromatic L-Amino Acid Decarboxylase, or AADC, deficiency, or PTC-AADC, our manufacturing capabilities and the potential financial impact and benefits of our leased biologics manufacturing facility and the potential achievement of development, regulatory and sales milestones and contingent payments that we may be obligated to make;

- our ability to maintain our marketing authorization of Translarna™ (ataluren) for the treatment of nonsense mutation Duchenne muscular dystrophy, or nmDMD, in the European Economic Area, or EEA, which is subject to the specific obligation to conduct and submit the results of Study 041 to the European Medicines Agency, or EMA, and annual review and renewal by the European Commission following reassessment of the benefit-risk balance of the authorization by the EMA;

- our ability to complete Study 041, a multicenter, randomized, double-blind, 18-month, placebo-controlled clinical trial of Translarna for the treatment of nmDMD followed by an 18-month open label extension, according to the protocol agreed with the EMA, and by the EMA's deadline;

- our ability to utilize results from Study 041 to support a marketing approval for Translarna for the treatment of nmDMD in the United States;

- the anticipated period of market exclusivity for Emflaza® (deflazacort) for the treatment of DMD in the United States under the Orphan Drug Act of 1983, or Orphan Drug Act;

- our expectations with respect to the commercial status of Evrysdi® (risdiplam) and our program directed against spinal muscular atrophy in collaboration with F. Hoffmann La Roche Ltd and Hoffmann La Roche Inc., which we refer to collectively as Roche, and the Spinal Muscular Atrophy Foundation, or the SMA Foundation, and our estimates regarding future revenues from sales-based royalty payments or the achievement of milestones in that program;

- our expectations and the potential financial impact and benefits related to our Collaboration and License Agreement with a subsidiary of Ionis Pharmaceuticals, Inc., including with respect to the timing of regulatory approval of Tegsedi® (inotersen) and Waylivra® (volanesorsen) in countries in which we are licensed to commercialize them, the commercialization of Tegsedi and Waylivra, and our expectations with respect to royalty payments by us based on our potential achievement of certain net sales thresholds;

- the timing and scope of our commercialization of our products and product candidates;
- our ability to obtain additional and maintain existing reimbursed named patient and cohort early access programs, or EAP programs, for our products on adequate terms, or at all;
- our estimates regarding the potential market opportunity for our products or product candidates, including the size of eligible patient populations and our ability to identify such patients;
- our estimates regarding expenses, future revenues, third-party discounts and rebates, capital requirements and needs for additional financing, including our ability to maintain the level of our expenses consistent with our internal budgets and forecasts and to secure additional funds on favorable terms or at all;
- the timing and conduct of our ongoing, planned and potential future clinical trials and studies in our splicing, gene therapy, Bio-e, metabolic and oncology programs and studies of emvododstat for COVID-19 as well as studies in our products for maintaining authorizations, label extensions and additional indications, including the timing of initiation, enrollment and completion of the trials and the period during which the results of the trials will become available;
- our ability to realize the anticipated benefits of our acquisitions or other strategic transactions, including the possibility that the expected impact of benefits from the acquisitions or strategic transactions will not be realized or will not be realized within the expected time period, significant transaction costs, the integration of operations and employees into our business, our ability to obtain marketing approval of our product candidates we acquired from the acquisitions or other strategic transactions and unknown liabilities;
- the rate and degree of market acceptance and clinical utility of any of our products or product candidates;
- the ability and willingness of patients and healthcare professionals to access our product and product candidates through alternative means if pricing and reimbursement negotiations in the applicable territory do not have a positive outcome;
- the timing of, and our ability to obtain additional marketing authorizations for our products and product candidates;
- the ability of our products and our product candidates to meet existing or future regulatory standards;
- our ability to maintain the current labeling under the marketing authorization in the EEA or expand the approved product label of Translarna for the treatment of nmDMD;
- the potential receipt of revenues from future sales of our products or product candidates;
- the potential impact that completion of Study 041 may have on our revenue growth;
- our sales, marketing and distribution capabilities and strategy, including the ability of our third-party manufacturers to manufacture and deliver our products and product candidates in clinically and commercially sufficient quantities and the ability of distributors to process orders in a timely manner and satisfy their other obligations to us;
- our ability to establish and maintain arrangements for the manufacture of our products and product candidates that are sufficient to meet clinical trial and commercial launch requirements;
- our ability to complete any post-marketing requirements imposed by regulatory agencies with respect to our products;

- our ability to operate and grow our manufacturing capabilities for our gene therapy platform;
- our expectations with respect to the potential financial impact and benefits of our leased biologics manufacturing facility and our ability to satisfy our obligations under the terms of the lease agreement for such facility;
- our ability to satisfy our obligations under the indenture governing our 3.00% convertible senior notes due August 15, 2022 and under the indenture governing our 1.50% convertible senior notes due September 15, 2026;
- our regulatory submissions, including with respect to timing and outcome of regulatory review;
- our plans to advance our earlier stage programs and pursue research and development of other product candidates, including our splicing, gene therapy, Bio-e, metabolic and oncology programs;
- whether we may pursue business development opportunities, including potential collaborations, alliances, and acquisition or licensing of assets and our ability to successfully develop or commercialize any assets to which we may gain rights pursuant to such business development opportunities;
- the potential advantages of our products and any product candidate;
- our intellectual property position;
- the impact of government laws and regulations;
- the impact of litigation that has been or may be brought against us or of litigation that we are pursuing against others; and
- our competitive position;

We may not actually achieve the plans, intentions or expectations disclosed in our forward-looking statements, and you should not place undue reliance on our forward-looking statements. Actual results or events could differ materially from the plans, intentions and expectations disclosed in the forward-looking statements we make. We have included important factors in the cautionary statements included in this Annual Report on Form 10-K, particularly under the heading "Summary of Risk Factors" and the risk factors detailed further in Part I, Item 1A. Risk Factors that we believe could cause actual results or events to differ materially from the forward-looking statements that we make.

Our forward-looking statements do not reflect the potential impact of any future acquisitions, mergers, dispositions, joint ventures or investments we may make.

You should read this Annual Report on Form 10-K and the documents that we have filed as exhibits to this Annual Report on Form 10-K completely and with the understanding that our actual future results may be materially different from what we expect. We do not assume any obligation to update any forward-looking statements whether as a result of new information, future events or otherwise, except as required by applicable law.

In this Annual Report on Form 10-K, unless otherwise stated or the context otherwise requires, references to "PTC," "PTC Therapeutics," "we," "us," "our," "the Company," and similar references refer to PTC Therapeutics, Inc. and, where appropriate, its subsidiaries. The trademarks, trade names and service marks appearing in this Annual Report on Form 10-K are the property of their respective owners.

All website addresses given in this Annual Report on Form 10-K are for information only and are not intended to be an active link or to incorporate any website information into this document.

SUMMARY OF RISK FACTORS

Below is a summary of the principal risk factors that make an investment in our common stock speculative or risky. This summary does not address all of the risks and uncertainties that we face. Additional risks and uncertainties not presently known to us or that we presently deem less significant may also impair our business operations. Additional discussion of the risks summarized in this risk factor summary, and other risks that we face, can be found in Item 1A. Risk Factors, of this Annual Report on Form 10-K, and should be carefully considered, together with other information in this Annual Report on Form 10-K and our other filings with the Securities Exchange Commission, before making an investment decision regarding our common stock. The forward-looking statements discussed above are qualified by these risk factors. If any of the following risks occur, our business, financial condition, results of operations and future growth prospects could be materially and adversely affected.

Summary of Risk Factors

- We face risks related to the COVID-19 pandemic;
- We may fail to obtain regulatory approval for PTC-AADC for the treatment of AADC deficiency within our expected timeline or at all;
- We could experience manufacturing problems, shortages of raw materials or failure of our key suppliers with respect to our gene therapy product candidates;
- We have limited experience manufacturing gene therapy products or product candidates on our own and could encounter problems and delays in operating our biologics manufacturing facility;
- The process for administering PTC-AADC is complex and includes specific specialized requirements that could delay or prevent the regulatory approval and commercialization of PTC-AADC for the treatment of AADC deficiency;
- Regulatory requirements governing gene therapy products have changed frequently and may continue to change in the future;
- Our gene therapy product candidates and the process for administering such product candidates may cause undesirable side effects or have other negative properties;
- Our gene therapy approach may be perceived as unsafe or may result in unforeseen adverse events;
- Failure to obtain or maintain adequate insurance coverage and reimbursement for our products and product candidates could limit our ability to market those products and decrease our ability to generate product revenue;
- We may be unable to continue to execute our commercial strategy for our products, fail to obtain renewal of, or satisfy the conditions of our marketing authorization for our products;
- The marketing authorization granted by the European Commission for Translarna for the treatment of nmDMD is limited to ambulatory patients aged two years and older located in the EEA and is also subject to annual reassessment of the benefit-risk balance by the EMA as well as the specific obligation to conduct Study 041, and may be varied, suspended or withdrawn by the European Commission if we fail to satisfy those requirements;
- There is substantial risk that we will not be able to utilize the results from Study 041 to support a marketing approval for Translarna for the treatment of nmDMD in the United States;
- There is substantial risk that regulators in regions where we have not yet sought or are currently seeking marketing authorization will not agree with the results from our clinical trials and existing real-world data for Translarna for the treatment of nmDMD;
- The clinical trials of our products or our product candidates may fail to demonstrate safety and efficacy to the satisfaction of regulators;
- We or our collaborators may experience any of a number of possible unforeseen events in connection with clinical trials related to our products and product candidates;
- Because we are often developing products and product candidates for the treatment of diseases in which there is little clinical experience and, in some cases, using new endpoints or methodologies, there is increased risk that the outcome of our clinical trials will not be favorable;
- We may experience delays or difficulties in the enrollment of patients in our clinical trials;
- We may identify serious adverse side effects during the development or further development of any product or product candidate;
- Our product candidates may be subject to marketing and distribution restrictions;

- Our products and product candidates may fail to achieve market acceptance in the medical community;
- We may be unable to establish or maintain sales, marketing and distribution capabilities or enter into agreements with third parties to market, sell and distribute our products or product candidates;
- A substantial portion of our commercial sales currently occurs in territories outside of the United States which subjects us to additional business risks and laws and regulations governing export restrictions and economic sanctions;
- We face substantial competition;
- Our products or product candidates may become subject to unfavorable pricing regulations, third-party reimbursement practices or healthcare reform initiatives;
- We have incurred significant losses since our inception and expect to continue to incur significant operating expenses for the foreseeable future. We may need additional funding and we may never generate profits from operations or maintain profitability;
- We may engage in strategic transactions to acquire assets, businesses, or rights to products, product candidates or technologies or from collaborations or make investments in other companies or technologies that could harm our business and dilute our stockholders' ownership;
- We may not be able to comply with applicable laws and regulations for our products or product candidates;
- We may not be able to obtain orphan drug exclusivity for our products or product candidates in either the United States or the EU;
- We may fail to maintain the non-patent market exclusivity period under the Orphan Drug Act to commercialize Emflaza for the treatment of DMD in the United States;
- Legislative and regulatory changes affecting the pharmaceutical industry or the healthcare system more broadly may negatively affect our business;
- We may fail to properly allocate our resources;
- We contract with third parties for the supply, manufacture and distribution of our products and certain of our product candidates and these third parties may encounter issues that affect our business;
- We rely on third parties to conduct our preclinical and clinical trials and other essential services;
- We currently depend, and expect to continue to depend, on collaborations with third parties for the development and commercialization of some of our products and product candidates;
- Our business and operations would suffer in the event of computer system failures, cyber-attacks or a deficiency in our, or our collaborators' or third-party vendors', cyber-security;
- We may be subject to product liability and other civil lawsuits;
- We may be unable to retain our key executives;
- We may encounter difficulties in managing our growth as a company;
- We may be unable to obtain or maintain patent protection for our technology and products;
- We may become involved in lawsuits to protect or enforce our patents or other intellectual property or in connection with allegations that we are infringing on third party intellectual property rights;
- Without patent protection, our marketed products may face generic competition;
- We may not obtain or maintain adequate trademark protection for our brand names;
- Our rights to develop and commercialize PTC-AADC and our other gene therapy product candidates are subject, in part, to the terms and conditions of licenses granted to us by others;
- We may not have sufficient cash flow from our business to make payments on our debt;
- The price of our common stock may be volatile and fluctuate substantially; and
- The issuance of additional shares of our common stock or the sale of shares of our common stock by our stockholders could dilute our stockholders' ownership interest.

PART I

Item 1. Business

Overview

We are a science-driven global biopharmaceutical company focused on the discovery, development and commercialization of clinically differentiated medicines that provide benefits to patients with rare disorders. Our ability to innovate to identify new therapies and to globally commercialize products is the foundation that drives investment in a robust and diversified pipeline of transformative medicines. Our mission is to provide access to best-in-class treatments for patients who have few or no treatment options. Our strategy is to leverage our strong scientific and clinical expertise and global commercial infrastructure to bring therapies to patients. We believe that this allows us to maximize value for all of our stakeholders.

Our Pipeline

We have a portfolio pipeline that includes several commercial products and product candidates in various stages of development, including clinical, pre-clinical and research and discovery stages, focused on the development of new treatments for multiple therapeutic areas for rare diseases. The chart and the disclosure directly below summarizes the status of our clinical-stage programs and commercial products as of the date of this report, including those with our strategic partners:

- ***Global Commercial Footprint***
  - ***Global DMD Franchise –*** We have two products, Translarna™ (ataluren) and Emflaza® (deflazacort), for the treatment of Duchenne muscular dystrophy, or DMD, a rare, life threatening disorder. Translarna has marketing authorization in the European Economic Area, or EEA, and Brazil for the treatment of nonsense mutation Duchenne muscular dystrophy, or nmDMD, in ambulatory patients aged two years and older and in Russia for the treatment of nmDMD in patients aged two years and older. Emflaza is approved in the United States for the treatment of DMD in patients two years and older.
  - ***Tegsedi® (inotersen) and Waylivra® (volanesorsen) –*** We hold the rights for the commercialization of Tegsedi and Waylivra for the treatment of rare diseases in countries in Latin America and the Caribbean pursuant to our Collaboration and License Agreement with a subsidiary of Ionis Pharmaceuticals, Inc. Tegsedi has received marketing authorization in the United States, European Union, or the EU, and Brazil for the treatment of stage 1 or stage 2 polyneuropathy in adult patients with hereditary transthyretin

amyloidosis, or hATTR amyloidosis. Waylivra has received marketing authorization in the EU and Brazil, for the treatment of familial chylomicronemia syndrome, or FCS. We have initiated our commercial launch for Tegsedi for the treatment of hATTR amyloidosis in Brazil and Waylivra for the treatment of FCS in Brazil. Additionally, we submitted an application to ANVISA in December 2021 for the approval of Waylivra for the treatment of familial partial lipodystrophy, or FPL, and we expect a regulatory decision on approval in the second half of 2022.

- ***Evrysdi® (risdiplam)*** **–** We have a spinal muscular atrophy, or SMA, collaboration with F. Hoffman-La Roche Ltd. and Hoffman-La Roche Inc., which we refer to collectively as Roche, and the Spinal Muscular Atrophy Foundation, or SMA Foundation. The SMA program has one approved product, Evrysdi, which was approved by the U.S. Food and Drug Administration, or the FDA, in August 2020 for the treatment of SMA in adults and children two months and older and by the European Commission in March 2021 for the treatment of 5q SMA in patients two months and older with a clinical diagnosis of SMA Type 1, Type 2 or Type 3 or with one to four SMN2 copies. Evrysdi also received marketing authorization for the treatment of SMA in Brazil in October 2020 and Japan in June 2021. In January 2022, the FDA granted priority review of a supplemental new drug application for Evrysdi to expand the indication to include pre-symptomatic infants under two months old with SMA.

- ***Diversified Development Pipeline***
  - ***Splicing Platform*** **–** In addition to our SMA program, our splicing platform also includes PTC518, which is being developed for the treatment of Huntington's disease, or HD. We announced the results from our Phase 1 study of PTC518 in healthy volunteers in September 2021 and expect to initiate a Phase 2 study of PTC518 for HD in the first quarter of 2022.
  - ***Gene Therapy Platform*** **–** We have a pipeline of gene therapy product candidates for rare monogenic diseases that affect the central nervous system, or CNS, including PTC-AADC for the treatment of Aromatic L-Amino Acid Decarboxylase, or AADC, deficiency, a rare CNS disorder arising from reductions in the enzyme AADC that result from mutations in the dopa decarboxylase gene. In January 2020, we submitted a marketing authorization application, or MAA, for PTC-AADC for the treatment of AADC deficiency in the EEA to the European Medicines Agency, or EMA, and we expect an opinion from the Committee for Medicinal Products for Human Use, or CHMP, in April 2022. We are also preparing a biologics license application, or BLA, for PTC-AADC for the treatment of AADC deficiency in the United States, and we anticipate submitting a BLA to the FDA in the second quarter of 2022.
  - ***Bio-e Platform*** **–** The two most advanced molecules in our Bio-e platform are vatiquinone and PTC857. We initiated a registration-directed Phase 2/3 placebo-controlled trial of vatiquinone in children with mitochondrial disease associated seizures in the third quarter of 2020 and anticipate results from this trial to be available in the fourth quarter of 2022. We also initiated a registration-directed Phase 3 trial of vatiquinone in children and young adults with Friedreich ataxia in the fourth quarter of 2020 and anticipate results from this trial to be available in the second quarter of 2023. In the third quarter of 2021, we completed a Phase 1 trial in healthy volunteers to evaluate the safety and pharmacology of PTC857. We expect to initiate a Phase 2 trial of PTC857 for amyotrophic lateral sclerosis, or ALS, in the second quarter of 2022.
  - ***Metabolic Platform*** **–** We initiated a registration-directed Phase 3 trial for PTC923 for phenylketonuria, or PKU, in the third quarter of 2021 and expect results from this trial to be available by the end of 2022.
  - ***Oncology Platform*** **–** We have two oncology agents that are in clinical development, unesbulin, formerly known as PTC596, and emvododstat. We completed our Phase 1 trials evaluating unesbulin in leiomyosarcoma, or LMS, and diffuse intrinsic pontine glioma, or DIPG, in the fourth quarter of 2021. We expect to initiate a registration-directed Phase 2/3 trial of unesbulin for the treatment of LMS in the second quarter of 2022 and we expect to initiate a registration-directed Phase 2 trial of unesbulin for the treatment of DIPG in the third quarter of 2022. We also completed our Phase 1 trial evaluating emvododstat, a dihydroorotate dehydrogenase inhibitor, in acute myelogenous leukemia, or AML, in the fourth quarter of 2021.
  - ***Emvododstat for COVID-19*** **–** In June 2020, we initiated a Phase 2/3 clinical trial evaluating the efficacy and safety of emvododstat in patients hospitalized with COVID-19. In February 2021, we announced the completion of the first stage of the Phase 2/3 trial. We expect results from this trial to be available in the first half of 2022.

- ***Multi-platform Discovery***
  - We continue to invest in our pre-clinical product pipeline across all of our platforms by committing significant resources to research and development programs and business development opportunities within our areas of scientific expertise, including potential collaborations, alliances, and acquisitions or licensing of assets that complement our strategic mission to provide access to best-in-class treatments for patients who have an unmet medical need.

Global Commercial Footprint

Global DMD Franchise

Duchenne muscular dystrophy (DMD)

Muscular dystrophies are genetic disorders involving progressive muscle wasting and weakness. DMD is the most common and one of the most severe types of muscular dystrophy. DMD occurs when a mutation in the dystrophin gene prevents the cell from making a functional dystrophin protein. Dystrophin is a muscle membrane associated protein and is critical to the structural and membrane stability of muscle fibers in skeletal, diaphragm and heart muscle. The absence of normally functioning dystrophin results in muscle fragility, such that muscle injury occurs when muscles contract or stretch during normal use. As muscle damage progresses, connective tissue and fat replace muscle fibers, resulting in inexorable muscle weakness.

Because the dystrophin gene is located on the X chromosome, DMD occurs primarily in young boys, although approximately 10% of female carriers show some disease symptoms. DMD is rare, and estimates of occurrence include approximately 1 in every 3,500 live male births, according to Parent Project Muscular Dystrophy and approximately 1 in every 5,000 live male births according to Ryder (2017) in the European Journal of Human Genetics. We estimate that there are between approximately 10,000 to 15,000 DMD patients in the United States. Several different types of mutation in the dystrophin gene can result in DMD, including deletion, duplication and nonsense mutations. A test known as multiplex ligation-dependent probe amplification (MLPA) can detect large deletions and duplications, which account for approximately 75% of all mutations. However, gene sequencing is required to identify small mutations such as nonsense mutations. We estimate that nonsense mutations account for approximately 13% of cases of DMD. Without treatment, patients with DMD typically lose walking ability by their early teens, require ventilation support in their late teens, and eventually experience premature death due to heart and lung failure. Even with medical care, most people with DMD die from cardiac or respiratory failure before or during their 30s.

Marketing authorization matters

Translarna for the treatment of nonsense mutation Duchenne muscular dystrophy

European Economic Area

We received marketing authorization from the European Commission in August 2014 for Translarna for the treatment of nmDMD in ambulatory patients aged five years and older in the 31 member states of the EEA, subject to annual renewal and other conditions. In July 2018, the European Commission approved a label-extension request to our marketing authorization for Translarna in the EEA to include patients from two to up to five years of age. In September 2018, we submitted to the EMA a label-extension request to our marketing authorization in the EEA to include patients who are non-ambulatory but the request received a negative opinion and the indication was not added. In July 2020, the European Commission approved the removal of the statement "efficacy has not been demonstrated in non-ambulatory patients" from the indication statement for Translarna.

The marketing authorization is subject to annual review and renewal by the European Commission following reassessment by the EMA of the benefit-risk balance of continued authorization, which we refer to as the annual EMA reassessment. In June 2021, the European Commission renewed our marketing authorization, making it effective, unless extended, through August 5, 2022. In February 2022, we submitted a marketing authorization renewal request to the EMA.

This marketing authorization is further subject to a specific obligation to conduct and submit the results of an 18 month, placebo-controlled trial, followed by an 18 month open-label extension, which we refer to together as Study 041. We expect results from the placebo-controlled trial to be available in mid-2022. We then expect to submit a report on the placebo-controlled trial and the open-label extension data that has been collected to date to the EMA by the end of the third quarter of 2022, as required.

Marketing authorization is required in order for us to engage in any commercialization of Translarna in the EEA, including through participation in the market access process and related pricing and reimbursement negotiations, on a country-by-country basis with each country in the EEA, and is also required to make Translarna available under early access programs, or EAP programs. There is substantial risk that if we are unable to renew our EEA marketing authorization during any annual renewal cycle, if our product label is materially restricted, or if Study 041 does not provide the data necessary to maintain our marketing authorization, we would lose all, or a significant portion of, our ability to generate revenue from sales of Translarna in the EEA and other territories.

See "Item 1. Business-Commercial Matters-Market Access Considerations" and "Item 1A. Risk Factors-Risks Related to the Development and Commercialization of our Product and our Product Candidates" and "-Risks Related to Regulatory Approval of our Product and our Product Candidates" for further information regarding the marketing authorization in the EEA, the market access process and related risks.

As the marketing authorization holder, we are obligated to monitor the use of Translarna for nmDMD to detect, assess and take required action with respect to information that could impact the safety profile of Translarna and to report this information, through pharmacovigilance submissions, to the EMA. Following its assessment of these submissions, the EMA can recommend to the European Commission actions ranging from the continued maintenance of the marketing authorization to its withdrawal.

United States

Translarna is an investigational new drug in the United States. During the first quarter of 2017, we filed an NDA for Translarna for the treatment of nmDMD over protest with the FDA. In October 2017, the Office of Drug Evaluation I of the FDA issued a Complete Response Letter, or CRL, for the NDA, stating that it was unable to approve the application in its current form. In response, we filed a formal dispute resolution request with the Office of New Drugs of the FDA. In February 2018, the Office of New Drugs of the FDA denied our appeal of the CRL. In its response, the Office of New Drugs recommended a possible path forward for our ataluren NDA submission based on the accelerated approval pathway. This would involve a re-submission of an NDA containing the current data on effectiveness and safety of ataluren with new data to be generated on dystrophin production in nmDMD patients' muscles. We followed the FDA's recommendation and collected, using newer technologies via procedures and methods that we designed, such dystrophin data in a new study, Study 045, and announced the results of Study 045 in February 2021. Study 045 did not meet its pre-specified primary endpoint. We expect results from the placebo-controlled trial of Study 041 to be available in mid-2022, and subject to a positive outcome in that study, we expect to re-submit the NDA.

See "Item 1. Business-Government Regulation-The new drug and biologic approval process" below for further discussion with respect to the NDA process. See "Item 1. Business-Translarna (ataluren)" and "Item 1A. Risk Factors-Risks Related to the Development and Commercialization of our Product and our Product Candidates" and "-Risks Related to Regulatory Approval of our Product and our Product Candidates" for further detail regarding the results of our completed trials and studies of Translarna for the treatment of nmDMD, our regulatory strategy in the United States, our history with submissions to the FDA and the related risks to our business.

Other Territories

Translarna received marketing authorization for the treatment of nmDMD in Israel and South Korea in 2015, Chile in 2018, Brazil in 2019 and Russia in 2020 and these licenses are currently active. Many territories outside of the EEA, including Israel, South Korea and Chile, reference and depend on the determinations by the EMA when considering the grant of a marketing authorization. It is unlikely that we would be able to maintain our marketing authorizations in these regions in the event the EMA decides not to renew or otherwise modifies or withdraws our marketing authorization in the

EEA. In addition, the marketing authorization for Translarna in Brazil and Russia are subject to renewal every five years. We have been pursuing and expect to continue to pursue marketing authorizations for Translarna for the treatment of nmDMD in other regions.

Emflaza for the treatment of Duchenne muscular dystrophy in the United States

Emflaza, both in tablet and suspension form, received approval from the FDA in February 2017 as a treatment for DMD in patients five years of age and older in the United States. In June 2019, the FDA approved our label expansion request for Emflaza for patients two to five years of age. We estimate that there are between approximately 10,000 and 15,000 DMD patients in the United States.

Emflaza has a seven-year exclusive marketing period in the United States for its approved indications, commencing on the date of FDA approval, under the provisions of the Orphan Drug Act of 1983, or the Orphan Drug Act. See "Item 1. Business-Government Regulation" for further discussion with respect to marketing protection we rely on.

Tegsedi and Waylivra

In August 2018 we entered into a Collaboration and License Agreement with Akcea Therapeutics, Inc., or Akcea, a subsidiary of Ionis Pharmaceuticals, Inc., or Ionis, for the commercialization by us of Tegsedi, Waylivra and products containing those compounds in countries in Latin America and the Caribbean, or the PTC Territory. See "Item 1. Business-Our Collaborations, License Agreements and Funding Arrangements-Tegsedi and Waylivra" below for further discussion with respect to this collaboration and license agreement.

Tegsedi

Tegsedi, a product of Ionis' proprietary antisense technology, is an antisense oligonucleotide, or ASO, inhibitor of human transthyretin, or TTR, production. Tegsedi is the world's first RNA-targeted therapeutic to treat patients with hereditary transthyretin amyloidosis, or hATTR amyloidosis. In October 2019, it received marketing authorization from ANVISA, the Brazilian health regulatory authority, for the treatment of stage 1 or stage 2 polyneuropathy in adult patients with hATTR amyloidosis in Brazil. Our marketing authorization for Tegsedi in Brazil is subject to renewal every five years. It has also received marketing authorization in the United States and EU for the same indication. We have initiated our commercial launch for Tegsedi for the treatment of hATTR amyloidosis in Brazil and are continuing to make Tegsedi available in certain other countries within Latin America and the Caribbean through EAP programs.

hATTR amyloidosis is a progressive, systemic and fatal inherited disease caused by the abnormal formation of the TTR protein and aggregation of TTR amyloid deposits in various tissues and organs throughout the body, including in peripheral nerves, heart, intestinal tract, eyes, kidneys, central nervous system, thyroid and bone marrow. The progressive accumulation of TTR amyloid deposits in these tissues and organs leads to sensory, motor and autonomic dysfunction often having debilitating effects on multiple aspects of a patient's life. Patients with hATTR amyloidosis often present with a mixed phenotype and experience overlapping symptoms of polyneuropathy and cardiomyopathy.

Ultimately, hATTR amyloidosis generally results in death within three to fifteen years of symptom onset. Therapeutic options for the treatment of patients with hATTR amyloidosis are limited and there are currently no disease-modifying drugs approved for the disease. There are an estimated 50,000 patients with hATTR amyloidosis worldwide, including approximately 6,000 patients with polyneuropathic hATTR amyloidosis in Latin America.

Waylivra

Waylivra is an ASO that has received marketing authorization in the EU for the treatment of FCS, subject to certain conditions. The United States and EU regulatory agencies have granted orphan drug designation to Waylivra for the treatment of FCS. In connection with the marketing approval for Waylivra in the EU, the European Commission is requiring Akcea to provide results of a study based on a registry of patients to investigate how blood checks and adjustments to frequency of injections are carried out in practice and how well they work to prevent thrombocytopenia and bleeding in FCS patients taking Waylivra. In August 2021, ANVISA approved Waylivra as the first treatment for FCS

in Brazil and we have initiated our commercial launch in Brazil while continuing to make Waylivra available in certain other countries within Latin America and the Caribbean through EAP programs. Our marketing authorization for Waylivra in Brazil is subject to renewal every five years.

FCS is an ultra-rare disease caused by impaired function of the enzyme lipoprotein lipase, or LPL, and characterized by severe hypertriglyceridemia (>880mg/dL) and a risk of unpredictable and potentially fatal acute pancreatitis. Because of limited LPL function, people with FCS cannot break down chylomicrons, lipoprotein particles that are 90% triglycerides. In addition to pancreatitis, FCS patients are at risk of chronic complications due to permanent organ damage. They can experience daily symptoms including abdominal pain, generalized fatigue and impaired cognitions that affect their ability to work. People with FCS also report major emotional and psychosocial effects including anxiety, social withdrawal, depression and brain fog. There is no effective therapy for FCS currently available.

Additionally, we submitted an application to ANVISA in December 2021 for the approval of Waylivra for the treatment of FPL and we expect a regulatory decision on approval from ANVISA in the second half of 2022. FPL is a rare genetic metabolic disease characterized by selective, progressive loss of body fat (adipose tissue) from various areas of the body leading to ectopic fat deposition in liver and muscle and development of insulin resistance, diabetes, dyslipidemia and fatty liver disease. Individuals with FPL often have reduced subcutaneous fat in the arms and legs and the head and trunk regions may or may not have loss of fat. Conversely, affected individuals may also have excess subcutaneous fat accumulation in other areas of the body, especially the neck, face and intra-abdominal regions.

Evrysdi

Our SMA program, as described below, has one approved product, Evrysdi, which was approved by the FDA in August 2020 for the treatment of SMA in adults and children two months and older and by the European Commission in March 2021 for the treatment of 5q SMA in patients two months and older with a clinical diagnosis of SMA Type 1, Type 2 or Type 3 or with one to four SMN2 copies. Evrysdi also received marketing authorization for the treatment of SMA in Brazil in October 2020 and Japan in June 2021. In January 2022, the FDA granted priority review of a supplemental new drug application for Evrysdi to expand the indication to include pre-symptomatic infants under two months old with SMA.

SMA is a genetic neuromuscular disease characterized by muscle wasting and weakness. The disease generally manifests early in life. SMA is caused by mutation or deletion of the Survival of Motor Neuron 1, or SMN1, gene that encodes the survival of motor neuron, or SMN, protein. The SMN protein is critical to the health and survival of the nerve cells in the spinal cord responsible for muscle contraction. A second gene, Survival of Motor Neuron 2, or SMN2, is very similar to SMN1, contains a T nucleotide at position 6 in exon 7 and produces low, insufficient levels of functional SMN protein due to alternative splicing of exon 7. According to the SMA Foundation, SMA is the leading genetic cause of death in infants and toddlers. Approximately 1 in 10,000 children is born with the disease. We estimate that there are between 20,000 to 30,000 children and adults living with SMA in the United States, Europe and Japan.

Using our splicing technology and in collaboration with the SMA Foundation and Roche, we identified highly potent small molecule splicing modifiers that, in non-clinical studies in cultured cells derived from patients with SMA, increased both the inclusion of exon 7 in the SMN2 messenger RNA, or mRNA, transcript and the levels of SMN protein produced by the SMN2 gene. Importantly, in studies in transgenic mice carrying only the SMN2 gene, these orally bioavailable compounds penetrated the blood-brain barrier and increased the levels of full-length SMN2 mRNA and protein in brain, spinal cord, muscle and other tissues. In these same mouse studies, treatment with these compounds resulted in increased survival, restoration of body weight, prevention of motor neuron loss and improved motor function.

In November 2011, we entered into a License and Collaboration Agreement, or the SMA License Agreement, by and among us, Roche and, for the limited purposes set forth therein, the SMA Foundation under the SMA program, which included a $30 million upfront payment, the potential for up to $460 million in milestone payments, and royalties on net sales. Roche is financially responsible for pursuing clinical development of compounds from the research program under the collaboration and then commercializing any resulting products. We have recognized $160.0 million in milestone payments from Roche as of December 31, 2021, and we had recognized $59.4 million royalties on net sales pursuant to the SMA License Agreement as of December 31, 2021. We also previously received $13.3 million in sponsored research funding for this program from the SMA Foundation.

In July 2020, we entered into a Royalty Purchase Agreement with RPI 2019 Intermediate Finance Trust, or RPI, and, for the limited purposes set forth in the agreement, Royalty Pharma PLC, or the Royalty Purchase Agreement. Pursuant to the Royalty Purchase Agreement, we sold to RPI 42.933%, or the Assigned Royalty Payment, of our right to receive sales-based royalty payments, or the Royalty, on worldwide net sales of Evrysdi and any other product developed pursuant to the SMA License Agreement. In consideration for the sale of the Assigned Royalty Payments, RPI paid us $650.0 million in cash consideration. We have retained a 57.067% interest in the Royalty and all economic rights to receive the remaining potential regulatory and sales milestone payments under the SMA License Agreement. The Royalty Purchase Agreement will terminate 60 days following the earlier of the date on which Roche is no longer obligated to make any payments of the Royalty pursuant to the SMA License Agreement and the date on which RPI has received $1.3 billion in respect of the Assigned Royalty Payments.

The Evrysdi clinical development program is comprised of several studies evaluating Evrysdi in a broad SMA patient population covering the ages from newborns to 60 years old. The four ongoing studies are Firefish (infantile onset SMA; age at enrollment of one to seven months), Sunfish (later onset SMA; age at enrollment of two to 25 years), Jewelfish (patients who previously received other SMA targeted therapies; age at enrollment of six months to 60 years), and Rainbowfish (pre-symptomatic patients; age at enrollment of newborns to 6 weeks).

The Sunfish study was initiated in October 2016. Sunfish is a two-part clinical study, initiated in pediatric and adult type 2 and type 3 SMA patients to investigate the safety, tolerability, and efficacy of Evrysdi. Based on the results from part one of Sunfish, dosing for the second part of the study was selected and the pivotal part two of Sunfish initiated in October 2017, which triggered a $20.0 million milestone payment to us from Roche. The majority of the patients in the study were older, had more progressed disease, and had lower baseline scores on motor function scales relative to other clinical studies in this population. The study showed statistically significant results in primary and key secondary endpoints. The primary endpoint of part 2 was changed from baseline in the total Motor Function Measure 32, or MFM-32, score at Month 12. Both part 1 and part 2 of the study are being followed by an ongoing open-label extension.

In December 2016, a two-part clinical study, called Firefish, initiated in infants with type 1 SMA to investigate safety, tolerability, and efficacy of Evrysdi. Both parts of Firefish are open-label studies. Part one of Firefish was a dose-finding study in 21 infants. The primary objective of part 1 was to assess the safety profile of Evrysdi in infants and determine the dose for part 2. After 16 months of treatment, over 82% (14/17) of the high dose babies achieved a greater than or equal to 4-point increase in CHOP-INTEND score compared to baseline, a rating to evaluate the motor skills of patients with type 1 SMA developed by the Children's Hospital of Philadelphia. Moreover, 86% (18/21) of infants were event-free after receiving Evrysdi for 16 months. Previously published natural history data indicate that in comparable historic cohorts the median age of event-free survival for type 1 SMA infants is between 8 and 10.5 months. In addition, SMN protein level increases of up to 6.5-fold were observed after 28 days of dosing and the increase was sustained.

Based on the results from part 1 of Firefish, part 2 of Firefish was initiated in March 2018 and completed recruitment in November 2018 with 41 type 1 SMA infants enrolled. The study met its primary endpoint of proportion of infants who are sitting without support after 12 months of treatment, as assessed in the Gross Motor Scale of the Bayley Scales of Infant and Toddler development – Third Edition (BSID-III) (defined as sitting without support for 5 seconds). 12 out of 41 babies demonstrated the ability to sit without support in order to meet the primary endpoint in part two. Natural history indicates that type 1 SMA babies never achieve this milestone.

Jewelfish, an open-label study investigating the safety, tolerability, pharmacokinetics, and pharmacokinetics/pharmacodynamic relationship of Evrysdi in patients aged from 6 months to 60 years with SMA previously treated with one of several experimental or approved SMA therapies, initiated in the first quarter of 2017. Preliminary pharmacodynamic data from twelve Jewelfish patients presented in October 2018 at the World Muscle conference demonstrated sustained >2-fold increase in median SMN protein levels versus baseline over 12 months of treatment. Also, Evrysdi was well tolerated, with no drug-related adverse events leading to withdrawal from the study. The study has completed recruitment.

Rainbowfish is an open-label, single-arm, multicenter study, investigating the efficacy, safety, pharmacokinetics and pharmacodynamics of Evrysdi in babies, from birth to six weeks of age (at first dose) with genetically diagnosed SMA who are not yet presenting with symptoms. The study is currently recruiting. Included in the supplemental new drug

application we submitted to the FDA to expand Evrysdi's indication to include pre-symptomatic infants under two months old with SMA was interim data from Rainbowfish. This data showed that 80 percent of pre-symptomatic infants with SMA treated with Evrysdi for at least 12 months achieved motor milestones such as sitting without support, rolling, crawling, standing unaided, and walking independently.

Diversified Development Pipeline

Our pipeline has a number of development programs in the clinical stages. These include splicing, gene therapy, Bio-e, metabolic and oncology programs and studies of emvododstat for COVID-19 as well as studies in our current commercial products for maintaining authorizations, label extensions and additional indications.

Splicing Platform

Our splicing platform focuses on the development of innovative therapies for diseases, such as SMA, that involve regulation of mRNA splicing in the cell.

In addition to Evrysdi and our SMA program, our splicing platform also includes PTC518, which is being developed for the treatment of HD. HD is a neurodegenerative and progressive brain disorder caused by a toxic gain-of-function triplet repeat expansion in the Huntingtin gene resulting in uncontrolled movements and cognitive loss. There are currently no drugs or disease-modifying therapies approved to delay the onset or slow the progression of HD. We believe that there are approximately 135,000 HD patients globally. PTC518 is an orally bioavailable molecule with broad central nervous system and systemic distribution that has been designed to target Huntingtin protein expression with high selectivity and specificity. We announced the results from our Phase 1 study of PTC518 in healthy volunteers in September 2021 demonstrating dose-dependent lowering of huntingtin messenger ribonucleic acid and protein levels, that PTC518 efficiently crosses blood brain barrier at significant levels and that PTC518 was well tolerated. We expect to initiate a Phase 2 study of PTC518 in the first quarter of 2022.

Gene Therapy Platform

Our gene therapy platform focuses on the development of innovative therapies for rare, debilitating diseases of the CNS. Our lead gene therapy product candidate is PTC-AADC for the treatment of AADC deficiency. AADC deficiency is a rare CNS disorder arising from reductions in the enzyme AADC that result from mutations in the DOPA decarboxylase gene. AADC is the enzyme responsible for the conversion of L-dopa to dopamine. Dopamine is a key neurotransmitter that acts within the striatum (caudate and putamen), a component of the brain's deep grey matter, to modulate output of neurons that project to the motor and premotor cortices of the brain that plan and execute normal motor function. Dopamine is required in the brain for humans to develop and maintain proper motor function.

AADC deficiency is a monogenic disorder of neurotransmitter synthesis that manifests in young children and most commonly results in profound developmental delay, often seen as complete arrest of motor development. AADC deficiency generally causes the inability to develop motor control, resulting in breathing, feeding, and swallowing problems, frequent hospitalizations, and the need for life-long care. On average, patients with AADC deficiency die in the first decade of life due to profound motor dysfunction and secondary complications such as choking, hypoxia, and pneumonia. Currently, no treatment options are available for the underlying cause of the disorder, and care is limited to palliative options with significant burden on caregivers.

The prevalence of AADC deficiency has been estimated to be approximately 5,000 patients worldwide, with a live-birth incidence of up to 1 in 40,000 worldwide. While several diagnostic tests for AADC deficiency are available, we believe the condition remains largely undiagnosed or misdiagnosed and may be confused with cerebral palsy.

PTC-AADC is an adeno-associated virus, or AAV, gene therapy, which has been assessed in two completed clinical trials, and one ongoing trial. The two completed trials include a total of 18 children with severe AADC deficiency who were treated with a one-time total dose of 1.8×10^{11} vg of PTC-AADC during a single procedure in which the gene therapy was administered directly to the region of the brain, called the putamen, where dopamine is made and released. The targeted micro-dosing approach administering small amounts of gene therapy directly to focal regions of affected cells in the

putamen has the benefit of keeping the supply requirements for materials low, improving access of the therapeutic gene to key cells, potentially limiting immune and complement-mediated responses and reducing the risk of off-target uptake and excretion of the gene therapy by the liver and kidneys. To date, results from these trials suggest that patients may have a gain of motor functions and improvement in cognitive scales following gene therapy administration and have shown significant increases in motor function, which contrasts with the published natural history.

The two completed clinical trials, AADC-1601, a trial in which patients were enrolled under individual compassionate use consents, and AADC-010, were both single-arm, open-label, interventional trials that enrolled a total of 18 patients. The primary and secondary objectives of these trials were to assess the safety and efficacy of PTC-AADC administered via bilateral putaminal-infusions in patients with severe AADC deficiency at a total one-time dose of 1.8×10^{11} vg. Study enrollment required a diagnosis of AADC deficiency, defined as decreased homovanilic acid, or HVA, and ***5-***hydroxyindoleacetic acid, or 5-HIAA, and elevated levels of L-DOPA in the cerebrospinal fluid, or CSF, the presence of more than one DDC gene mutation, and the presence of clinical symptoms of AADC deficiency (including developmental delay, hypotonia, dystonia, and oculogyric crisis), and a patient age of older than 2 years.

Patients were evaluated monthly for safety assessments and every three months for efficacy assessments that included tests of motor developmental testing (Peabody Developmental Motor Scale, Second Edition, or PDMS-2, and Alberta Infant Motor Scale, or AIMS) through the first year after treatment with PTC-AADC and at periodic intervals thereafter through five years following treatment. The PDMS-2 and AIMS are validated scales used to assess motor skills in young children. Pharmacodynamic testing of CNS AADC activity over time included analyses of CSF neurotransmitter metabolites and F-DOPA PET imaging intervals, also through five years.

8 patients were enrolled in the AADC-1601 study. 10 patients were enrolled in the AADC-010 study. In both studies, the average age of patients was less than 5 years of age.

At baseline, patients had no functional movement and failed to achieve any motor milestones, including head control, sitting or standing capabilities, consistent with the published natural history of severe AADC deficiency. Compared to baseline, at one-year and at five-years after PTC-AADC administration, patients had objective evidence of de novo dopamine production as visualized by F-DOPA PET imaging of the brain, consistent with successful and stable gene expression and enzyme activity over time.

Based on preliminary analysis, following administration of PTC-AADC, the combined group of patients showed significant improvements from baseline capabilities at one-year post-treatment in functional motor skills assessed with the PDMS-2 total score, as well as on the locomotion, grasping, visual-motor integration and stationary subscales. Significant improvements from baseline at one-year post-treatment were also observed for the combined group of patients on the AIMS total score and on the prone, supine, sit and stand subscales.

Compared to published natural history data, patients in these trials showed statistically significant improvements at both two- and five-year post-treatment in achievement of motor milestones of full head control (at 2 and 5 years), sitting unassisted (at 2 and 5 years) and standing with support (at 5 years), reinforcing the clinical benefit and sustainability of functional motor improvements.

Surgical injection of PTC-AADC in both completed trials was well tolerated, with no adverse events occurring during the surgical procedure. Adverse events were generally associated with the disease state. The most frequent adverse event associated with PTC-AADC was dyskinesia and these events completely resolved over time. No serious adverse events have been attributed to PTC-AADC.

The ongoing clinical trial, AADC-011, is a single-center, open-label trial to assess the efficacy and safety of PTC-AADC in patients with AADC deficiency. The primary outcomes for this trial include assessing a change in the PDMS-2 score and measuring the change in the neurotransmitter metabolite HVA or 5-HIAA in the cerebrospinal fluid. 10 patients have been enrolled and treated to date. With these 10 patients, we now have 28 patients from our three trials being evaluated in safety and efficacy studies.

An end-of-phase 2 meeting was held with the FDA in July 2017, and the clinical, non-clinical and chemistry, manufacturing and control, or CMC, data available to date from the two completed clinical trials were reviewed. The FDA provided feedback indicating that the clinical and non-clinical data available to date were sufficient to support the submission of a BLA without undertaking additional trials or studies at this time. In a late 2019 interaction with the FDA, the agency requested additional information concerning the use of the commercial delivery system for PTC-AADC in young patients. Based on the FDA input, we intend to provide additional information concerning the use of the commercial cannula for PTC-AADC in young patients. Our ability to gather such information was previously delayed by hospitals generally canceling elective surgeries in response to the COVID-19 pandemic and other ongoing administrative delays resulting from the COVID-19 pandemic. We expect to submit a BLA to the FDA in the second quarter of 2022.

In January 2020, we submitted an MAA to the EMA for the treatment of AADC deficiency with PTC-AADC in the EEA. As a result of the COVID-19 pandemic, certain of the third-party development and manufacturing organizations that we contract with for analytical testing prioritized materials and testing kits to support COVID-19 testing, diverted employees to support COVID-19 related programs and reduced their workforce to comply with social distancing requirements imposed in connection with the COVID-19 pandemic. As a result of this shift in resources, we experienced a delay in generating analytical data needed to respond to questions sent by the EMA regarding our MAA for PTC-AADC for the treatment of AADC deficiency in the EEA. Following a clock stop extension, we submitted responses to the EMA's questions. Subsequently, due to delays related to responsive measures to the COVID-19 pandemic taken in Europe, including travel bans and quarantines, the CHMP required additional time to complete its pre-approval inspections and imposed a clock stop extension with respect to our MAA for PTC-AADC. In the fourth quarter of 2021, the EMA requested additional data in support of our manufacturing process. We expect an opinion from the CHMP in April 2022.

PTC-AADC for the treatment of AADC deficiency has orphan drug designation in the United States and EU, and rare pediatric disease designation in the United States, and upon BLA approval the FDA may grant us a priority review voucher.

If PTC-AADC for the treatment of AADC deficiency receives FDA approval, we expect that PTC-AADC would have a twelve-year exclusive marketing period in the United States for the approved indication, commencing on the date of FDA approval, under the provisions of the Biologics Price Competition and Innovation Act of 2009, or BPCIA, as well as a concurrent seven-year exclusive marketing period, which would commence on the date of FDA approval, under the provisions of the Orphan Drug Act. We expect to rely on the twelve-year BPCIA regulatory exclusivity and concurrent seven-year Orphan Drug Act exclusivity to commercialize PTC-AADC in the United States, if it is approved. Due to its orphan designation in the EMA, we anticipate that PTC-AADC would have similar market exclusivities in the EU, if it is approved.

See "Item 1. Business-Government Regulation-The new drug and biologic approval process" below for further discussion with respect to the BLA and MAA process. See "Item 1A. Risk Factors-Risks Related to our Gene Therapy Platform" and "-Risks Related to Regulatory Approval of our Product and our Product Candidates" for further detail regarding the related risks to the development, regulatory process and commercialization of gene therapy products.

Bio-e Platform

Our Bio-e platform consists of small molecule compounds that target oxidoreductase enzymes that regulate oxidative stress and inflammatory pathways central to the pathology of a number of CNS diseases. Oxidation-reduction, or redox, reactions are an essential component of the generation and regulation of energy in living systems. These reactions are regulated through a set of enzymes known as oxidoreductase enzymes that uniquely require the transfer of an electron, or a redox chemical reaction, to affect their biological activity.

One of the advanced molecules in our Bio-e platform is vatiquinone. Vatiquinone is a small molecule orally bioavailable compound that has been in development for inherited mitochondrial diseases and related genetic disorders of oxidative stress. Vatiquinone targets 15-lipoxygenase, or 15-LO, a key regulator of oxidative stress, lipid-based neuro-inflammation, alpha-synuclein oxidation and aggregation and cell death. In the third quarter of 2020, we initiated a registration-directed Phase 2/3 randomized, placebo-controlled trial of vatiquinone in approximately 60 children with mitochondrial disease associated seizures, called MIT-E. All subjects will be followed for one month to ensure a baseline seizure frequency, and then will be randomized to receive vatiquinone or placebo for six months. We have experienced

delays in enrolling this trial as some patients have been unable or hesitant to travel to clinical trial sites due to the COVID-19 pandemic and now anticipate results from this trial to be available in the fourth quarter of 2022. Mitochondrial disease associated seizures is a highly morbid condition of refractory seizures in patients with inherited mitochondrial disease. We estimate that there are approximately 20,000 patients with mitochondrial disease associated seizures globally. The clinical rationale for the MIT-E trial is based on reports of decreased seizure frequency, disruption of status epilepticus and reduced mortality risk and disease-associated morbidity recorded through compassionate use studies of vatiquinone in mitochondrial disease patients conducted in the United States and EU.

Additionally, we initiated a registration-directed Phase 3 trial of vatiquinone in approximately 110 patients with Friedreich ataxia in the fourth quarter of 2020, called MOVE-FA. The MOVE-FA trial is an 18-month parallel arm, placebo-controlled study evaluating vatiquinone versus placebo in children and young adults with Friedreich ataxia. We have completed enrollment for the MOVE-FA trial and we anticipate results to be available in the second quarter of 2023. Friedreich ataxia is a rare and life-shortening neurodegenerative disease caused by a single defect in the FXN gene which causes reduced production of the frataxin protein. We believe that there are approximately 25,000 Friedreich ataxia patients globally. Vatiquinone has previously been studied in Friedreich ataxia patients in a Phase 2 trial that included a six-month placebo-controlled phase followed by an 18-month open label extension. In this trial, long-term vatiquinone treatment (18-24 months) was associated with an improvement in overall disease severity and neurological function relative to natural history. Vatiquinone has been dosed in over 500 subjects and has been generally well-tolerated in the clinic.

The other advanced molecule in our Bio-e platform is PTC857, a small molecule orally bioavailable compound that targets 15-LO and is in development for the potential treatment of adult CNS patients. In the third quarter of 2021, we completed a Phase 1 trial in healthy volunteers to evaluate the safety and pharmacology of PTC857. PTC857 was found to be well-tolerated with no reported serious adverse events while demonstrating predictable pharmacology. We expect to initiate a Phase 2 trial of PTC857 for ALS in the second quarter of 2022. ALS is a rapidly progressing neurodegenerative disease caused by oxidative damage which leads to neuronal cell death and muscular atrophy. We believe that there are approximately 150,000 ALS patients globally.

Metabolic Platform

PTC923 is an oral formulation of synthetic sepiapterin, a precursor to intracellular tetrahydrobiopterin, which is a critical enzymatic cofactor involved in metabolism and synthesis of numerous metabolic products. PTC923 has been pursued as a possible treatment for orphan metabolic diseases associated with defects in the tetrahydrobiopterin biochemical pathways, including PKU. PKU is an inborn error of metabolism caused predominantly by mutations in the phenylalanine hydroxylase gene resulting in toxic buildup of the amino acid phenylalanine, or Phe, in the brain, and, if left untreated, severe and irreversible disabilities such as permanent intellectual disability, seizures, delayed development, behavioral problems and possibly psychiatric disorders can occur. We believe that there are approximately 58,000 PKU patients globally. In December 2019, it was announced that the Phase 2 trial for PTC923 as a potential treatment for PKU met its primary and secondary endpoints, achieving statistically-significant and clinically-meaningful reduction in blood Phe levels compared to both baseline and an active control group. We initiated a registration-directed Phase 3 trial for PTC923 for PKU in the third quarter of 2021 and expect results from this trial to be available by the end of 2022.

Oncology Platform

We have two oncology agents that are in clinical development, unesbulin and emvododstat. Unesbulin is a small molecule inhibitor of tubulin polymerization that is associated with cell cycle arrest. In addition, administration is associated with a hyperphosphorylation of tumor BMI1 protein that subsequently leads to BMI1 protein degradation and reduction in BMI1 protein function. We have assessed unesbulin in a Phase 1 multi-center study in patients with advanced solid tumors. We are also assessing unesbulin for the treatment of diffuse intrinsic pontine glioma, or DIPG. DIPG is a rapidly fatal pediatric cancer with 90% of patients dying within two years of diagnosis. There are approximately 300 patients diagnosed annually in the United States. We completed a Phase 1 dose-escalation trial in DIPG patients in the fourth quarter of 2021 and we expect to initiate a registration-directed Phase 2 trial of unesbulin for the treatment of DIPG in the third quarter of 2022.

Unesbulin is also being evaluated in leiomyosarcoma, or LMS, in patients who have relapsed or are refractory to current treatments. LMS is a type of sarcoma that manifests as malignant soft tissue tumors of muscle tissue. Preclinical

evaluations suggested that unesbulin had synergistic effects in combination with dacarbazine. Approximately 4,000 patients are diagnosed with LMS annually in the United States. We completed a Phase 1 dose escalation study of unesbulin for LMS in the fourth quarter of 2021. Unesbulin in combination with dacarbazine was found to be well-tolerated and a dose was selected for subsequent trials. We expect to initiate a registration-directed Phase 2/3 trial of unesbulin for the treatment of LMS in the second quarter of 2022.

We completed our Phase 1 trial evaluating emvododstat, a small molecule dihydrooratate dehydrogenase inhibitor that inhibits de novo pyrimidine nucleotide synthesis, in AML in the fourth quarter of 2021. We expect to provide further updates regarding our emvododstat program at a later date.

AML is a rapidly progressing hematologic cancer that causes uncontrolled growth of immature blast cells in the bone marrow preventing formation of normal blood cells. It may arise as a primary cancer or result from patient exposure to prior cytotoxic and/or radiation therapy. Approximately 20,000 new patients are diagnosed annually in the United States.

We received grant funding of $5.4 million for our oncology platform from the Wellcome Trust. To the extent that we develop and commercialize program intellectual property, excluding emvododstat, on a for-profit basis ourselves or in collaboration with a partner (provided we retain overall control of worldwide commercialization), we may become obligated to pay to Wellcome Trust development and regulatory milestone payments. Our first such milestone payment of $0.8 million to Wellcome Trust occurred in the second quarter of 2016. For additional information, see "Item 1. Business – Our Collaborations and Funding Arrangements".

Emvododstat for COVID-19

In June 2020, the FDA authorized the initiation of a Phase 2/3 clinical trial evaluating emvododstat as a potential treatment for COVID-19. Emvododstat is an oral investigational drug with a novel dual-mechanism of action that we believe has the potential to address the two crucial elements of COVID-19: (i) the high viral replication and (ii) the uncontrolled inflammatory response that ensues after infection. The integrated Phase 2/3 study, which has been initiated and is being conducted in two stages, will evaluate the efficacy and safety of emvododstat in patients hospitalized with COVID-19. The primary objective of the study is to evaluate the clinical efficacy of emvododstat compared with placebo assessed by time to respiratory improvement in adult individuals hospitalized with COVID-19. In February 2021, we announced the completion of the first stage of the Phase 2/3 trial. We expect results from this trial to be available in the first half of 2022. For a discussion of the risks related to the development of emvododstat as a potential treatment for COVID-19, please see "Item 1A. Risk Factors-Risks Related to the Development and Commercialization of our Product and our Product Candidates - *We face risks related to the development of emvododstat as a potential treatment for COVID-19 and we may ultimately be unsuccessful in developing a treatment for the virus in a timely manner or at all. Even if we are able to produce a drug that successfully treats the virus, there is significant competition in the search for a treatment for COVID-19 and our product would not be the only commercially available treatment.*".

Translarna (ataluren)

Mechanism of action

We discovered Translarna by applying our technologies to identify molecules that promote or enhance the suppression of nonsense mutations. Nonsense mutations are implicated in a variety of genetic disorders. Nonsense mutations create a premature stop signal in the translation of the genetic code contained in mRNA and prevent the production of full-length, functional proteins. Based on our research, we believe that Translarna interacts with the ribosome, which is the component of the cell that decodes the mRNA molecule and manufactures proteins, to enable the ribosome to read through premature nonsense stop signals on mRNA and allow the cell to produce a full-length, functional protein. As a result, we believe that Translarna has the potential to be an important therapy for genetic disorders which are the result of a nonsense mutation. Genetic tests are available for many genetic disorders, including those noted above, to determine if the underlying cause is a nonsense mutation. Translarna has been generally well-tolerated in all of our clinical trials to date, which have enrolled over 1,000 individuals to date.

Planned and ongoing clinical development of Translarna in nonsense mutation Duchenne muscular dystrophy

Study 041

Overview. As a specific obligation to our marketing authorization in the EEA, we are required to conduct and submit to the EMA the results of a three-year clinical trial to confirm the efficacy and safety of Translarna in the treatment of ambulatory patients with nmDMD aged five years or older. The trial is comprised of two stages: an 18-month randomized, double-blind, placebo controlled clinical trial followed by an 18-month open label extension period. We refer to the 18-month clinical trial portion as "Stage 1" and the 18-month extension period as "Stage 2". We refer to Stage 1 and Stage 2 together as Study 041. As a condition to our marketing authorization, we are required to submit results from Stage 1 and the data that has been collected to date for Stage 2 to the EMA by the end of the third quarter of 2022. The protocol for Study 041 has been approved by the CHMP. We expect results from Stage 1 of Study 041 to be available in mid-2022.

For a discussion of the risks related to conducting clinical trials, in general, and Study 041, in particular, please see "Item 1A. Risk Factors-Risks Related to the Development and Commercialization of our Product and our Product Candidates" and "-Risks Related to Regulatory Approval of our Product and our Product Candidates".

Enrollment. According to the study protocol, Study 041 enrolled nmDMD patients aged five years and above who achieve a 6-minute walk distance, or 6MWD, equal to or greater than 150 meters at three pre-treatment evaluation times (screening, baseline day one and baseline day two), tested as set forth in the protocol. Qualified participants also needed to perform timed function tests of running/walking 10 meters, climbing/descending four stairs and standing from supine within 30 seconds at both screening and baseline, and meet the other criteria set forth in the protocol.

We completed enrollment of Study 041 in the fourth quarter of 2020. Of the 363 patients enrolled in Study 041, 185 patients meet the criteria for inclusion in the primary analysis population, which we refer to as the modified intention-to-treat population, or mITT. Patients included in the mITT must be at least 7, but less than 16, years old, with a 6MWD of equal to or greater than 300 meters and a stand from supine time of five seconds or more, each as tested at screening and baseline.

Objectives and endpoints. The primary objective of Study 041 is to evaluate the effect of Translarna on ambulation and endurance as assessed by the 6-minute walk test, or 6MWT. Based on the study protocol, the primary analysis of Stage 1 will evaluate the difference in slope of change in 6MWD from baseline to week 72 between Translarna and placebo in the mITT population. Data from participants who do not qualify for inclusion in the mITT will be used for summary and analysis of efficacy endpoints.

Slope of change in 6MWD over 144 weeks will also be assessed as a secondary endpoint at the conclusion of Stage 2, and the consistency of the results at 144 weeks against week 72 will be assessed. Changes in 6MWD from baseline to week 72 and week 144 respectively will also be assessed as secondary endpoints.

A secondary objective of Study 041 is to determine the effects of Translarna on ambulation and burst activity as assessed by timed function tests (10-meter run/walk, 4-stair stair-climb, and 4-stair stair descend). Each timed function test will be analyzed as a secondary endpoint for both the mITT and ITT populations, at the end of Stage 1 and Stage 2. A separate analysis will evaluate 10-meter run/walk results in participants with a baseline 6MWD below 300 meters. An additional analysis will evaluate a composite endpoint of average change in times to run/walk 10 meters, climb 4 stairs, and descend 4 stairs. We will also assess each of time to loss of ambulation, stair-climbing and stair-descending over 72 weeks and over 144 weeks.

Determination of the effects of Translarna on lower-limb muscle function as assessed by the North Star Ambulatory Assessment, or NSAA, a functional scale designed for boys affected by DMD, will serve as an additional secondary objective. NSAA scores will be analyzed as secondary endpoints for both the mITT and ITT populations, at the end of Stage 1 and Stage 2. A separate analysis for Stage 2 will evaluate changes in total score in participants with a baseline 6MWD of equal to or greater than 400 meters and under 7 years of age. We will also assess the risk of loss of NSAA items over 72 weeks and 144 weeks.

The safety profile of Translarna also will be evaluated throughout Stage 1 and Stage 2 as a secondary objective.

Certain exploratory endpoints will also be assessed in Study 041. In patients aged 7 years and above, change from baseline in upper limb function will be assessed using both functional testing and parent/caregiver-reported questionnaires. In patients under 7 years of age, muscle strength will be assessed by change from baseline in myometry parameters. At pre-qualified sites only, magnetic resonance imaging will be used to assess change from baseline in muscle fat fraction. The effects of Translarna on pulmonary function will be assessed by change from baseline in forced vital capacity. In addition, subject- and parent/caregiver-reported questionnaires and at-home diaries will be assessed to evaluate the effect of Translarna on health-related quality of life (HRQL) changes from baseline.

Stratification. In Stage 1, participants will be randomized 1:1 to placebo or Translarna (10, 10, 20 mg/kg). The randomization will be stratified based on type of concomitant corticosteroid used at baseline (deflazacort versus prednisone/prednisolone), maximum of the two valid 6-minute walk tests performed at baseline day 1 and day 2 (<300 meters versus ≥300 to <350 meters, versus ≥350 to <400 meters, versus ≥400 meters), and time to stand from supine at baseline (<5 seconds versus ≥5 seconds).

Observational study, data collection, and open label, extension trials of Translarna for treatment of nmDMD

We are undertaking a multi-center, observational post-approval study of patients receiving Translarna on a commercial basis, or Study 025o, as required by the Pharmacovigilance Risk Assessment Committee of the EMA and in collaboration with TREAT-NMD and the Cooperative International Neuromuscular Research Group. During the study we will gather data on the safety, effectiveness, and prescription patterns of Translarna in routine clinical practice. We have successfully enrolled more than 200 patients in Study 025o and we expect to follow their progress over five years.

Pursuant to a temporary managed access agreement entered into in July 2016 between us, the UK National Institute for Health and Care Excellence, or NICE, National Health Services England, or NHS England, and other interested parties, the NorthStar Network is collecting data on the efficacy of Translarna for the treatment of nmDMD as measured by the NorthStar Ambulatory Assessment test. Patients receiving Translarna will be compared to an historical natural history population as well as a matched control group in order to assess response to treatment over the period specified in the managed access agreement.

An open label, extension trial involving patients who participated in ACT DMD is also ongoing, across multiple sites in the United States, Europe and other territories. Two open label extension trials involving patients from the United States, Europe, Israel, Australia, and Canada who had participated in our prior trials for nmDMD are also ongoing. In certain limited territories where Translarna is available via a commercial or EAP program, we have begun to wind down the studies and are investigating the potential impact that additional site closures may have on our research and development expense.

Completed clinical trials of Translarna in nonsense mutation Duchenne muscular dystrophy

Phase 2 pediatric study

As part of our pediatric development commitments under our marketing authorization in the EEA and to support the potential expansion of the Translarna label to younger patients with nmDMD, we initiated a Phase 2 pediatric clinical study to evaluate the safety and pharmacokinetics of Translarna in patients two to five years of age. The study, initiated in June 2016, included a four-week screening period, a four-week study period, and a 48-week extension period for patients who complete the four-week study period (52 weeks total treatment). In July 2018, the EMA approved a label-extension request to our marketing authorization for Translarna in the EEA to include patients from two to up to five years of age, based on data from this study.

Phase 3 clinical trial of Translarna for nmDMD (ACT DMD)

In October 2015, we announced results from ACT DMD, also referred to as Study 020, our Phase 3, double-blind, placebo-controlled, 48-week clinical trial to evaluate the safety and efficacy of Translarna in patients with nmDMD. ACT DMD involved 228 patients at 53 sites across 18 countries.

In the overall intent-to-treat, or ITT, study population, the primary endpoint of change from baseline at week 48 in the 6MWT, showed a 15 meter benefit in favor of Translarna, which did not meet statistical significance.

A summary of the safety and efficacy results from ACT DMD is outlined below.

Safety and tolerability. The results of ACT DMD confirmed the favorable safety profile of Translarna seen in our 48-week, 174-patient Phase 2b double-blind, placebo controlled clinical trial evaluating the long-term safety and efficacy of Translarna in patients with nmDMD completed in 2009, or the Phase 2b trial.

Translarna was generally well tolerated at both dose levels in our Phase 2b clinical trial. There were no study discontinuations due to adverse events. Most treatment-emergent adverse events were mild or moderate in severity. Investigators' attributions of drug-related adverse effects were generally similar across the placebo and Translarna arms. The most common adverse events in this trial were vomiting (46.6% overall), headache (29.3%), diarrhea (24.1%), nasopharyngitis (20.7%), fever (19.0%), cough (19.0%) and upper abdominal pain (17.8%). These events were generally balanced across treatment arms and are typical of pediatric illnesses. Adverse events with at least a 10% incidence in any treatment arm that were seen with increased frequency from the placebo group to the Translarna 40 mg dose group to the Translarna 80 mg dose group were nausea (12.3% for placebo, 14.0% for the Translarna 40 mg group and 16.7% for the Translarna 80 mg group), abdominal pain (7.0% for placebo, 12.3% for the Translarna 40 mg group and 16.7% for the Translarna 80 mg group), pain in extremity (10.5% for placebo, 12.3% for the Translarna 40 mg group and 13.3% for the Translarna 80 mg group), flatulence (7.0% for placebo, 8.8% for the Translarna 40 mg group and 11.7% for the Translarna 80 mg group) and nasal congestion (7.0% for placebo, 8.8% for the Translarna 40 mg group and 10.0% for the Translarna 80 mg group). There were no serious adverse events observed during the trial that were considered possibly or probably related to Translarna. Determination of relatedness of the serious adverse event to Translarna was made by the trial investigator, based on his or her judgment.

Translarna was generally well tolerated in ACT DMD. There were two study discontinuations due to adverse events, including one in the Translarna arm (constipation) and one in the placebo arm (disease progression). Most treatment-emergent adverse events were mild or moderate in severity. The most common adverse events in this trial were vomiting (20.4% overall), nasopharyngitis (20.0%), headache (18.3%), and fall (17.8%). These events were generally balanced across treatment arms and are typical of pediatric illnesses and/or patients with DMD. Adverse events with at least a 10% incidence in either treatment arm that were seen with increased frequency from the placebo group to the Translarna 40 mg dose group were vomiting (18.3% for placebo, 23.6% for the Translarna 40 mg group), nasopharyngitis (19.1% for placebo, 20.9% for the Translarna 40 mg group), fall (17.4% for placebo, 18.3% for the Translarna 40 mg group), cough (11.3% for placebo, 16.5% for the Translarna 40 mg group) diarrhea (8.7% for placebo, 17.4% for the Translarna 40 mg group), and pyrexia (10.4% for placebo, 13.9% for the Translarna 40 mg group). An overview of adverse events in this trial is shown in the table below.

Overview of treatment-emergent adverse events in Phase 3 clinical trial (as-treated population)

Parameter	Placebo N=115	Translarna 40 mg group N=115	All patients N=230
Patients with ≥1 adverse event	101 (87.8)%	10,3(89.6)%	20,4(88.7)%
Adverse events by severity			
Grade 1 (mild)	54 (47.0)%	6,1(53.0)%	11,5(50.0)%
Grade 2 (moderate)	37 (32.2)%	3,5(30.4)%	7,2(31.3)%
Grade 3 (severe)	9 (7.8)%	76(.1)%	167(.0)%
Grade 4 (life-threatening)	—	—	—

Adverse events by relatedness			
Unrelated	47 (40.9)%	4,4(38.3)%	9,1(39.6)%
Unlikely	30 (26.1)%	2,0(17.4)%	5,0(21.7)%
Possible	18 (15.7)%	2,7(23.5)%	4,5(19.6)%
Probable	6 (5.2)%	1,2(10.4)%	187(.8)%
Discontinuations due to adverse events	1 (0.9)%	10(.9)%	20(.9)%
Serious adverse events	4 (3.5)%	43(.5)%	83(.5)%
Deaths	—	—	—

There were no serious adverse events observed during the trial that were considered possibly or probably related to Translarna. Determination of relatedness of the serious adverse event to Translarna was made by the trial investigator, based on his or her judgment.

Intent to Treat (ITT) Population. The primary efficacy endpoint in ACT DMD was change in 6MWD from baseline to week 48. In the ITT population, a 15 meter benefit (p=0.213) was observed in the primary endpoint which did not meet statistical significance.

Secondary endpoints in the trial included the proportion of patients with at least 10% worsening in 6MWD at week 48 of the trial compared to baseline, or 10% 6MWD worsening, and change in timed function tests of time to run/walk 10 meters, climb four stairs and descend four stairs. The hazard ratio for Translarna versus placebo was 0.75 (p=0.160) for 10% 6MWD worsening. Benefits trended in favor of Translarna over placebo in the timed function tests in the ITT population, including observed results in time to run/walk 10 meters (1.2 seconds; p=0.117), time to climb four stairs (1.8 seconds; p=0.058), and time to descend four stairs (1.8 seconds; p=0.012).

Additional endpoints included the NSAA test and the Pediatric Outcomes Data Collection Instrument, or PODCI, a validated tool for measuring quality of life in pediatric patients with orthopedic conditions. These additional endpoints favored Translarna in the ITT population but did not meet statistical significance.

Pre-Specified Analyses. The statistical analysis plan submitted to the FDA for ACT DMD set forth pre-specified analyses of efficacy to be conducted, including subgroups of patients with baseline 6MWD less than 350 meters and patients with baseline 6MWD of greater than or equal to 300 and less than 400 meters, which we refer to as our key subgroups.

The pre-specification of our key subgroups was scientifically justified based upon knowledge of the biology and natural history of the disease and the evolving understanding of the of the six minute walk test as used to assess DMD patients. We considered the pre-specified less than 350 meter baseline 6MWD population as a key subgroup based on the knowledge that 350 meters represents a transition point for patients towards a more rapid decline in walking ability as supported by analysis from our Phase 2b trial. Furthermore, we considered the pre-specified 300 to 400 meter baseline 6MWD population as a key subgroup based on an increasing understanding of the sensitivity limitations of the six minute walk test as an endpoint in 48-week studies. Natural history data suggest that the 6MWT may not be the optimal tool to demonstrate efficacy in patients with either a baseline 6MWD of less than 300 meters, as these patients have significant muscle loss as monitored by magnetic resonance spectroscopy and are at high risk for losing ambulation regardless of treatment, or in high walking patients, such as those with a baseline 6MWD at or greater than 400 meters, as these patients are likely to remain stable over a 48 week testing period.

By defining these key subgroups, we thereby also defined corresponding subgroups of patients with baseline 6MWD greater than or equal to 350 meters, greater than or equal to 400 meters, and less than 300 meters. We also pre-specified a meta-analysis of the combined results from ACT DMD and the Phase 2b ambulatory decline phase patients.

Pre-specified sub-group analysis. We saw strong evidence of clinical benefit in the pre-specified subgroup of patients with baseline 6MWD between 300 and 400 meters. Specifically, we observed a benefit in Translarna-treated patients of 47 meters (nominal p=0.007) in the 6MWT in this subgroup. This was consistent with an observed benefit of 49 meters (nominal p=0.026) in our Phase 2b clinical trial in the 300 to 400 meters baseline 6MWD population. We also saw clinically meaningful benefit for Translarna over placebo in each of the timed function tests, including observed results in time to run/walk 10 meters (2.1 seconds; nominal p=0.066), time to climb four stairs (3.6 seconds; nominal p=0.003), and

time to descend four stairs (4.3 seconds; nominal p<0.001). The hazard ratio for Translarna versus placebo was 0.79 (nominal p=0.418) for 10% 6MWD worsening. In addition, a benefit of 4.5 points over placebo (nominal p=0.041) was observed in the NSAA test, which we believe is clinically meaningful. We believe that the benefits observed in this key pre-specified subgroup support the use of the 6MWT in the patients with a walking ability in the 300 to 400 meters range and the understanding that the reliability of the 6MWT over a 48 week period was limited at both the lower and upper ends of our 6MWD enrollment range.

In the pre-specified subgroup of patients with baseline 6MWD less than 350 meters, we observed a benefit of 24 meters (nominal p=0.210) in favor of Translarna in the 6MWT. An analysis of the results from our Phase 2b clinical trial in the less than 350 meters baseline 6MWD population, defined post-hoc, demonstrated a 68 meter benefit in the 6MWT (nominal p=0.006). In the timed function tests for the subgroup of ACT DMD patients with baseline 6MWD less than 350 meters, we observed benefits for Translarna over placebo in time to run/walk 10 meters (2.3 seconds; nominal p=0.033), time to climb four stairs (4.2 seconds; nominal p=0.019) and time to descend four stairs (4.0 seconds; nominal p=0.007).

Typically, a trial result is statistically significant if the chance of it occurring when the treatment is like placebo is less than one in 20, resulting in a p-value of less than 0.05. A nominal p-value is the result of one particular comparison when more than one comparison is possible, such as when two active treatments are compared to placebo or when two or more subgroups are analyzed.

As described above, we believe the 6MWT lacks sensitivity to detect a clinical effect in patients with baseline less than 300 meters in a 48-week trial. However, the timed function tests trended in favor of patients treated with Translarna with a baseline 6MWD below 300 meters, including observed benefit over placebo in time to run/walk 10 meters (2.5 seconds; nominal p=0.066), time to climb four stairs (2.4 seconds; nominal p=0.790), and time to descend four stairs (2.1 seconds; nominal p=0.595). We believe the positive trends in this population reflect that short muscle burst activity tests may be a better clinical measure for patients that are at a more advanced stage of disease progression. Consistent with the natural history of ambulatory DMD patients with 6MWD greater than 400 meters, which indicates stability in walking ability over a 48 week period, we observed no meaningful difference in 6MWT between patient groups. Similarly, we observed no meaningful difference in 6MWT between patient groups with baseline 6MWD greater than 350 meters.

Pre-specified meta-analysis. The meta-analysis combined efficacy results from the ACT DMD ITT population and Phase 2b ambulatory decline phase subgroup. The Phase 2b ambulatory decline phase group includes the patients from our randomized, double-blind, placebo controlled, Phase 2b clinical trial in patients with nmDMD who would have met the enrollment criteria of ACT DMD.

Results from the meta-analysis showed a statistically significant 21 meter improvement in 6MWD (p = 0.015) favoring Translarna.

Additionally, the meta-analysis showed statistically significant benefit for Translarna over placebo across each timed function test including time to run/walk 10 meters (1.4 seconds; p=0.025), time to climb four stairs (1.6 seconds; p =0.018) and time to descend four stairs (2.0 seconds; p=0.004). The hazard ratio for Translarna versus placebo was 0.66 (p=0.023) for 10% 6MWD worsening. We believe that we are able to demonstrate a statistically significant outcome in the 6MWD in the meta-analysis, despite the significant variability in baseline 6MWD among patients in both ACT DMD and the Phase 2b trial's ambulatory decline phase, due to the substantially larger patient population available in the pooled analysis.

Retrospective Analysis. We also looked back at the observed results in the meta-analysis for all patients with a baseline 300 to 400 meter 6MWD from ACT DMD and the Phase 2b trial. The meta-analysis of these data demonstrated a 45 meter benefit (nominal p<0.001) in the 6MWT as well as clinically meaningful benefits across each secondary endpoint timed function test, including benefit over placebo in time to run/walk 10 meters (2.2 seconds; nominal p=0.008), time to climb four stairs (3.4 seconds; nominal p<0.001) and time to descend four stairs (4.3 seconds; nominal p<0.001). This meta-analysis of patients with baseline 6MWD of 300 to 400 meters was not pre-specified and is defined post-hoc.

A retrospective analysis performed after unblinding trial results can result in the introduction of bias if the analysis is inappropriately tailored or influenced by knowledge of the data and actual results. In addition, nominal p-values cannot be compared to the benchmark p-value of 0.05 to determine statistical significance without being adjusted for the testing of

multiple dose groups or analyses of subgroups. Because of these limitations, regulatory authorities typically give greatest weight to results from pre-specified analyses and adjusted p-values and less weight to results from post-hoc, retrospective analyses and nominal p-values.

Statistical Considerations. The pre-specified meta-analysis results, which favored Translarna in the 6MWT and each of the timed function tests, are considered statistically significant. In the pre-specified subgroups of ACT DMD patients with a baseline 6MWD less than 350 meters and 300 to 400 meters, the p-values for the 6MWT and each of the timed function tests are considered nominal. For information with respect to the use of nominal p-values and post-hoc analyses, see Item 1A. Risk Factors, "*Our conclusions regarding the activity and potential efficacy of Translarna in nmDMD are primarily based on retrospective, subgroup and meta-analyses of the results of our Phase 2b and ACT DMD clinical trials of Translarna for the treatment of nmDMD. Other than with respect to certain of our meta-analyses, results of our analyses are expressed as nominal p-values, which are generally considered less reliable indicators of efficacy than adjusted p-values. In addition, retrospective analyses are generally considered less reliable than pre-specified analyses.*"

Participation Criteria and Stratification. Certain key inclusion criteria were specified in the ACT DMD trial protocol for enrollment: the patient had to be 7 through 16 years of age; at the screening visit the patient had to be able to walk no more than 80% of predicted 6MWD compared to healthy boys matched for age and height, but had to be able to walk at least 150 meters during the 6MWT; and the patient must have used systemic corticosteroids for a minimum of six months prior to start of treatment. The ACT DMD trial protocol provided for the exclusion of patients from the trial if, among other things, they recently used systemic aminoglycoside antibiotics, recently initiated or changed corticosteroid therapy or previously received Translarna treatment. Patients enrolled in ACT DMD underwent 48 weeks of blinded treatment prior to the final analysis and the randomization was stratified based on age (<9 years versus ≥9), baseline 6MWD (<350 versus ≥350 meters), and duration of prior use of corticosteroids (<12 months versus ≥12 months).

Study 045

Following the FDA's recommendation to collect dystrophin data using validated quantification methods, we initiated Study 045 to evaluate the ability of ataluren to increase dystrophin protein levels in boys with nmDMD. The study, a Phase 2 open label clinical study of 20 boys with nmDMD from ages two to seven, was initiated in the fourth quarter of 2018. Study 045 did not meet its pre-specified primary endpoint. Patients received baseline biopsies prior to the initiation of treatment and follow-up biopsies scheduled at 40 weeks following the start of treatment. However, certain patients were delayed in obtaining the final study muscle biopsies performed at our clinical trial site at the University of California, Los Angeles as a result of the COVID-19 pandemic. 8 of 20 patients were unable to undergo biopsies at week 40, and these patients had their second biopsies between 62 and 70 weeks of treatment. Full-length dystrophin levels were measured using both the Electrochemiluminescence, or ECL assay, as the primary endpoint and Immunohistochemistry, or IHC, assay as the secondary endpoint.

The ITT population included the 20 patients enrolled in the study. However, one subject was determined to be non-compliant, as he only took half of the study drug, and one subject did not have adequate biopsy samples to establish baseline levels. Therefore, 18 patients were compliant with the study drug and had evaluable biopsy samples. These 18 patients are considered the evaluable population. 10 of these 18 patients had their second biopsy at week 40 and 8 had their second biopsy between weeks 62 and 70. Patient characteristics, including age and steroid use were consistent across both cohorts.

Overall in the ITT population, there was an increase in dystrophin expression from baseline, on both ECL as the primary endpoint and IHC as the secondary endpoint, but these did not meet a p-value of <0.05. Nevertheless, when studying the 18 patients in the evaluable cohort, we identified a greater increase in dystrophin expression, and this increase did reach a nominal p-value of 0.04 in the analysis of the IHC assay. Also, over 80% of the evaluable subjects demonstrated an increase in dystrophin expression. 8 patients in the evaluable population had longer treatment exposure, ranging from 62-70 weeks, and these 8 patients had markedly greater levels of dystrophin increase with an average of approximately 24% in the ECL assay. We believe that these results suggest that longer duration of treatment resulted in greater biological effect, which is consistent with the long-term Translarna treatment benefit we have previously reported from our other clinical studies and our international drug registry for DMD patients receiving Translarna.

We also measured creatine kinase, or CK, levels of patients in Study 045 as an objective measure of muscle damage. Dystrophin acts as a shock absorber during a muscle contraction and would be expected to protect against muscle damage and therefore reduce CK levels. Consistent with an increase in the level of dystrophin, we observed a marked reduction of approximately 20% in creatine kinase and that longer treatment with Translarna was associated with a greater magnitude of biological effect.

Multi-platform Discovery

We continue to invest in our pre-clinical product pipeline by committing significant resources to research and development programs and business development opportunities within our areas of scientific expertise, including potential collaborations, alliances, and acquisitions or licensing of assets that complement our strategic mission to provide access to best-in-class treatments for patients who have an unmet medical need.

Our Approach

Our approach to drug discovery and development is to target rare diseases with high-unmet needs using a variety of tools, including approaches that intervene in RNA, DNA and energy production pathways. Post-transcriptional control processes are the events that occur in a cell following the transcription of DNA into RNA. These processes regulate, for example, how long RNA molecules last in the cell, how exons in precursor messenger RNA, or pre-mRNA, molecules are spliced, and how efficiently mRNA molecules are translated to proteins. Additionally, several regions of mRNA do not code for the protein and are known as untranslated regions, or UTRs. They are unique to specific mRNAs or groups of mRNAs and are directly involved in the post-transcriptional control of protein production. Interactions of cellular factors with the UTRs in the mRNA determine when and how much protein is produced as well as how mRNA is degraded and eliminated from the cell.

Splicing

Post-transcriptional control processes are the events that occur in a cell following the transcription of DNA into RNA. These processes regulate, for example, how long RNA molecules last in the cell, how exons in precursor messenger RNA, or pre-mRNA, molecules are spliced, and how efficiently mRNA molecules are translated to proteins. In the majority of human protein-encoding genes, the sequence encoding the mature mRNA transcript is not contiguous in the pre-mRNA but rather has intervening non-coding regions called introns that interrupt the coding sequences, called exons. These introns are removed from the final mRNA product by a process called splicing that also joins the exons together such that only the exons are retained in the mature mRNA.

We use our splicing technology to identify molecules that modulate splicing of the pre-mRNA. Pre-mRNA splicing is a series of highly organized biochemical reactions. Approximately 94% of all human genes encode pre-mRNAs that undergo splicing. In addition, through splicing, one gene can often generate several mRNA products that include a different set of exons through a process called alternative splicing which results in mature mRNA that encodes different, related proteins. Splicing can be therapeutically targeted, in many human diseases, including SMA, Huntington's disease, muscular dystrophy and various forms of cancer. We have developed several high-throughput drug discovery technology platforms that enable us to identify small molecule modifiers of pre-mRNA splicing. These technologies rely on sensitive quantification of pre-mRNA isoforms directly in human cells or tissue samples. Using this technology, we have successfully identified orally bioavailable small molecules that correct splicing of SMN2 mRNA. An example of one of these molecules is Evrysdi, which was approved in August 2020 by the FDA for the treatment of SMA in adults and children two months and older. Based on this experience, we believe that other small molecule drug candidates can be rapidly identified that modify splicing of pre-mRNA, promote inclusion of specific exons into mRNA, including pseudoexons, or force skipping of undesired exons from the mature mRNA. We believe that this technology is potentially widely applicable to a large number of target genes across many therapeutic areas.

Nonsense suppression

The protein coding region of mRNA contains the information for the amino acid sequence of the protein product, Additionally, certain sequences in the mRNA encode signals to start protein production and others to stop protein

production. Mutations in DNA can result in stop signals within the mRNA that cause protein production to be stopped prematurely. These are termed premature stop codons.

We use our nonsense suppression technology to identify molecules that promote or enhance readthrough of premature stop codons in the mRNA. The presence of a premature stop codon results in translation termination before a full-length protein can be produced. Our nonsense suppression technologies identify small molecules that increase readthrough at the premature stop codon by facilitating the incorporation of a defined set of amino acids at the site of the premature stop codon resulting in the production of a full-length protein. We anticipate that this approach will be applicable to a wide variety of therapeutic areas.

In some instances, the nonsense, or premature stop, codon can cause the degradation of the mRNA through a process called nonsense-mediated decay. In addition to identifying molecules that increase readthrough, we are identifying molecules that can enhance the nonsense suppression effect of readthrough agents, such as Translarna, by preventing the decay of nonsense mutation containing mRNAs, a process known as nonsense mediated decay. We have developed a high throughput screen to identify molecules that increase the level of and stabilize premature stop codon-containing mRNAs. We can evaluate the effect of these molecules alone and in combination with Translarna in cell-based models of disease, identify lead compounds and initiate a chemical optimization program. We are currently in the process of evaluating compounds as single agents and in combination with readthrough compounds in preparation for an optimization program.

Gene therapy

Gene therapy is a technique that uses genes to treat or prevent disease through several approaches including 1) replacing a mutated gene that causes disease with a healthy copy of the gene, 2) inactivating, or "knocking out," a mutated gene that is functioning improperly or 3) introducing a new gene into the body to help fight a disease. Utilizing our CNS delivery strategy and technologies, we are focused on developing gene therapy product candidates that are engineered and optimized to provide durable treatments, and potentially functional cures, for CNS diseases for which there are currently no approved treatments. By directly administering low doses our therapies using non-pathogenic AAV to deliver therapeutic genes to the target non-dividing neuronal cells in the CNS, which we term targeted micro-dosing, we believe we maximize the probability of achieving a therapeutic benefit and mitigate systemic antibody, cellular immunity and complement-based reactions, minimize the stimulation of new immune responses, and reduce off-target effects.

We believe that our gene therapy platform will enable us to treat patients across a range of CNS disease indications. Our detailed knowledge and expertise in rare CNS diseases has enabled us to develop a gene therapy platform which we believe has important competitive advantages, is highly differentiated and provides practical approaches for delivery of gene therapies to the CNS in a range of disease indications. Our platform utilizes advanced, commercially-available delivery devices, instrumentation and software to optimize targeting to the region of the CNS known to be involved in the cause of the disease. Targeted micro-dosing ensures direct delivery to the CNS, thereby avoiding systemic administration, mitigating systemic immune and complement responses, minimizing the generation of newly mounted immunity to the gene therapy, and bypassing uptake and excretion of the gene therapy vector by organs such as the liver and kidney which further enhances safety. Our targeted micro-dosing strategy has the added benefit of requiring significantly lower gene therapy doses than systemic dosing would require. Our low dose requirements provide for efficient manufacturing approaches that reduce supply risks, enhance product quality, and lower production costs. Our direct delivery processes have also resulted in a deep understanding of routes of administration that result in effective gene therapy delivery to target cells.

Our gene therapy platform includes an asset targeting Friedreich ataxia. We expect to initiate a clinical study for this program in the fourth quarter of 2022. Additionally, the gene therapy platform includes two other programs targeting CNS disorders, including Angelman syndrome, a rare, genetic, neurological disorder characterized by severe developmental delays. We continue to work towards submitting a filing in support of the first-in-human study for this program.

Energy production and oxidative stress

Energy production in cells is critical to their survival. On the other hand, processes that induce oxidative stress in cells can negatively impact them. Energy production takes place in a part of the cell called mitochondria. The mitochondria use the

transport of electrons via chemical reactions called redox reactions in their cell membranes to produce adenosine triphosphate, or ATP, which is the central energy molecule inside cells. This process of moving electrons to produce ATP is termed electron transfer or transport. The redox reactions, however, can also cause oxidative stress. We use our expertise in energy production via electron transfer chemical reactions and in oxidative stress to develop potentially first-in-class therapeutics for unmet medical needs. One area of our focus is on inherited mitochondrial diseases. Mitochondrial diseases often derive from defects in energy production and oxidative stress pathway. These diseases commonly result in severe neurological impairment and death at an early age. Through our screening processes, we have identified multiple drug targets which we are assessing in nonclinical studies with the aim of identifying additional product candidates to take into clinical development. Similar strategies potentially can be used for broader sets of diseases. We believe such approaches to these types of intractable diseases have the potential to lead to novel therapies to address areas of high unmet medical need.

Our Collaborations, License Agreements and Funding Arrangements

We currently have ongoing collaborations with Roche and the SMA Foundation for SMA, collaboration and license agreements with National Taiwan University, or NTU, for PTC-AADC, a collaboration and license agreement with Akcea for Tegsedi and Waylivra and a license agreement with Shiratori Pharmaceutical Co., Ltd., or Shiratori, relating to the manufacturing processes and technology for PTC923. We also have received grant funding from Wellcome Trust pursuant to funding agreements under which we have continuing obligations.

Roche and the SMA Foundation

Overview. In November 2011, we entered into a license and collaboration agreement with Roche and the SMA Foundation to further develop and commercialize compounds identified under our SMA sponsored research program with the SMA Foundation and to research other small molecule compounds with potential for therapeutic use in patients with SMA. The research term of this agreement was terminated effective December 31, 2014. The ongoing collaboration is governed by a joint steering committee consisting of an equal number of representatives of us, the SMA Foundation and Roche. We, the SMA Foundation and Roche have agreed to endeavor to make decisions by consensus, but if the joint steering committee cannot reach agreement after following a specified decision resolution procedure, Roche's decision will control. However, Roche may not exercise its final decision-making authority with respect to certain specified matters, including any decision that would increase our or the SMA Foundation's obligations, reduce our or the SMA Foundation's rights, expand Roche's rights, or reduce Roche's obligations under the license and collaboration agreement.

Commercialization. We have granted Roche worldwide exclusive licenses, with the right to grant sublicenses, to our patent rights and know-how with respect to such compounds and products. Roche is responsible for pursuing worldwide clinical development of compounds from the research program and has the exclusive right to develop and commercialize compounds from the collaboration.

Payments and Contingent Payments. Pursuant to the license and collaboration agreement, Roche paid us an upfront non-refundable payment of $30.0 million. During the research term, which was terminated effective December 31, 2014, Roche provided us with funding, based on an agreed- upon full-time equivalent rate, for an agreed-upon number of full- time equivalent employees that we contributed to the research program. We are eligible to receive up to an aggregate of $135.0 million in payments if specified development and regulatory milestones are achieved and up to an aggregate of $325.0 million in payments if specified sales milestones are achieved. We are also entitled to tiered royalties ranging from 8% to 16% on worldwide net product sales of products developed pursuant to the collaboration. Roche's obligation to pay us royalties will expire generally on a country-by- country basis at the latest of the expiration of the last-to-expire patent covering a product in the given country, the expiration of regulatory exclusivity for that product in such country or 10 years from the first commercial sale of that product in such country. However, the royalties payable to us may be decreased in certain circumstances. For example, the royalty rate in a particular country is reduced if the product is not protected by patents in that country and no longer entitled to regulatory exclusivity in that country. We remain responsible for making any payments to the SMA Foundation that may become due under our pre-existing sponsored research agreement with the SMA Foundation.

As of December 31, 2021, we had recognized a total of $160.0 million in milestone payments and $59.4 million royalties on net sales pursuant to the SMA License Agreement. As of December 31, 2021, there are no remaining development and regulatory event milestones that we can receive. The remaining potential sales milestones as of December 31, 2021 are $300.0 million upon achievement of certain sales events.

Pursuant to the Royalty Purchase Agreement, we sold to RPI the Assigned Royalty Payment, in consideration for $650.0 million. We have retained a 57.067% interest in the Royalty and all economic rights to receive the remaining potential regulatory and sales milestone payments under the SMA License Agreement. The Royalty Purchase Agreement will terminate 60 days following the earlier of the date on which Roche is no longer obligated to make any payments of the Royalty pursuant to the SMA License Agreement and the date on which RPI has received $1.3 billion in respect of the Assigned Royalty Payments.

Termination. Unless terminated earlier, the license and collaboration agreement will expire on the date when no royalty or other payment obligations are or will become due under the agreement. Roche's termination rights under the license and collaboration agreement include the right to terminate the agreement at any time after November 22, 2013 on a product-by-product and country-by-country basis upon three months' notice before the launch of the applicable product or upon nine months' notice thereafter; and the right to terminate the agreement in specified circumstances following a change of control of us. The license and collaboration agreement provides that we or Roche may terminate the agreement in the event of an uncured breach by the other party of a material provision of the agreement, or in the event of the other party's bankruptcy or insolvency. Upon termination of the collaboration agreement by Roche for convenience or termination by us as a result of Roche's breach, bankruptcy, change of control or patent challenge, we have the right to assume the development and commercialization of product candidates arising from the license and collaboration agreement. In that event, we may become obligated to pay royalties to Roche on sales of any such product.

SMA Foundation

Overview. In June 2006, we entered into a sponsored research agreement with the SMA Foundation under which we and the SMA Foundation have collaborated in the research and preclinical development of small molecule therapeutics for SMA. As discussed above, we are also collaborating with the SMA Foundation and Roche to further develop these compounds. Pursuant to the sponsored research agreement, as amended, the SMA Foundation provided us with $13.3 million in funding. The SMA Foundation is not obligated to provide any further funding under this agreement.

Continuing financial obligations. We may become obligated to pay the SMA Foundation single-digit royalties on worldwide net product sales of any collaboration product that we successfully develop and subsequently commercialize or, with respect to collaboration products we outlicense, including Evrysdi, a specified percentage of certain payments we receive from our licensee. As discussed above, we have outlicensed rights to Roche pursuant to a license and collaboration agreement. We are not obligated to make such payments unless and until annual sales of a collaboration product exceed a designated threshold. Our obligation to make such payments would end upon our payment to the SMA Foundation of an aggregate of $52.5 million, which we refer to as the repayment amount.

Reversion rights. In specified circumstances, including those involving our decision to discontinue development or commercialization of a collaboration product, our uncured failure to meet agreed timelines or those that might arise following our change of control, we may be obligated to grant the SMA Foundation exclusive or non-exclusive sublicensable rights under our intellectual property, in certain collaboration products, among other rights, to assume the development and commercialization of such collaboration products and to provide the SMA Foundation with other transitional assistance, which we refer to as a reversion. In some such cases, we may be entitled to receive licensing fee payments from the SMA Foundation and single-digit royalties on sales of the applicable collaboration product, which amounts we collectively refer to as reversion payments. In other cases, the SMA Foundation is not required to make any payments to us in connection with the licenses it receives from us.

Termination. Unless terminated earlier, the sponsored research agreement will continue until the earliest of the SMA Foundation's receipt of the repayment amount or, if there was a reversion, either our receipt of all reversion payments that the SMA Foundation may be obligated to make to us or, if the SMA Foundation is not obligated to make reversion payments, the expiration of the last-to-expire patent we licensed to the SMA Foundation in connection with such reversion.

The sponsored research agreement provides that either party may terminate the agreement in the event of an uncured material breach by the other party or in the event of the other party's bankruptcy or insolvency.

National Taiwan University

We have two agreements with NTU relating to PTC-AADC: a collaborative research agreement, originally entered into between Agilis Biotherapeutics, Inc., or Agilis, and NTU, in September 2015, as amended, or the NTU Collaboration Agreement; and a license and technology transfer agreement, originally entered into between Agilis, NTU and Professor Wuh-Liang (Paul) Hwu, in December 2015, or the NTU Licensing Agreement.

NTU Collaboration Agreement

Overview. The NTU Collaboration Agreement governs the collaboration between us and NTU with respect to the research and clinical trials for AADC deficiency gene therapy, or the Research. Pursuant to the NTU Collaboration Agreement, NTU is responsible for performing the research and clinical trials and we are responsible for providing related funding. In accordance with such obligations, NTU completed a Phase 1/2 trial, AADC-010, in Taiwan of PTC-AADC, known as GT-AADC at the time, for the treatment of AADC deficiency and is conducting an ongoing Phase 2b trial, AADC-011, in Taiwan of PTC-AADC for the treatment of AADC deficiency and is collaborating on certain other ongoing activities with third parties. We are responsible for any regulatory submissions for PTC-AADC for the treatment of AADC deficiency.

Funding obligations. Our funding obligations consist of funding payments for NTU's research paid upon the achievement of certain milestones. As of December 31, 2021, an aggregate amount of $2.6 million in funding payments has been paid to NTU. An additional $1.2 million would become due and payable to NTU upon a potential approval by the EMA of the MAA for PTC-AADC.

Intellectual property. All intellectual property developed or obtained by NTU relating to the Research will be owned by NTU. The NTU Collaboration Agreement provided us a right of first refusal for an exclusive, worldwide, royalty bearing license for the results of the Research, which Agilis exercised in 2015 in connection with entering into the Licensing Agreement.

Termination. The NTU Collaboration Agreement expires on December 31, 2022, with automatic annual extensions subject to our written approval. The NTU Collaboration Agreement can be terminated for certain specified breaches by either party upon 30 or 60 days' notice, depending on the breach and following a specified cure period. Upon termination at our election, NTU is obligated to return to us any unused funding payments made to NTU that have not yet been utilized, and we are obligated to pay any non-cancellable expenses incurred by NTU, as of the date of termination.

NTU Licensing Agreement

Overview. Pursuant to the NTU Licensing Agreement, NTU granted to us an exclusive, perpetual license, with the right to grant sublicenses through all tiers, to research and use the intellectual property, data, chemistry, manufacturing and controls, or CMC, records, documents, confidential information, materials and know-how pertaining to the Research, including PTC-AADC for the treatment of AADC deficiency, under the NTU Collaboration Agreement, or the Technology, and to develop, make, manufacture, use, sell, import and market the Technology and any other products made, invented, developed or incorporated by or with the Technology, or the Licensed Products. Subject to any regulatory delays or issues, we are obligated to research, use and develop the Technology to manufacture Licensed Products by December 23, 2025. Additionally, we are obligated to obtain marketing approval of PTC-AADC for the treatment of AADC deficiency, either by the FDA or by the EMA, by December 31, 2024.

Funding Obligations. NTU received a lump sum of $100,000 upon execution of the NTU Licensing Agreement. Additionally, NTU will be entitled to receive contingent payments from us based on (i) the achievement of certain clinical and regulatory milestones up to an aggregate maximum amount of $2.0 million, (ii) annual license maintenance fees, (iii) a low double-digit percentage royalty of annual net sales of Licensed Products, and (iv) a percentage of sublicense revenue, ranging from low-twenties to mid-twenties. The annual license maintenance fees are non-refundable, but creditable against annual net sales payments.

Intellectual Property. All intellectual property relating to the manufacture, production, assembly, use or sale of Technology and any Licensed Products derived thereof are owned by NTU.

Termination. The NTU Licensing Agreement expires on December 23, 2035. Upon expiration, we will have a fully paid-up, perpetual, royalty-free exclusive license to the Technology. We may terminate the NTU Licensing Agreement upon 60 days' written notice to NTU in the event of (a) the failure of a pivotal clinical study, or serious adverse event in a clinical study, with respect to PTC-AADC for the treatment of AADC deficiency, that prevents continuing such clinical study under reasonable circumstances or (b) the rejection of a BLA with the FDA or an MAA with the EMA, or equivalent biologics approval application in another territory with respect to PTC-AADC for the treatment of AADC. In such termination event, we must pay $100,000 to NTU within 30 days of termination and NTU would retain all rights to the Technology. We may terminate the NTU Licensing Agreement for material breach by another party following a 30-day cure period. NTU may terminate the NTU Licensing Agreement for our failure to pay any undisputed license fees or net sales or sublicensing royalty fees within the applicable deadline following a 30-day cure period.

Tegsedi and Waylivra

Overview. PTC Therapeutics International Limited, our subsidiary, entered into a Collaboration and License Agreement, or the Tegsedi-Waylivra Agreement, dated August 1, 2018 by and between us and Akcea, for the commercialization by us of Tegsedi, Waylivra and products containing those compounds, which we refer to collectively as the Products, in countries in Latin America and the Caribbean, or the PTC Territory. In addition, Akcea has granted to us a right of first negotiation, or ROFN, to commercialize AKCEA-TTR-Lrx, a follow-on product candidate to inotersen, on an exclusive basis in the PTC Territory. We are responsible for all meetings, communications and other interactions with regulatory authorities in the PTC Territory. The activities of the parties pursuant to the Tegsedi-Waylivra Agreement is overseen by a Joint Steering Committee, composed of an equal number of representatives appointed by each of us and Akcea.

Commercialization. Under the terms of the Tegsedi-Waylivra Agreement, Akcea has granted to us an exclusive right and license, with the right to grant certain sublicenses, under Akcea's product-specific intellectual property to develop, manufacture and commercialize the Products in the PTC Territory. In addition, Akcea has granted to us a non-exclusive right and license, with the right to grant certain sublicenses, under Akcea's core intellectual property and manufacturing intellectual property to develop, manufacture and commercialize the Products in the PTC Territory and to manufacture the Products worldwide in accordance with a supply agreement with Akcea. Akcea has in-licensed certain of the Akcea intellectual property from its parent company, Ionis. Each party has agreed not to, independently or with any third party, commercialize any competing oligonucleotide product in the PTC Territory for the same gene target as inotersen.

Payments and Contingent Payments. We paid to Akcea an upfront licensing fee of $18.0 million, consisting of an initial payment of $12.0 million paid in connection with entering into the Tegsedi-Waylivra Agreement in August 2018, and a second payment of $6.0 million that was paid after Waylivra received regulatory approval from the EMA in May 2019. In addition, Akcea was eligible to receive milestone payments, on a Product-by-Product basis, of $4.0 million upon receipt of regulatory approval for a Product from ANVISA, subject to a maximum aggregate amount of $8.0 million for all such Products. We paid Akcea $4.0 million upon our receipt of marketing authorization from ANVISA in October 2019 for the treatment of stage 1 or stage 2 polyneuropathy in adult patients with hATTR amyloidosis in Brazil with Tegsedi and an additional $4.0 million upon our receipt of marketing authorization from ANVISA in August 2021 for the treatment of FCS. Akcea is also entitled to receive royalty payments in the mid-twenty percent range of net sales on a country-by-country and Product-by-Product basis, commencing on the earlier to occur of (1) 12 months after the first commercial sale of such Product in Brazil or (2) the date when we, our affiliates or sublicensees have recognized revenue of $10.0 million or more in cumulative net sales for such Product in the PTC Territory. The royalty payments are subject to reduction in certain circumstances as set forth in the Tegsedi-Waylivra Agreement.

Right of first negotiation. Akcea has granted to us a ROFN to commercialize AKCEA-TTR-Lrx in the PTC Territory, subject to negotiation of the terms of a definitive agreement and certain other terms and conditions. Such a definitive agreement would provide for a royalty rate to be paid by us for AKCEA-TTR-Lrx equal to the royalty rate we have agreed to pay for Tegsedi under the Tegsedi-Waylivra Agreement, or in the mid-twenty percent range of net sales, and the term of such royalty payments would be the same as the term of the Tegsedi royalty payments. During a specified period in the

Agreement, neither Akcea nor Ionis may enter into an agreement or grant any license to AKCEA-TTR-Lrx that is inconsistent with PTC's ROFN.

Termination. The Tegsedi-Waylivra Agreement will continue until the expiration of the last to expire royalty term with respect to all Products in all countries in the PTC Territory. Either party may terminate the Tegsedi-Waylivra Agreement on written notice to the other party if such other party is in material breach of its obligations thereunder and has not cured such breach within 30 days after notice in the case of a payment breach or 60 days after notice in the case of any other breach.

Shiratori

Overview. In connection with our acquisition of Censa Pharmaceuticals, Inc., or Censa, in May 2020, we became a party to a license agreement dated as of February 8, 2015, as amended, between Shiratori and Censa, or the Shiratori License Agreement. Pursuant to the Shiratori License Agreement, Shiratori granted Censa the sole and exclusive worldwide right and license, with the right to sublicense, under certain licensed know-how, or the Licensed Know-How, and licensed patents, or the Licensed Patents, relating to manufacturing processes and technology for sepiapterin, to research, have researched, develop, have developed, use, import, export, market, have marketed, offer for sale, sell and have sold, and otherwise commercialize any final pharmaceutical product in finished form containing sepiapterin as an active pharmaceutical ingredient, including PTC923, collectively the Sepiapterin Products, covered by the Licensed Patents or using the Licensed Know-How in all countries and territories of the world outside of Japan, or the Sepiapterin Territory.

Payments and Contingent Payments. Under the Shiratori License Agreement, we are obligated to pay to Shiratori a low single digit percentage of annual net sales of the Sepiapterin Products in each country in the Sepiapterin Territory until the expiration of the last-to-expire Licensed Patent controlled by Shiratori covering the relevant country followed by an obligation to pay a reduced royalty rate for a specified period of time thereafter. We are also obligated to pay to Shiratori certain regulatory and development milestones.

Termination. Unless earlier terminated, the Shiratori License Agreement will continue in full force and effect on a country-by-country and product-by-product basis until the obligation to pay royalties with respect to the sale of such Sepiapterin Product in such country expires. The parties may agree to mutually terminate the Shiratori License Agreement. Shiratori may elect to terminate the Shiratori License Agreement upon sixty days' prior written notice to us in the event that we fail to (i) achieve regulatory approval for a Sepiapterin Product in either the United States or EU by February 8, 2026 or (ii) commercially launch a Sepiapterin Product in the United States or European Union by February 8, 2027. We may elect to terminate the Shiratori License Agreement upon sixty days' prior written notice to Shiratori.

Wellcome Trust

We have two separate funding agreements with Wellcome Trust for the research and development of small molecule compounds in connection with our oncology platform and antibacterial program. Pursuant to the agreement relating to the antibacterial program, Wellcome Trust awarded us a $5.0 million grant of which we received $4.8 million between 2011 and 2015. We are no longer actively pursuing an antibacterial program and do not expect to receive additional funding under this agreement. The materials terms of these funding agreements are similar in substance, except as described below.

The other agreement, entered into in May 2010, relates to the research and development of small molecule compounds under our oncology platform, excluding emvododstat. Pursuant to this agreement, Wellcome Trust awarded us a $5.4 million grant, of which approximately $0.9 million was paid in connection with execution of the agreement and the balance of which was paid to us in 2010 and 2012 based on our achievement of specified milestones.

Development and commercialization. We own all intellectual property that arises from the conduct of the research programs under these funding agreements, which we refer to as program intellectual property, and are responsible for developing and commercializing the program intellectual property, including unesbulin (for our oncology platform), and other compounds. However, we will require Wellcome Trust's written consent prior to any such development or commercialization. If Wellcome Trust withholds such consent and we and Wellcome Trust are not able to resolve

Wellcome Trust's concerns, the parties have agreed to follow a specified dispute resolution procedure that gives neither party final decision-making authority.

Reversion rights. Under both funding agreements, if we fail to take reasonable steps to develop or commercialize program intellectual property during specified timeframes, we may be obligated to grant exclusive rights to Wellcome Trust or its nominee under the program intellectual property, along with non-exclusive rights under our background intellectual property, so that Wellcome Trust or its nominee can assume such development and commercialization. If we grant such a license, we would be entitled to a share of any consideration received by Wellcome Trust in connection with any subsequent development or commercialization of program intellectual property on a for-profit basis, which share would be proportionate to our contribution to the development and commercialization.

Continuing financial obligations-oncology platform. To the extent that we develop and commercialize program intellectual property on a for-profit basis ourselves or in collaboration with a partner (provided we retain overall control of worldwide commercialization), we may become obligated to pay to Wellcome Trust development and regulatory milestone payments and single-digit royalties on sales of any research program product under our oncology platform, excluding emvododstat. We made the first development milestone payment of $0.8 million to Wellcome Trust under this agreement during the second quarter of 2016. Additional development and regulatory milestone payments up to an aggregate of $22.4 million may become payable by us under the agreement. For example, in the event a Phase 2 clinical study of a research program candidate, such as unesbulin, is commenced, a milestone payment of $2.5 million would become payable by us to Wellcome Trust upon the earlier to occur of the first dose administered to the last patient enrolled in the study or the termination of dosing of all patients in the study. We expect to initiate a registration-directed Phase 2/3 trial of unesbulin for the treatment of LMS in the second quarter of 2022 and we expect to initiate a registration-directed Phase 2 trial of unesbulin for the treatment of DIPG in the third quarter of 2022.

Additional continuing financial obligations. Our obligation to pay the royalties described above would continue on a country-by-country basis until the longer of the expiration of the last patent in the program intellectual property in such country covering the research program product and the expiration of market exclusivity of such product in such country. To the extent that we develop and commercialize program intellectual property on a for-profit basis through outlicensing, we will be obligated to pay to Wellcome Trust a specified share of any consideration we receive from our licensee, provided that Wellcome Trust would be entitled to receive a minimum amount equal to its original contribution. We would incur no payment obligations to Wellcome Trust to the extent that we elect to develop and commercialize program intellectual property on a non-profit basis.

Termination. Unless terminated earlier, each funding agreement will continue until we have received the full amount of the grant, the research program has ended, the last-to-expire of the patents in the program intellectual property has expired, any agreement entered into for the exploitation of the program intellectual property or our background intellectual property has expired, and there are no remaining payment obligations relating to the exploitation of the program intellectual property or our background intellectual property. Each funding agreement provides that either party may terminate the agreement in the event of an uncured material breach by the other party or in the event of the other party's bankruptcy or insolvency and that Wellcome Trust may terminate the agreement under specified circumstances, including, among others, in specified circumstances following a change in control of us or if Wellcome Trust believes that an uncorrected serious failure exists in the progress, management or conduct of the research program or that an act or omission by us is incompatible with or has an adverse effect on Wellcome Trust's charitable objectives or reputation.

If Wellcome Trust terminates either or both funding agreements in specified circumstances, including as a result of our material breach, bankruptcy or insolvency, or following our change of control, we may be obligated to assign to Wellcome Trust ownership of the applicable program intellectual property, grant to Wellcome Trust royalty-free non-exclusive rights under the applicable background intellectual property for the continuation of the research program (if applicable) and the development and commercialization of the applicable program intellectual property, and provide Wellcome Trust with other specified transitional assistance.

Certain specified rights and obligations of the parties will generally survive termination of the funding agreements, including Wellcome Trust's right to receive payments from us with respect to development and commercialization of program intellectual property on a for-profit basis.

If a funding agreement terminates prior to the end of a research program, we are obligated to return all funding we received from Wellcome Trust that is unspent at the date of termination (after deduction of costs and non-cancellable commitments incurred prior to such date).

Our Ongoing Acquisition-Related Obligations

From time to time, we have engaged in strategic transactions to expand and diversify our product pipeline, including through the acquisition of assets or businesses. In connection with these acquisitions, we have entered into agreements through which we have ongoing obligations, including obligations to make contingent payments upon the achievement of certain development, regulatory and net sales milestones or upon a percentage of net sales of certain products.

Complete Pharma Holdings, LLC

On April 20, 2017, we completed our acquisition of all rights to Emflaza, or the Emflaza Transaction. The Emflaza Transaction was completed pursuant to an asset purchase agreement, dated March 15, 2017, as amended on April 20, 2017, or the Emflaza Asset Purchase Agreement, by and between us and Marathon Pharmaceuticals, LLC (now known as Complete Pharma Holdings, LLC), or Marathon. The assets acquired by us in the Emflaza Transaction include intellectual property rights related to Emflaza, inventories of Emflaza, and certain contractual rights related to Emflaza. We assumed certain liabilities and obligations in the Emflaza Transaction arising out of, or relating to, the assets acquired in the Emflaza Transaction.

Upon the closing of the Emflaza Transaction, we paid to Marathon total upfront consideration comprised of $75.0 million in cash, funded through cash on hand, and 6,683,598 shares of our common stock. The number of shares of common stock issued at closing was determined by dividing $65.0 million by the volume weighted average price per share of the Company's common stock on the Nasdaq Global Select Market, or Nasdaq, for the 15 trading-day period ending on the third trading day immediately preceding the closing. Beginning in 2018, Marathon is entitled to receive contingent payments from us based on annual net sales of Emflaza, up to a specified aggregate maximum amount over the expected commercial life of the asset, and a single $50.0 million sales-based milestone, in each case subject to the terms and conditions of the Emflaza Asset Purchase Agreement.

Agilis Biotherapeutics, Inc.

On August 23, 2018, we completed our acquisition of Agilis pursuant to an Agreement and Plan of Merger, dated as of July 19, 2018, or the Agilis Merger Agreement, by and among us, Agility Merger Sub, Inc., a Delaware corporation and our wholly owned, indirect subsidiary, Agilis and, solely in its capacity as the representative, agent and attorney-in-fact of the equityholders of Agilis, Shareholder Representative Services LLC, or the Merger.

Upon the closing of the Merger, we paid to Agilis equityholders total upfront consideration comprised of $49.2 million in cash and 3,500,907 shares of our common stock, or the Closing Stock Consideration. The Closing Stock Consideration was determined by dividing $150.0 million by the volume-weighted average price per share of our common stock on Nasdaq for the 10 consecutive trading-day period ending on the second trading-day immediately preceding the closing of the Merger. Agilis equityholders may become entitled to receive contingent payments from us based on the achievement of certain development, regulatory and net sales milestones, as well as based upon a percentage of net sales of certain products.

On April 29, 2020, we, certain of the former equity holders of Agilis, or the Participating Rightholders, and, for the limited purposes set forth in the agreement, Shareholder Representative Services LLC, entered into a Rights Exchange Agreement, or the Rights Exchange Agreement. Pursuant to the Right Exchange Agreement, we issued 2,821,176 shares of our common stock and paid $36.9 million, in the aggregate, to the Participating Rightholders in exchange for the cancellation and forfeiture by the Participating Rightholders of their rights to receive certain milestone-based contingent payments under the Agilis Merger Agreement.

Our outstanding obligations under the Agilis Merger Agreement include obligations to pay up to an aggregate maximum amount of $20.0 million upon the achievement of certain development milestones, up to an aggregate maximum amount

of $361.0 million upon the achievement of certain regulatory milestones, up to a maximum aggregate amount of $150.0 million upon the achievement of certain net sales milestones and a percentage of annual net sales for Friedreich ataxia and Angelman syndrome during specified terms, ranging from 2% to 6%, pursuant to the terms of the Agilis Merger Agreement.

BioElectron Technology Corporation

On October 25, 2019, we completed the acquisition of substantially all of the assets of BioElectron Technology Corporation, or BioElectron, pursuant to an Asset Purchase Agreement by and between the Company and BioElectron, dated October 1, 2019, or the BioElectron Asset Purchase Agreement.

Upon the closing of the Asset Acquisition, we paid to BioElectron total upfront consideration of $10.0 million, funded with cash on hand, less (i) transaction expenses incurred by BioElectron, (ii) the amount of outstanding indebtedness of BioElectron including a $4.0 million loan advance to BioElectron plus accrued and unpaid interest thereon and (iii) $1.5 million held in an escrow account to secure potential indemnification obligations owed to us. Subject to the terms and conditions of the BioElectron Asset Purchase Agreement, BioElectron may become entitled to receive contingent milestone payments of up to $200.0 million (in cash or in shares of our common stock, as determined by us) from us based on the achievement of certain regulatory and net sales milestones. Subject to the terms and conditions of the BioElectron Asset Purchase Agreement, BioElectron may also become entitled to receive contingent payments based on a percentage of net sales of certain products.

Censa Pharmaceuticals, Inc.

On May 29, 2020, we acquired Censa pursuant to an Agreement and Plan of Merger, dated as of May 5, 2020, or the Censa Merger Agreement, by and among us, Hydro Merger Sub, Inc., our wholly owned, indirect subsidiary, and, solely in its capacity as the representative, agent and attorney-in-fact of the securityholders of Censa, Shareholder Representative Services LLC, or the Censa Merger.

Upon the closing of the Censa Merger, we paid to the Censa securityholders (i) cash consideration of $15.0 million, which consisted of an upfront payment of $10.4 million and an additional $4.6 million for the net assets on Censa's opening balance sheet as of the date of the acquisition, and (ii) 845,364 shares of our common stock, which were valued at $42.9 million based on the closing stock price on the acquisition date. The number of shares issued was determined using a 30-day VWAP pursuant to the Censa Merger Agreement.

In addition, pursuant to the Censa Merger Agreement, Censa securityholders will be entitled to receive contingent payments from us based on (i) the achievement of certain development and regulatory milestones up to an aggregate maximum amount of $217.5 million for PTC923's two most advanced programs and receipt of a priority review voucher from the FDA as set forth in the Censa Merger Agreement, (ii) $109 million in development and regulatory milestones for each additional indication of PTC923, (iii) the achievement of certain net sales milestones up to an aggregate maximum amount of $160.0 million, (iv) a percentage of annual net sales during specified terms, ranging from single to low double digits of the applicable net sales threshold amount, and (v) any sublicense fees paid to us in consideration of any sublicense of Censa's intellectual property to commercialize PTC923, on a country-by-country basis, which contingent payment will equal to a mid-double digit percentage of any such sublicense fees. We have the option to pay the initial $30 million development milestone, for the completion of enrollment of a Phase 3 clinical trial for PTC923 for PKU, if achieved, in cash or shares of our common stock.

Intellectual Property

Patents and trade secrets

Our success depends in part on our ability to obtain and maintain proprietary protection for our product candidates, technology and know-how, to operate without infringing the proprietary rights of others and to prevent others from infringing our proprietary rights. Our policy is to seek to protect our proprietary position by, among other methods, filing U.S. and certain ex-U.S. patent applications related to our proprietary technology, inventions and improvements that we

believe are important to the development of our business, where patent protection is available. We also rely on trade secrets, know-how, continuing technological innovation and in-licensing opportunities to develop and maintain our proprietary position.

As of January 31, 2022, our patent portfolio included a total of 142 active U.S. patents and 67 pending U.S. non-provisional patent applications, including continuations and divisional applications, that are owned, co-owned, or exclusively in-licensed. Our patent portfolio also includes numerous International and ex-U.S. patents and patent applications. The patent portfolio includes patents and patent applications with claims including composition of matter, pharmaceutical formulation and methods of use of our commercial products including ataluren, the active ingredient in the formulated product Translarna, and risdiplam, the active ingredient in the formulated product Evrysdi.

The patent rights relating to ataluren owned by us consist of 42 issued U.S. patents relating to composition of matter, methods of use, formulations, dosing regimens and methods of manufacture and multiple pending U.S. patent applications relating to methods of use, formulation, and dosing regimens. We do not license any material patent rights relating to ataluren to unaffiliated parties. The issued U.S. patents relating to composition of matter are currently scheduled to expire in 2024 and all U.S. patents that issue from U.S. patent applications arising from the composition of matter would also be scheduled to expire in 2024. Issued U.S. patents relating to therapeutic methods of use are currently scheduled to expire in 2026 and 2027, including patent term adjustment. We have patent rights that are the subject of granted patents or pending counterpart patent applications in a number of other jurisdictions, including Canada, certain South American countries, Europe, certain Middle Eastern countries, certain African countries, certain Asian countries and certain Eurasian countries. We own 14 European patents relating to composition of matter, uses, dosing regimens and methods of manufacture of ataluren, as well as multiple pending European patent applications relating to composition of matter, uses and formulations. Granted European patents will expire in 2024 for those patents drawn to composition of matter, in 2026 and 2027 for those patents drawn to dosing regimen, and in 2027 for those patents drawn to the manufacturing process. Except as indicated above, the anticipated expiration dates referred to above are without regard to potential patent term extension, patent term adjustment or other marketing exclusivities that may be available to us.

The patent rights relating to risdiplam owned by us and Roche consist of 5 issued co-owned U.S. patents relating to composition of matter, methods of use, and methods of manufacture and multiple pending U.S. patent applications co-owned or individually owned by us and Roche relating to composition of matter, methods of use, and formulation. We do not license any material patent rights relating to risdiplam to unaffiliated parties. The issued U.S. patents relating to composition of matter are currently scheduled to expire in 2033 and 2035. Our patent rights include granted patents or pending counterpart patent applications in a number of other jurisdictions, including Canada, certain South American countries, Europe, certain Middle Eastern countries, certain African countries, certain Asian countries and certain Eurasian countries. We own 3 European patents relating to composition of matter, and uses of risdiplam, as well as multiple pending European patent applications relating to composition of matter, uses and formulations. The expiration dates of the granted European patents relating to composition of matter are currently scheduled to expire in 2033 and 2035. Except as indicated above, these anticipated expiration dates are without regard to potential patent term extension, patent term adjustment or other marketing exclusivities that may be available to us.

The term of individual patents depends upon the legal term for patents in the countries in which they are obtained. In most countries, including the United States, the patent term is 20 years from the earliest filing date of a non-provisional patent application. In the United States, a patent's term may, in certain cases, be lengthened by patent term adjustment, which compensates a patentee for administrative delays by the U.S. Patent and Trademark Office in examining and granting a patent, or may be shortened if a patent is terminally disclaimed over an earlier filed patent. The term of a U.S. patent that covers a drug, biological product or medical device approved pursuant to a pre-market approval, or PMA, may also be eligible for patent term extension when FDA approval is granted, provided statutory and regulatory requirements are met. The length of the patent term extension is related to the length of time from an Investigational New Drug application's effective date until the approval date while the patent is in force. The Hatch-Waxman Act permits a patent term extension of up to five years beyond the expiration date set for the patent. Patent extension based on Hatch-Waxman Act cannot extend the remaining term of a patent beyond a total of 14 years from the date of product approval, only one patent applicable to each regulatory review period may be granted an extension and only those claims reading on the approved drug may be extended.

Analogous patent term extension provisions are available in Europe and certain other ex-U.S. jurisdictions to extend the term of a patent that covers an approved drug. One means of patent term extension in Europe after EMA approval is based on obtaining a Supplementary Protection Certificate, or SPC. We have applied for SPCs for ataluren in all applicable European countries in which we have a European patent and expect that all will be granted. The maximum patent term extension provided by an SPC is a total of 5 years from the date of patent term expiration. For example, in jurisdictions where an SPC with maximum patent term extension has been granted, the ataluren composition of matter patent would be scheduled to expire in 2029. In the future, if and when our product candidates receive approval by the FDA or other non-European ex-U.S. regulatory authorities, we expect to apply for patent term extensions on issued patents covering those products, depending upon the length of the clinical trials for each drug and other factors.

We have no patents covering Emflaza or the approved use of Emflaza. We rely on non-patent market exclusivity periods under the Orphan Drug Act to commercialize Emflaza in the United States. See "Item 1. Business-Government Regulation" for further information regarding the exclusivity periods that we expect to rely on.

If PTC-AADC is approved in the United States, we expect to rely on the non-patent market exclusivity periods under the Orphan Drug Act and the BPCIA to commercialize PTC-AADC in the United States. See "Item 1. Business-Government Regulation-BPCIA exclusivity" for further information regarding the exclusivity periods that we expect to rely on. We also expect to rely on orphan drug exclusivity in the EEA if PTC-AADC is approved by the EMA, as well as in other countries or regions where such exclusivity is available.

We may rely, in some circumstances, on trade secrets to protect our technology. However, trade secrets can be difficult to protect. We seek to protect our proprietary technology and processes, in part, using confidentiality agreements with our employees, consultants, scientific advisors, contractors and collaborators. We also seek to preserve the integrity and confidentiality of our data and trade secrets by maintaining physical security of our premises and physical and electronic security of our information technology systems. While we have confidence in these individuals, organizations and systems, such agreements or security measures may be breached, and we may not have adequate remedies for any breach. In addition, our trade secrets may otherwise become known or be independently discovered by competitors. To the extent that our employees, former employees, consultants, scientific advisors, contractors or collaborators use intellectual property owned by us or licensed to us by others in their work for us, trade secret disputes may arise. If such disputes arise in the U.S., we may protect our trade secrets and pursue remedies available under federal statute using either the Economic Espionage Act of 1996 and/or the Defend Trade Secrets Act of 2016 and, if necessary, under state law using either the Uniform Trade Secrets Act or other State law available in the applicable venue. If such disputes arise ex-US, we may protect our trade secrets and pursue remedies available under local or international law.

License agreements

We are a party to a number of license agreements under which we license patents, patent applications and other intellectual property from third parties. We enter into these agreements to augment our proprietary intellectual property portfolio. The licensed intellectual property covers some of the compounds that we are researching and developing, some post-transcriptional control targets and some of the scientific processes that we use. These licenses impose various diligence and financial payment obligations on us. We expect to continue to enter into these types of license agreements in the future.

We exclusively in-licensed know-how and materials related to the production and use of PTC-AADC. For a further discussion of the material agreements relating to our in-licensing of PTC-AADC for the treatment of AADC deficiency, see "Item 1. Business-Our Collaborations, License Agreements and Funding Arrangements-National Taiwan University." We also exclusively in-license or jointly own patent applications with claims directed to composition of matter, formulation and methods of use of other gene therapy products candidates currently in development.

Manufacturing

Other than as described below with respect to certain of our gene therapy product candidates, we do not currently own or operate functional manufacturing or distribution facilities for the production of clinical or commercial quantities of our products or product candidates or compounds that we are testing in our preclinical programs. We currently rely, and expect to continue to rely, on third parties for the manufacture, packaging, labeling and distribution of clinical and commercial

supplies of our products or product candidates that we may develop, other than small amounts of compounds that we may synthesize ourselves for preclinical testing.

The active pharmaceutical ingredients in our products and product candidates are provided by third-parties. We currently rely on a single source for the production of some of our raw materials and we obtain our supply of the drug substance for Translarna from two third-party manufacturers.

We engage two separate manufacturers to provide bulk drug product for Translarna. We have a relationship with three manufacturers that are capable of providing fill and finish services for our finished commercial and clinical Translarna product.

We currently obtain our supplies of Translarna and most of our other products and product candidates from our third-party manufacturers pursuant to agreements that include specific supply timelines and volume expectations. If a manufacturer should become unavailable to us for any reason, we would seek to obtain supply from another manufacturer engaged by us for the applicable product or service. In the event that we were unable to procure the applicable supply from a validated manufacturer, we believe that there are a number of potential replacements for each of our outsourced services, however we likely would experience delays in our ability to supply Translarna to patients or in advancing our clinical trials while we identify and qualify replacement suppliers.

We obtain our supply of the drug substance for Emflaza through a third-party manufacturer that is currently the only third-party manufacturer qualified to provide Emflaza drug substance for use in the United States. All of our drug product manufacturing, processing and packaging needs for Emflaza tablet and suspension product are fulfilled pursuant to two different exclusive supply agreements assumed by us in connection with our acquisition of Emflaza. We expect to fulfill all of our requirements for Emflaza tablets as well as secondary packaging of pre-filled Emflaza oral suspension bottles pursuant to one of these agreements, which has an automatic renewal provision subject to the termination rights of each party. We expect to fulfill all of our requirements for Emflaza suspension product pursuant to the other agreement. Through the seventh year anniversary of FDA approval of Emflaza, we are obligated to pay to the manufacturer of the Emflaza suspension product royalty payments, on a quarterly basis, based on a percentage (ranging from low to middle-low double digits) of, or a fixed payment with respect to, our annual net sales of suspension product in the United States, subject to reduction in accordance with the terms of the agreement. The royalty payments for the suspension product are subject to a minimum aggregate annual payment ranging from €0.5 million to €1.5 million per year.

If our drug substance provider or either of our drug product manufacturers was to be unable to provide drug substance or manufacture Emflaza product in sufficient quantities to meet projected demand, future sales could be adversely affected, which in turn could have a detrimental impact on our ability to maintain our marketing authorization in the United States and on our ability to commercialize Emflaza, which in turn would have a material adverse effect on our business, financial results and results of operations. Further, as we presently have no patent rights to protect the approved use of Emflaza, we rely on market exclusivity periods available to us under the Orphan Drug Act to commercialize Emflaza for DMD in the United States. As the holder of orphan exclusivity, we are required to assure the availability of sufficient quantities of Emflaza to meet the needs of patients. Failure to do so could result in loss of the drug's orphan exclusivity in the United States, which would have a material adverse effect on our ability to generate revenue from sales of Emflaza.

Translarna and Emflaza are manufactured in reliable and reproducible synthetic processes. Our raw materials are not scarce and are readily available subject to supply chain disruptions. We currently rely on a single source for the production of some raw materials and switching to an alternative source could, in some instances, take time and could lead to delays in manufacturing. While we have experienced delays in receiving certain raw materials in connection with supply chain disruptions caused by the COVID-19 pandemic, we maintain inventories for such materials such that these delays did not affect or delay our manufacturing in 2021, and no manufacturing delays are currently expected in 2022. The chemistry is amenable to scale up and does not require unusual equipment in the manufacturing process. We expect to continue to develop drug candidates that can be produced cost-effectively at contract manufacturing facilities or internally, in the case of our gene therapy platform.

We currently have contracts with multiple pharmacy and hospital distributors in the EU that distribute Translarna for limited commercial and EAP programs. We have engaged with third party logistic providers, or 3PLs, which distribute Translarna for the majority of our commercial and EAP programs on our behalf.

We utilize third parties for the commercial distribution of Emflaza, including a 3PL to warehouse Emflaza as well as specialty pharmacies to sell and distribute Emflaza to patients. The specialty pharmacies provide us with third-party call center services to provide patient support and financial services, prescription intake and distribution, reimbursement adjudication, and ongoing compliance support.

Pursuant to the Tegsedi-Waylivra Agreement, we have entered into a master supply agreement with Akcea whereby Akcea or its affiliates will manufacture and supply, or cause to be manufactured and supplied, Tegsedi and Waylivra in quantities sufficient to support the commercialization of Tegsedi and Waylivra in the PTC Territory. This is currently the only manufacturing and supply agreement that we have entered into for the drug substance of Tegsedi and Waylivra. If the master supply agreement is terminated and we are unable to find an alternative third party contractor, we may encounter delays in manufacturing Tegsedi and Waylivra.

We have a commercial manufacturing services agreement with MassBiologics of the University of Massachusetts Medical School, or MassBio, to provide sufficient quantities of our PTC-AADC program materials to meet anticipated clinical trial and potential commercial scale demands. In 2021, we began cGMP manufacturing (as defined below) of clinical material at our leased biologics manufacturing and laboratory space located in Hopewell Township, New Jersey, or the Hopewell Facility, for certain of our gene therapy product candidates other than PTC-AADC. We still rely on third-party manufacturers to complete product testing for all of our gene therapy product candidates that we manufacture at the Hopewell Facility as well as to provide sufficient quantities of certain program materials that we have not yet transitioned to the Hopewell Facility. We have personnel with manufacturing and quality experience to oversee our contract manufacturers.

We also expect to use the Hopewell Facility in the production of plasmid DNA and AAV vectors for gene therapy applications for potential external customers.

Manufacturers and suppliers of product candidates are subject to the FDA's current Good Manufacturing Practices, or cGMP, requirements, and other rules and regulations prescribed by ex-U.S. regulatory authorities. We depend on our third-party suppliers and manufacturers for continued compliance with cGMP requirements and applicable ex-U.S. standards.

Commercial Matters

Sales and marketing team

Our product revenue has primarily been attributable to sales of Translarna for the treatment of nmDMD in territories outside of the United States and to sales of Emflaza for treatment of DMD in the United States. We have employees across the globe, with the largest concentrations being in the United States, Latin America and Europe.

In addition, in select territories, we have engaged full time consultants, marketing partners and distribution partners to assist us with our international commercialization efforts for our products. We continue to evaluate new territories to determine in which geographies we might, if approved, choose to commercialize our products ourselves and in which geographies we might choose to collaborate with third parties. We expect that our internal team and partnership network will continue to grow, as needed, to maximize access to patients.

Customers

During 2021, our product revenue was primarily attributable to Translarna for the treatment of nmDMD and to Emflaza for treatment of DMD. Translarna for the treatment of nmDMD was available on a commercial basis or via reimbursed EAP programs in multiple territories outside of the United States. In some territories, orders for Translarna are placed directly with us and in other territories we have engaged with third-party distributors. As a result, orders for Translarna are generally received from hospital and retail pharmacies and, in some cases, one of our third-party partner distributors.

Our third-party distributors act as intermediaries between us and end-users and do not typically stock significant quantities of Translarna. The ultimate payor for Translarna is typically a government authority or institution or a third-party health insurer. The payment terms are generally 30 to 90 days after receipt of products.

Emflaza for treatment of DMD is available on a commercial basis throughout the United States. We utilize six specialty pharmacies to sell and distribute Emflaza to patients. The specialty pharmacies receive prescription orders for Emflaza directly from physicians and ship Emflaza directly to the end-user upon fulfillment of the order. As such, there is very little inventory of Emflaza stocked. The ultimate payor for Emflaza is typically a state health insurance program or a third-party health insurer. The payment terms are generally 30 to 90 days after receipt of products.

During 2021, two of our distributors each accounted for over 10% of our net product sales. Financial information about our net product revenues and other revenues generated in the principal geographic regions in which we operate and our long-lived assets is set forth in our financial statements and in Note 16, "Geographic Information" to our consolidated financial statements included in this Annual Report on Form 10-K.

Translarna and Emflaza can generally only be returned if agreed upon in writing by us and the product is not opened nor in receipt by the final user, except in the case of quality issues associated with the product. Product is generally shipped when a specific patient is approved by the applicable government or insurer and an individual prescription has been written. The right of return is eliminated as a matter of course when the product is dispensed to patients. Other than in connection with our transition to a new third party distributor, we have never had a request for a return of a material amount of product for either Translarna or Emflaza.

In some countries, including those in Latin America, orders for named patient sales may be for multiple months of therapy, which can lead to an unevenness in orders which could result in significant fluctuations in quarterly net product sales. For example, as a result of the COVID-19 pandemic, the Brazilian Ministry of Health is continuing to experience significant delays processing centralized group purchase orders. Almost all of our Brazilian product revenue for Translarna is attributable to such purchase orders. These centralized group purchase order delays have caused, and may continue to cause, fluctuations in our ability to generate revenue in Brazil. Similarly, Translarna orders placed through a distributor for the Ministry of Health of the Russian Federation are also intended to cover multiple months of therapy. Any fluctuations in quarterly net product sales in Russia resulting from these centralized group purchase orders may also be exacerbated by any delays.

Market Access Considerations

Translarna for the treatment of nmDMD is currently available on a commercial basis in multiple countries outside of the United States. We consider our products to be commercially available when we are permitted to market treatment to patients.

Translarna for the treatment of nmDMD is also currently available through EAP programs in select countries where funded named patient or cohort programs exist, both within the EEA and in other territories. These programs generally reference the EMA's determinations with respect to our marketing authorization in the EEA. As of today, Translarna is available under EAP or similar styled programs in various countries outside of the United States. Generally, EAP programs allow for access to Translarna pursuant to a named patient program, under which a physician requests access to Translarna on behalf of the specific, or "named" patient or pursuant to a cohort program, which allows for a broader temporary authorization for use for nmDMD meeting the inclusion criteria. Our EAP programs are named patient or similar styled programs in all territories other than France, which is a cohort program.

Our ability to make Translarna available via commercial or EAP programs is largely dependent upon our ability to maintain our marketing authorization in the EEA for Translarna for the treatment of nmDMD in ambulatory patients aged two years and older. The marketing authorization is subject to annual review and renewal by the European Commission following reassessment by the EMA as well as the specific obligation to conduct and submit the results of Study 041. Additionally, the marketing authorizations of Translarna in Brazil and Russia are subject to renewal every five years. See "Item 1. Business-Global commercial footprint-Global DMD franchise" and "Risk Factors-Risks Related to Regulatory Approval

of our Product and our Product Candidates" for further information regarding the marketing authorization in the EEA and related risks.

Our future revenues from our products and any other product candidates we may develop, depends largely on our ability to obtain and maintain reimbursement from governments and third-party insurers. Each country in the EEA has its own pricing and reimbursement regulations and many countries in the EEA have other regulations related to the marketing and sale of pharmaceutical products in the applicable country. The pricing and reimbursement process varies from country to country and can take a substantial amount of time from initiation to completion. As a result, our commercial launch of Translarna in the EEA has been and is expected to continue to be on a country-by-country basis and we generally will not be able to commence commercial sales of Translarna for the treatment of nmDMD pursuant to our marketing authorization in the EEA in any particular member state of the EEA until we conclude the applicable pricing and reimbursement negotiations and comply with any licensing, employment or related regulatory requirements in that country.

We have submitted pricing and reimbursement dossiers with respect to Translarna for the treatment of nmDMD in key EEA countries and have received both pricing and reimbursement approval on terms that are acceptable to us in a number of countries. The price that is approved by local governmental authorities pursuant to commercial pricing and reimbursement processes may be lower than the price for purchases of product in that country pursuant to a reimbursed early access program.

In some instances, reimbursement may be subject to challenge, reduction or denial by the government and other payers. For example, in France, EAP programs and commercial sales of a product can begin while pricing and reimbursement rates are under discussion with the applicable government health programs. In the event that the negotiated price of the product is lower than the amount reimbursed for sales made prior to the conclusion of price negotiations, we may become obligated to repay such excess amount to the applicable government health program. Such retroactive reimbursement would be made following the conclusion of price negotiations with the applicable government health authority.

For Emflaza, we are engaged in pricing, coverage and reimbursement discussions with third-party payors, such as state and federal governments, including Medicare and Medicaid, managed care providers, private commercial insurance plans and pharmacy benefit management plans. Decisions regarding the extent of coverage and the amount of reimbursement to be provided for Emflaza are made on a plan-by-plan, and in some cases, on a patient-by-patient basis. Coverage and reimbursement decisions by third-party payors, including the processing and adjudication of prescriptions, may vary from weeks to several months. Certain third-party payors routinely impose additional requirements before approving reimbursement of a prescription, including prior authorization and the requirement to try another therapy first. The specialty pharmacies we utilize provide patient services programs to support product access and, when eligible, out-of-pocket assistance.

Tegsedi for the treatment of hATTR amyloidosis and Waylivra for the treatment of FCS are currently available on a commercial basis in multiple countries outside of the United States and we have the right to commercialize these products in the PTC Territory. We have received marketing authorization from ANVISA for Tegsedi for the treatment of stage 1 or stage 2 polyneuropathy in adult patients with hATTR amyloidosis in Brazil and Waylivra for the treatment of FCS in Brazil. We have initiated our commercial launches of Tegsedi for the treatment of hATTR amyloidosis in Brazil and Waylivra for the treatment of FCS in Brazil. The marketing authorizations of Tegsedi and Waylivra in Brazil are subject to renewal every five years. We have also made both Tegsedi and Waylivra available in certain countries within the PTC Territory through EAP Programs. Our ability to make Tegsedi and Waylivra available via EAP programs within the PTC Territory is largely dependent upon the maintenance of the marketing authorizations in the EU, which in the case of Waylivra, is subject to certain conditions.

We record revenue net of estimated third party discounts and rebates. Allowances are recorded as a reduction of revenue at the time revenues from product sales are recognized. These allowances are adjusted to reflect known changes in factors and may impact such allowances in the quarter those changes are known.

For important information regarding market access and pricing and reimbursement considerations see "Item 1. Business-Pharmaceutical Pricing and Reimbursement" and "Item 1A. Risk Factors-Risks Related to the Development and

Commercialization of our Product and our Product Candidates" and "-Risks Related to Regulatory Approval of our Product and our Product Candidates".

Competition

The biotechnology and pharmaceutical industries are characterized by rapidly advancing technologies, intense competition and a strong emphasis on proprietary products. While we believe that our technologies, knowledge, experience and scientific resources provide us with competitive advantages, we face potential competition from many different sources, including commercial pharmaceutical and biotechnology enterprises, academic institutions, government agencies and private and public research institutions. Any product candidates that we successfully develop and commercialize will compete with existing therapies and new therapies that may become available in the future. In addition, other gene therapy companies may in the future decide to utilize existing technologies to address unmet needs that could potentially compete with our product candidates.

Many of our competitors may have significantly greater financial resources and expertise in research and development, manufacturing, preclinical testing, conducting clinical trials, obtaining regulatory approvals and marketing approved products than we do. These competitors also compete with us in recruiting and retaining qualified scientific and management personnel, as well as in acquiring technologies complementary to, or necessary for, our programs. Smaller or early stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies.

Our commercial opportunity could be reduced or eliminated if our competitors develop and commercialize products that are safer, more effective, have fewer side effects, are more convenient or are less expensive than any products that we may develop. In addition, our ability to compete may be affected because in some cases insurers or other third-party payors seek to encourage the use of generic products. This may have the effect of making branded products less attractive, from a cost perspective, to buyers.

The key competitive factors affecting the success of our products and product candidates are likely to be its efficacy, safety, convenience, price and the availability of coverage and reimbursement from government and other third-party payors.

The competition for our products and product candidates includes the following:

- ***Translarna for nmDMD.*** There is currently no marketed therapy, other than Translarna in the EEA, which has received approval for the treatment of the underlying cause of nmDMD. Sarepta Therapeutics, or Sarepta, has received approval in the United States for two treatments (Exondys 51 (eteplirsen) and Vyondys 53 (golodirsen)) addressing the underlying cause of disease for different mutations in the DMD gene. Additionally, the FDA granted accelerated approval to Viltepso (viltolarsen) from NS Pharma for the treatment of DMD in patients with exon 53 skipping and Sarepta (Casimersen (SRP 4045) for the treatment of DMD in patients with exon 45 skipping. Viltepso (viltolarsen) from NS Pharma is also approved in Japan. Other biopharmaceutical companies are developing treatments addressing the underlying cause of disease for different mutations in the DMD gene, including, Daiichi Sankyo (DS-5141)), Nippon Shinyaku (Viltolarsen (NS-065/NCNP-01) and NS-089/NCNP-02)), and Astellas (AT-702). Other pharmaceutical companies are developing micro dystrophin gene therapies for patients with DMD regardless of genotype, including Sarepta (SRP-9001), Pfizer (PF-06939926) and Solid Biosciences (SGT-001).
- ***Emflaza for DMD.*** The FDA has not approved a corticosteroid specifically for DMD in the United States other than Emflaza. However, prednisone/prednisolone, which is not approved for DMD in the United States, is generically available and has been prescribed off label for DMD patients. ReveraGen BioPharma and Santhera are developing a glucocorticoid antagonist (vamorolone) for DMD patients with anticipated NDA filing in 2022.
- ***Evrysdi.*** Evrysdi also faces competition. For example, in December 2016, the FDA approved Spinraza (nusinersen), a drug developed by Ionis and marketed by Biogen, to treat SMA. Zolgensma (onasemnogene abeparvovec), a gene therapy drug developed by AveXis, Inc., (acquired by Novartis in 2018) is approved in the United States and Japan for the treatment of SMA in patients under 2 years of age and in Europe for babies and young children who weigh up to 21 kilograms. Other companies are also pursuing product candidates for the

treatment of SMA, including Kowa (sodium valproate), Catalyst Pharmaceuticals (amifampridine), Scholar Rock (SRK-015), Roche Pharmaceuticals (RO7204239) and Cytokinetics (reldesemtiv).

- ***Waylivra.*** Waylivra faces competition from drugs like Myalept (metreleptin). Myalept, produced by Novelion Therapeutics, Inc., is currently approved for use in generalized lipodystrophy patients. Additionally, Ionis is developing AKCEA-APOCIII-LRx for the treatment of FCS.
- ***Tegsedi.*** Tegsedi faces competition from drugs like Onpattro (patisiran) which was launched by Alnylam in the United States in 2018 and received approval in Brazil for the treatment of hATTR amyloidosis in 2020. Vyndaqel (tafamids meglumine) and Vyndamax (tafamidis) are commercialized in the United States, EU and some countries in Latin America by Pfizer. Other companies are also pursuing product candidates for the treatment of ATTR Amyloidosis with polyneuropathy including Alnylam (vutrisiran), BridgeBio Pharma (AG 10), Proclara Biosciences (NPT 189), Prothena (PRX 004) and SOM Biotech (tolcapone).
- ***PTC-AADC.*** Currently, no treatment options are available for the underlying cause of AADC deficiency, and care is limited to palliative options with significant burden on caregivers. Additionally, we are not aware of any late-stage development product candidates for AADC deficiency.
- ***PTC518 for Huntington's disease.*** There are currently no drugs or disease-modifying therapies approved to delay the onset or slow the progression of Huntington disease. However, Novartis (branaplam), uniQure (AMT-130), Roche and Ionis (tominersen) and Wave Life Sciences (WVE-003) are all developing product candidates for treatment of Huntington disease.
- ***Vatiquinone for Friedreich ataxia.*** While there are currently no disease modifying treatment options available for Friedreich ataxia, omaveloxolone, which is being developed by Reata Pharmaceuticals and RT-001, which is being developed by Retrotope, are each late stage product candidates being investigated for the treatment of Friedreich ataxia.
- ***Vatiquinone for mitochondrial disease associated seizures.*** There are no disease modifying drugs approved for the treatment of mitochondrial disease associated seizures and we are not aware of any late-stage development product candidates for mitochondrial disease associated seizures.
- ***PTC857 for ALS.*** Current standard of care for ALS is Rilutek (riluzole), currently available as a generic and other formulations, and Radicava (edaravone). Amylyx Pharmaceuticals (AMX-0035) has submitted an NDA to the FDA and an MAA to EMA. There are multiple other late stage product candidates being developed for the treatment of ALS including Ionis (Jacifusen), Clene Nanomedicine (CNM-Au8), MediciNova (Ibudilast), AB Science (AB-1010 mastinib mesylate), and Prilenia Therapeutics (Pridopidine).
- ***PTC923 for PKU.*** If approved, PTC923 could face competition from Kuvan (sapropterin dihydrochloride), including generic versions, and Palynziq (pegvaliase-pqpz), each of which is approved for the treatment of PKU. Furthermore, Homology (HMI-102) and BioMarin (BMN 307) each are developing gene therapy product candidates for the treatment of PKU.
- ***Unesbulin for LMS.*** First line treatment for LMS is surgery where appropriate and then chemotherapy options including doxorubicin, gemcitabine, dacarbazine and docetaxel for unresectable metastatic disease. For second line treatment, two drugs are approved for soft tissue sarcoma including LMS and these are Yondelis (trabectedin) and Votrient (pazopanib). Most LMS patients require multiple lines of therapy.
- ***Unesbulin for DIPG.*** There is no approved treatment for DIPG and very little improvement have been observed over the past 40 years. The current standard of care is radiation therapy which can shrink the tumor, though response is transient.
- ***Emvododstat for COVID-19.*** If approved, emvododstat could face significant competition as many other companies and governmental organizations have expended resources to find a treatment for COVID-19. The FDA has approved the use of the Pfizer and Moderna COVID-19 vaccines and authorized the use of the Johnson & Johnson COVID-19 vaccine in the United States. The FDA has approved Gilead's antiviral drug Velkury (remdesivir) for the treatment of COVID-19. The FDA has also granted emergency use authorizations to Merck's molnupiravir, Pfizer's Paxlovid (nirmatrelvir tablets and ritonavir tablets, co-packaged for oral use) and monoclonal antibodies, among other products, for the treatment and prevention of COVID-19.

Government Regulation

Government authorities in the United States, at the federal, state and local level, and in other countries extensively regulate, among other things, the research, development, testing, quality control, approval, manufacturing, labeling, post-approval monitoring and reporting, recordkeeping, packaging, promotion, storage, advertising, distribution, marketing and sales and

export and import of biopharmaceutical products such as those we are developing. In addition, sponsors of biopharmaceutical products and drug products participating in Medicaid and Medicare are required to comply with mandatory price reporting, discount, and rebate requirements. The process of obtaining regulatory approvals and the subsequent compliance with appropriate federal, state, local and ex-U.S. statutes and regulations require the expenditure of substantial time and financial resources. See "Item 1A. Risk Factors-Risks Related to Regulatory Approval of our Product and our Product Candidates" for important information regarding some of the risks to our business arising as a result of government regulation.

U.S. government regulation

In the United States, the FDA regulates drugs and biologic products, including gene therapy products, under the Federal Food, Drug, and Cosmetic Act, or the FDCA, the Public Health Service Act, or the PHSA, and regulations and guidance implementing these laws. The FDCA, PHSA and their corresponding regulations govern, among other things, the testing, manufacturing, safety, efficacy, labeling, packaging, storage, record keeping, distribution, reporting, advertising and other promotional practices involving drugs and biologic products. Applications to the FDA are required before conducting human clinical testing of drugs or biologic products. Failure to comply with the applicable FDA requirements at any time pre- or post-approval may result in a delay of approval or administrative or judicial sanctions. These sanctions could include the FDA's imposition of a clinical hold on trials, refusal to approve pending applications or supplements, withdrawal of an approval, issuance of warning or untitled letters, product recalls, product seizures, operating restrictions such as the total or partial suspension of production or distribution, injunctions, fines, civil penalties or criminal prosecution, among other actions further described in this filing. Any agency or judicial enforcement action could have a material adverse effect on us.

Regulatory requirements governing our business are also evolving. For example, the FDA has issued a growing body of guidance documents on CMC, clinical investigations and other areas of gene therapy development, all of which are intended to facilitate the industry's development of gene therapy products. Moreover, in light of the COVID-19 pandemic, the FDA has issued a number of guidance documents to assist companies navigating product development and manufacturing concerns raised by COVID-19 and with respect to products intended for COVID-19.

The new drug and biologic approval process

In the United States, the information that must be submitted to the FDA in order to obtain approval to market a new drug or biologic product varies depending upon whether the drug is a new product whose safety and efficacy have not previously been demonstrated in humans or a drug whose active ingredients and certain other properties are the same as those of a previously approved drug. A New Drug Application, or NDA, is the vehicle through which the FDA approves a new pharmaceutical drug product for sale and marketing in the United States. A BLA is the vehicle through which the FDA approves a new biologic product for sale and marketing in the United States.

To market a new drug or biologic product in the United States, a sponsor generally must undertake the following:

- completion of preclinical laboratory tests, animal studies and formulation studies under the FDA's Good Laboratory Practice, or GLP, regulations and other applicable laws or regulations;
- submission to the FDA of an investigational new drug application, or IND, for clinical testing, which must become effective before clinical trials may begin at United States clinical trial sites;
- approval by an independent Institutional Review Board, or IRB, and in the case of certain gene therapy studies, an Institutional Biosafety Committee, or IBC, prior to initiation and subject to continuing review;
- completion of adequate and well-controlled clinical trials to establish safety and efficacy, in the case of a drug product candidate, or safety purity, and potency, in the case of a biologic product candidate for its intended use, performed in accordance with Good Clinical Practices, or GCP, and the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, or ICH, E6 GCP guidelines. Certain gene therapy research must also be conducted in accordance with the NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules, or NIH Guidelines;
- development of manufacturing processes to ensure the product candidate's identity, strength, quality, purity, and potency;

- submission and FDA acceptance of an NDA, in the case of a drug product candidate, or BLA in the case of a biologic product candidate, and satisfactory completion of an FDA Advisory Committee meeting, if applicable;
- satisfactory completion of an FDA inspection of the manufacturing facility or facilities at which the product is produced to assess compliance with cGMPs, which require that the facilities, methods and controls are adequate to preserve the product's identity, strength, quality and purity, as well as satisfactory completion of an FDA inspection of selected clinical sites and selected clinical investigators to determine GCP compliance; and
- FDA review and approval of the NDA or BLA to permit commercial marketing for particular indications for use.

Preclinical Studies and IND Submission

Preclinical tests include laboratory evaluations of product chemistry, pharmacology, stability, toxicity and product formulation, as well as animal studies to assess potential safety and efficacy. In order to begin clinical testing, a sponsor must submit an IND to the FDA, which includes, among other things, the results of the preclinical tests, manufacturing information, analytical data, proposed clinical protocols, and any available clinical data or literature on the product candidate. Some preclinical testing may continue after the IND is submitted. The IND must become effective before human clinical trials may begin. An IND will automatically become effective 30 days after receipt by the FDA, unless before that time the FDA raises concerns or questions about issues such as the conduct of the trials as outlined in the IND. In that case, the IND sponsor and the FDA must resolve any outstanding FDA concerns or questions before clinical trials can proceed. In other words, submission of an IND may not result in the FDA allowing clinical trials to commence. Clinical holds also may be imposed by the FDA at any time before or during trials due to safety concerns or non-compliance. As a result, submission of an IND may not result in FDA authorization to commence or continue a clinical trial.

Clinical Trials

Clinical trials involve the administration of an investigational product to human subjects under the supervision of qualified investigators. Clinical trials are conducted in accordance with protocols detailing, among other things, the objectives of the study, the parameters to be used in monitoring safety, the effectiveness criteria to be evaluated, and a statistical analysis plan. A protocol for each clinical trial and subsequent protocol amendments must be filed with the FDA as part of the IND. In accordance with GCP requirements, all research subjects or their legally authorized representatives must provide their informed consent in writing prior to their participation in a clinical trial. Each clinical trial must be reviewed and approved by an IRB and is subject to ongoing IRB monitoring. The IRB must approve the protocol, protocol amendments, the informed consent form, and communications to study subjects before a study commences at the site. An IRB considers among other things, whether the risks to individuals participating in the trials are minimized and are reasonable in relation to anticipated benefits, and whether the planned human subject protections are adequate. The IRB must continue to oversee the clinical trial while it is being conducted. In the case of certain gene therapy studies, an IBC at the local level may also review and maintain oversight over the particular study, in addition to the IRB. If the product candidate is being investigated for multiple intended indications, separate INDs may also be required. Progress reports detailing the results of the clinical trials must be submitted at least annually to FDA and the IRB and more frequently if serious adverse events or other significant safety information is found. Certain reports may also be required to be submitted to the IBC.

Additionally, some clinical trials are overseen by an independent group of qualified experts organized by the clinical trial sponsor, known as a data safety monitoring board or committee. This group regularly reviews accumulated data and advises the study sponsor regarding the continuing safety of the trial. This group may also review interim data to assess the continuing validity and scientific merit of the clinical trial. The data safety monitoring board receives special access to unblinded data during the clinical trial and may advise the sponsor to halt the clinical trial if it determined there is an unacceptable safety risk for subjects or on other grounds, such as no demonstration of efficacy.

Information about certain clinical trials must be submitted within specific timeframes to the NIH to be publicly posted on the Clinicaltrials.gov website. Sponsors or distributors of investigational products for the diagnosis, monitoring, or treatment of one or more serious disease or conditions must also have a publicly available policy on evaluating and responding to requests for expanded access. Investigators must also provide certain information to clinical trial sponsors to allow the sponsors to make certain financial disclosures to the FDA.

The manufacture of investigational drugs and biologics for the conduct of human clinical trials is subject to cGMP requirements. Investigational drugs and biologics and active ingredients and therapeutic substances imported into the United States are also subject to regulation by the FDA. Further, the export of investigational products outside the United States is subject to regulatory requirements of the receiving country as well as U.S. export requirements under the FDCA.

In general, for the purposes of NDA and BLA approval, human clinical trials typically are conducted in three sequential phases, but the phases may overlap or be combined. Phase 1 clinical trials may be conducted in patients or healthy volunteers to evaluate the product's safety, dosage tolerance, structure-activity relationships, mechanism of action, absorption, metabolism distribution, excretion, and pharmacokinetics and, if possible, seek to gain an early indication of its effectiveness. Phase 2 clinical trials usually involve controlled trials in a larger but still relatively small number of subjects from the relevant patient population to evaluate dosage tolerance and appropriate dosage; identify possible short-term adverse effects and safety risks; and provide a preliminary evaluation of the efficacy of the drug or biologic product for specific indications.

Phase 2 clinical trials are sometimes denoted by companies as Phase 2a or Phase 2b clinical trials. Phase 2a clinical trials typically are clinical trials of a drug or biologic product candidate in a smaller patient population and are designed to provide earlier information on safety and efficacy. Phase 2b clinical trials typically involve larger numbers of patients or longer durations of therapy and may involve comparison with placebo, standard treatments or other active comparators.

Phase 3 clinical trials usually further evaluate clinical efficacy and test further for safety in an expanded patient population at geographically dispersed clinical trial sites, to generate enough data to provide statistically significant evidence of clinical efficacy and safety of the product candidate for approval. Phase 3 clinical trials usually involve comparison with placebo, standard treatments or other active comparators. These trials are well-controlled and are intended to establish the overall risk- benefit profile of the product or product candidate and provide an adequate basis for physician labeling. Phase 3 clinical trials are usually larger, more time consuming, more complex and more costly than Phase 1 and Phase 2 clinical trials.

Additional kinds of data may also help support a BLA or NDA, such as patient experience data and real world evidence. Real world evidence may also be used to assist in clinical trial design or support an NDA for already approved products. For genetically targeted populations and variant protein targeted products intended to address an unmet medical need in one or more patient subgroups with a serious or life threatening rare disease or condition, the FDA may allow a sponsor to rely upon data and information previously developed by the sponsor or for which the sponsor has a right of reference, that was submitted previously to support an approved application for a product that incorporates or utilizes the same or similar genetically targeted technology or a product that is the same or utilizes the same variant protein targeted drug as the product that is the subject of the application.

Clinical trials may not be completed successfully within any specified period, if at all. The FDA, the sponsor, or a data safety monitoring board may suspend or terminate clinical trials at any time on various grounds, including a finding that the subjects are or would be exposed to an unreasonable and significant risk of illness or injury. Similarly, an IRB can suspend or terminate approval of a clinical trial if the trial is not being conducted in accordance with the IRB's requirements or if the research has been associated with unexpected serious harm to patients. IBCs can also require that research activities be ceased if applicable requirements are not being met. The FDA typically requires that an NDA or BLA include data from two adequate and well-controlled clinical trials, but, in certain circumstances, approval may be based upon a single adequate and well-controlled clinical trial plus confirmatory evidence or a single large multicenter trial without confirmatory evidence. In some cases, the FDA may condition approval of an NDA or BLA on the applicant's agreement to conduct additional clinical trials to further assess the product's safety and effectiveness after NDA or BLA approval. Such post-approval trials are typically referred to as Phase 4 studies. The results of Phase 4 studies can confirm or refute the effectiveness of a product candidate, and can provide important safety information.

Concurrent with clinical trials, companies usually complete additional preclinical studies and must also develop additional information about the physical characteristics of the drug or biologic product candidate as well as finalize a process for manufacturing the product candidate in commercial quantities in accordance with cGMP requirements. The manufacturing process must be capable of consistently producing quality batches of the product candidate and, among other requirements, the sponsor must develop methods for testing the identity, strength, quality, potency and purity of the final biologic

product. Additionally, appropriate packaging must be selected and tested and adequate stability studies must be conducted to demonstrate that the product candidate does not undergo unacceptable deterioration over its shelf life.

Additional FDA Expedited Review and Approval Programs

The FDA has various programs that are intended to expedite or simplify the process for the development and FDA review of certain products that are intended for the treatment of serious or life threatening diseases or conditions, and demonstrate the potential to address unmet medical needs or present a significant improvement over existing therapy. The purpose of these programs is to provide important new therapeutics to patients earlier than under standard FDA review procedures.

To be eligible for a Fast Track designation, the FDA must determine, based on the request of a sponsor, that a product candidate is intended to treat a serious or life threatening disease or condition and demonstrates the potential to address an unmet medical need. If Fast Track designation is obtained, sponsors may be eligible for more frequent development meetings and correspondence with the FDA. In addition, the FDA may initiate review of sections of an application before the application is complete. This ‘‘rolling review’’ is available if the applicant provides and the FDA approves a schedule for the remaining information. Applicable user fees must also be paid before the FDA will commence its review. In some cases, a Fast Track product may be eligible for accelerated approval or priority review.

The FDA may give a priority review designation to product candidates that are intended to treat serious conditions and, if approved, would provide significant improvements in the safety or effectiveness of the treatment, diagnosis, or prevention of the serious condition. A priority review means that the goal for the FDA is to review an application within six months, rather than the standard review of ten months under current Prescription Drug User Fee Act, or PDUFA, guidelines.

The FDA’s accelerated approval process allows for potentially faster development and approval of certain drugs or biologic products intended to treat serious or life-threatening illnesses that provide meaningful therapeutic benefit to patients over existing treatments. Under the accelerated approval process, the adequate and well-controlled clinical trials conducted with the drug or biologics product establish that the drug or biologics product has an effect on a “surrogate” endpoint that is reasonably likely to predict clinical benefit or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity, that is reasonably likely to predict an effect on irreversible morbidity or mortality, taking into account the severity, rarity, or prevalence of the condition and availability or lack of alternative treatments. Drugs or biologics products approved through the accelerated approval process are subject to certain post-approval requirements, including that the applicant complete Phase 4 clinical trials to demonstrate the drug’s or biological product’s clinical benefit. If the trials fail to verify the clinical benefit of the drug or biologics product, the FDA may withdraw approval of the application through a streamlined process. Promotional materials for a drug or biologic approved under the accelerated approval pathway are subject to FDA prior review.

Under the provisions of the Food and Drug Administration Safety and Innovation Act, or FDASIA, enacted in 2012, a sponsor can request designation of a product candidate as a ‘‘breakthrough therapy.’’ A breakthrough therapy is defined as a product that is intended, alone or in combination with one or more other products, to treat a serious or life-threatening disease or condition, and preliminary clinical evidence indicates that the product may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. Products designated as breakthrough therapies are eligible for intensive guidance on an efficient development program beginning as early as Phase 1 trials, a commitment from the FDA to involve senior managers and experienced review staff in a proactive collaborative and cross-disciplinary review, rolling review, and the facilitation of cross-disciplinary review.

Another expedited pathway is the Regenerative Medicine Advanced Therapy, or RMAT, designation. Qualifying products must be a cell therapy, therapeutic tissue engineering product, human cell and tissue product, or a combination of such products, and not a product solely regulated as a human cell and tissue product. The product must be intended to treat, modify, reverse, or cure a serious or life-threatening disease or condition, and preliminary clinical evidence must indicate that the product has the potential to address an unmet need for such disease or condition. Advantages of the RMAT designation include all the benefits of the Fast Track and breakthrough therapy designation programs, including early interactions with the FDA. These early interactions may be used to discuss potential surrogate or intermediate endpoints to support accelerated approval.

Companion Diagnostics and Other Combination Products

A drug or biologic product may be regulated as combination product if it is intended for use in conjunction with a medical device, such as a drug delivery device or *in vitro* diagnostic device, as further discussed below. In such cases, the use of the two products together (i.e., the drug/biological product and the device) must be shown to be safe and effective for the proposed intended use and the labeling of the two products must reflect their combined use. In some cases, the device component may require a separate premarket submission; for example, when the device component is intended for use with multiple drug products. Sponsors of clinical studies using investigational devices are required to comply with FDA's investigational device exemption regulations. Once approved or cleared, the sponsor of the device component submission (or the combination product submission, if both components are covered by one premarket submission) would need to comply with FDA's post-market device requirements, including establishment registration, device listing, device labeling, unique device identifier, quality system regulation, medical device reporting, and reporting of corrections and removals requirements.

If the safety or effectiveness of a drug or biologic product candidate for its proposed indication is dependent on the measurement or detection of specified biomarkers, the FDA may require the contemporaneous approval or clearance of an *in vitro* companion diagnostic device that measures such biomarkers, and require the labeling of both the drug/biological product and the companion diagnostic to including instructions for use of the two products together. The FDA has explained in guidance that *in vitro* diagnostic companion diagnostic devices may be used for a number of purposes, including identifying appropriate subpopulations for treatment. The type of premarket submission required for a companion diagnostic device will depend on the FDA classification of the device. A premarket approval, or PMA, application is required for high risk devices classified as Class III; a 510(k) premarket notification is required for moderate risk devices classified as Class II; and a *de novo* request may be used for novel devices not previously classified by FDA that are low or moderate risk. The guidance states that the FDA generally will not approve a drug or biologic that is dependent upon the use of a companion diagnostic device if no such device is contemporaneously FDA-approved or -cleared for the relevant indication. According to the guidance, however, the FDA may approve such a drug/biologic product without an approved/cleared companion diagnostic when the drug/ biologic "is intended to treat a serious or life-threatening condition for which no satisfactory alternative treatment exists" and the FDA determines that the benefits from the use of the drug/biologic "are so pronounced as to outweigh the risks from the lack of an" approved/cleared companion diagnostic. Under these circumstances, the FDA expects that a companion diagnostic would be subsequently approved/cleared, and that the drug/biologic labeling would be revised "to stipulate the use of the" companion diagnostic device. The FDA would also consider whether additional protections, such as risk evaluation and mitigation strategies, or REMS, or post-approval requirements, are necessary.

In a separate guidance, specific to DMD and related dystrophinopathies, the FDA has stated that a sponsor should contemporaneously develop a companion diagnostic device in situations where (1) the safety or efficacy of the drug or biologic product "may be related to the patient's specific dystrophin mutation or to another type of finding related to a biomarker," and (2) a suitable companion diagnostic device is not currently available. However, given "the serious and life-threatening nature of dystrophinopathies and the lack of satisfactory alternative treatments that currently exist," the guidance further states that the FDA may approve a drug/biologic "even if a companion diagnostic device is not yet approved or cleared, if the benefits are so pronounced as to outweigh the risks from the lack of an approved or cleared in vitro companion diagnostic device." During the review, the "FDA will determine the need for clearance or approval of the device." The FDA guidance documents represent the FDA's current thinking on a topic but do not establish legally enforceable responsibilities.

FDA Approval Process

Assuming successful completion of the required clinical testing, the results of the preclinical studies and of the clinical trials, together with other detailed information, including proposed labeling and information on the chemistry, manufacture and composition of the product, are submitted to the FDA in the form of an NDA or BLA requesting approval to market the product for one or more indications. In most cases, the NDA or BLA must be accompanied by a substantial user fee, though a waiver of such fees may be obtained under certain limited circumstances. Product candidates that are designated as orphan products are not subject to application user fees unless the application includes an indication other than the orphan indication. The user fees must be paid at the time of the first submission of the application, even if the application

is being submitted, by section, on a rolling basis. The FDA has 60 days from its receipt of an NDA or BLA to determine whether the application will be accepted for filing based on the FDA's threshold determination that it is sufficiently complete to permit a substantive review.

If the FDA determines that the NDA or BLA is incomplete, the FDA may refuse to file the application. If the FDA refuses to file an NDA or BLA, the applicant may refile the application with information addressing the FDA identified deficiencies, which refiling would be subject to FDA review before it is accepted for filing, or the applicant may request an informal conference with the FDA about whether the application should be filed. After the conference, the applicant may request that the application be filed over protest. When an application is filed over protest, the FDA is required to review the application as filed. Generally, the FDA does not favor the file over protest procedure. There are also certain consequences of filing an application over protest. For example, such an application would not be eligible for certain FDA communications over the course of the review cycle.

In addition, an applicant that receives an RTF can, in some circumstances, appeal the decision using the FDA's dispute resolution procedures. After the NDA or BLA submission is accepted for filing, the FDA reviews the NDA or BLA to determine, among other things, whether a product meets FDA's approval standard and whether the product is being manufactured in accordance with cGMP to assure and preserve the product's identity, strength, quality and purity. Under the goals and policies agreed to by the FDA under the PDUFA, the FDA has set the review goal of completing its review of 90% of all standard applications for new molecular entities and original BLAs within ten months of the 60-day filing date. Under the FDA's priority review program, however, the FDA set a review goal of completing its review of 90% of all applications for products that, if approved, would present significant improvements in the safety or effectiveness of the treatment, diagnosis, or prevention of serious conditions, within 6 months of the 60-day filing date. The FDA does not always meet its PDUFA goal dates for review of NDAs or BLAs. The review process and the PDUFA goal date may be extended by additional three-month review periods whenever the FDA requests or the NDA or BLA sponsor otherwise provides additional information or clarification regarding information already provided in the submission at any time during the review cycle. Additionally, this review period may change as the PDUFA statute must be reauthorized by Congress by September 2022. If, however, an application is filed with the FDA over protest, the FDA generally will not review amendments to the application during any review cycle and will not issue information requests to the applicant during the agency's review.

Under the Pediatric Research Equity Act of 2003, or PREA, NDAs or BLAs or supplements to NDAs or BLAs for a new active ingredient, dosage form, dosage regimen, or route of administration, unless subject to the below requirement for molecularly targeted cancer products, must contain data to assess the safety and effectiveness of the product for the claimed indications in all relevant pediatric subpopulations and to support dosing and administration for each pediatric subpopulation for which the product is safe and effective. The FDA may, on its own initiative or at the request of the applicant, grant deferrals for submission of data or full or partial waivers. PREA does not generally apply to products for an indication for which orphan designation has been granted. However, PREA compliance may be required if approval is sought for other indications for which the product has not received orphan designation.

The FDA Reauthorization Act of 2017 introduced a provision regarding required pediatric studies. Under this statute, for product candidates intended for the treatment of adult cancer which are directed at molecular targets that the FDA determines to be substantially relevant to the growth or progression of pediatric cancer, original application sponsors must submit, with the marketing application, reports from molecularly targeted pediatric cancer investigations designed to yield clinically meaningful pediatric study data, gathered using appropriate formulations for each applicable age group, to inform potential pediatric labeling. The FDA may, on its own initiative or at the request of the applicant, grant deferrals or waivers of some or all of this data, as above. Unlike PREA, orphan products are not exempt from this requirement.

The FDA will typically inspect one or more clinical sites to assure compliance with GCP before approving an NDA or BLA. The FDA also will inspect the facility or the facilities at which the product is manufactured before the NDA or BLA is approved. The FDA will not approve the product unless cGMP compliance is satisfactory. If the FDA determines the application, manufacturing process or manufacturing facilities are not acceptable, it will outline the deficiencies in the submission and often will request additional testing or information.

Notwithstanding the submission of any requested additional information, the FDA ultimately may decide that the application does not satisfy the regulatory criteria for approval.

We may encounter difficulties or unanticipated costs in our efforts to secure necessary FDA approvals, which could delay or prevent us from marketing our products. The FDA may refer applications for novel drug products or biologic products to an advisory committee for review, evaluation and recommendation as to whether the application should be approved and under what conditions. Specifically, for a product candidate for which no active ingredient (including any ester or salt of active ingredients) has previously been approved by the FDA, the FDA must either refer that product candidate to an advisory committee or provide in an action letter, a summary of the reasons why the FDA did not refer the product candidate to an advisory committee. The FDA may also refer other product candidates to an advisory committee if FDA believes that the advisory committee's expertise would be beneficial. The advisory committee process may cause delays in the approval timeline. The FDA is not bound by the recommendation of an advisory committee, but it considers such recommendations carefully, particularly any negative recommendations or limitations, when making drug or biologic product approval decisions.

After evaluating the marketing application and all related information, including the advisory committee recommendation, if any, and inspection reports regarding the manufacturing facilities and clinical trial sites, the FDA may issue an approval letter, or, in some cases, a Complete Response Letter, or CRL. A CRL indicates that the review cycle of the application is complete and the application is not ready for approval and describes all of the specific deficiencies that the FDA identified. A CRL generally contains a statement of specific conditions that must be met in order to secure final approval of the marketing application, and may require additional clinical or preclinical testing in order for the FDA to reconsider the application. The deficiencies identified may be minor, for example, requiring labeling changes; or major, for example, requiring additional clinical trials. If a CRL is issued, the applicant may either: resubmit the marketing application, addressing all of the deficiencies identified in the letter; withdraw the application; or request an opportunity for a hearing. The FDA has the goal of reviewing 90% of application resubmissions in either two or six months of the resubmission date, depending on the kind of resubmission. However, if the application that was the subject of a CRL was filed over protest, these review timeframes do not apply and any such resubmission will be reviewed by FDA as available resources permit. Moreover, even with submission of additional information, the FDA ultimately may decide that the application does not satisfy the regulatory criteria for approval. If and when those conditions have been met to the FDA's satisfaction, the FDA may issue an approval letter. An approval letter authorizes commercial marketing of the product with specific prescribing information for specific indications.

The testing and approval process requires substantial time, effort and financial resources, and may take years to complete. Data obtained from clinical trials are not always conclusive and may be susceptible to varying interpretations, which could delay, limit or prevent regulatory approval. The FDA may not grant approval on a timely basis, or at all.

Even if approval is granted, the FDA may limit the indications for use, approve narrow labeling relegating a drug or biologic product to second- line or later-line use, add limitations of use to the labeling or place other conditions on approvals, which could restrict the marketing of the products. Further, the FDA may require that certain contraindications, warnings or precautions be included in the product labeling, including black box warnings, require testing and surveillance programs to monitor the product after commercialization, or impose other conditions, including distribution restrictions or other risk management mechanisms under a REMS which can materially affect the potential market and profitability of the product. The FDA may also not approve label statements that are necessary for successful commercialization and marketing. After approval, some types of changes to the approved product, such as adding new indications or label claims, which may themselves require further clinical testing, or changing the manufacturing process are subject to further FDA review and approval.

The FDA may also withdraw the product approval if compliance with the pre-and post-marketing regulatory standards are not maintained or if problems occur after the product reaches the marketplace, among other consequences. Further, should new safety information arise, additional testing, product labeling, or FDA notification may be required.

Additional regulation for gene therapy clinical trials

In addition to the regulations discussed above, there are a number of additional standards that apply to clinical trials involving the use of gene therapy. The FDA has issued, and continues to issue, various guidance documents regarding the development and commercialization of gene therapies, which outline additional factors that the FDA will consider at each of the above stages of development and relate to, among other things: the proper preclinical and nonclinical assessment of gene therapies; the design and conduct of clinical trials, the CMC information that should be included in an IND application; the proper design of tests to measure product potency in support of an IND or BLA application; and long term patient and clinical study subject follow up and regulatory reporting. The FDA also issued guidance documents that address gene therapy considerations during the COVID-19 pandemic and a draft guidance specific to the development of gene therapy products for neurodegenerative diseases as such products may face special challenges related to CMCs and clinical and preclinical development, due to the nature of the products and potential patient population (e.g., children), the heterogeneity of neurodegenerative disorders, the route of administration, the volume of the product that can be administered, the delivery device, and the study population size.

Post-approval requirements

After FDA approval of a product is obtained, we are required to comply with a number of post-approval requirements, including, among other things, establishment registration and product listing, record-keeping requirements, reporting certain adverse reactions and production problems to the FDA, providing updated safety and efficacy information, and complying with requirements concerning advertising and promotional labeling. As a condition of approval of an NDA or BLA, the FDA may require the applicant to conduct additional clinical trials or other post market testing and surveillance to further monitor and assess the product's safety and efficacy. There also are continuing annual program user fee requirements for approved products, though orphan products may receive exemptions if certain criteria are met.

The FDA also has the authority to require a specific REMS to ensure the safe use of the drug or biologic. In determining whether a REMS is necessary, the FDA must consider the size of the population likely to use the product, the seriousness of the disease or condition to be treated, the expected benefit of the product, the duration of treatment, the seriousness of known or potential adverse events, and whether the product is a new molecular entity. A REMS may be required to include various elements, such as a medication guide or patient package insert, a communication plan to educate healthcare providers of the product's risks, limitations on who may prescribe or dispense the product, or other measures that the FDA deems necessary to assure the safe use of the drug. The REMS strategy must be approved by the FDA. In addition, the REMS must include a timetable to assess the strategy at 18 months, three years, and seven years after the strategy's approval. The FDA may also impose a REMS requirement on an approved product if the FDA determines, based on new safety information, that a REMS is necessary to ensure that the product's benefits outweigh its risks.

The FDA strictly regulates marketing, labeling, advertising and promotion of products that are placed on the market. Although physicians may prescribe a drug or biologic for off-label uses, manufacturers may only promote the product for the approved indications and in accordance with the approved labeling. The FDA and other agencies actively enforce the laws and regulations prohibiting the promotion of off-label uses. Failure to comply with the laws and regulations governing advertising and promotion can have negative consequences, including adverse publicity, warning and untitled letters from the FDA, requests for corrective advertising or communications with doctors, civil penalties or criminal prosecution, exclusion from participation in federal healthcare programs, mandatory compliance programs under corporate integrity agreements, suspension and debarment from government contracts, and refusal or orders under existing government contracts, among others.

In addition, the distribution of prescription pharmaceutical products is subject to the Prescription Drug Marketing Act, or PDMA, which regulates the distribution of samples at the federal level. The Drug Supply Chain Security Act, or DSCSA, added sections in the FDCA that require manufacturers, repackagers, wholesale distributors, dispensers, and third-party logistics providers to take steps to identify and trace certain prescription drugs and biologics to protect against the threats of counterfeit, diverted, stolen, contaminated, or otherwise harmful products in the supply chain. The DSCSA regulates the distribution of prescription pharmaceutical drugs and biologics, requiring passage of documentation to track and trace each prescription product at the saleable unit level through the distribution system. This documentation must be transferred electronically. Products subject to the DSCSA must only be transferred to appropriately licensed purchasers. The DSCSA

also requires manufacturers and repackagers to affix or imprint a unique product identifier (comprised of a standardized numerical identifier, lot number, and expiration date of the product) on product packages in both a human-readable and on a machine-readable data carrier. The standardized numerical identifier is comprised of the product's corresponding National Drug Code combined with a unique alphanumeric serial number. A product is misbranded if it does not bear the product identifier. The DSCSA also establishes several requirements relating to the verification of product identifiers. Further, under this legislation, sponsors have product investigation, quarantine, disposition, and notification responsibilities related to counterfeit, diverted, stolen, and intentionally adulterated products that would result in serious adverse health consequences or death to humans, as well as products that are the subject of fraudulent transactions or which are otherwise unfit for distribution such that they would be reasonably likely to result in serious health consequences or death. Similar requirements additionally are and will be imposed through this legislation on other companies within the biopharmaceutical product supply chain, such as distributors and dispensers, as well as certain sponsor licensees and affiliates. Implementation of the DSCSA requirements, such as the product identifier requirements has imposed and will continue to impose increased costs and administrative burdens and may lead to potential liability associated with the marketing and sale of products subject to these requirements. The PDMA, DSCSA, and state laws limit the distribution of prescription pharmaceutical product samples and impose requirements to ensure accountability in distribution.

Also, quality control and manufacturing procedures must continue to conform to cGMP after approval, including quality control and quality assurance and maintenance of records and documentation. Changes to the manufacturing process are strictly regulated and often require prior FDA approval or notification before being implemented. FDA regulations also require investigation and correction of any deviations from cGMP and specifications, and impose reporting and documentation requirements upon the sponsor and any third-party manufacturers that the sponsor may decide to use.

Manufacturers and others involved in the manufacture and distribution of such products also must register their establishments with the FDA and certain state agencies. Both domestic and ex-U.S. manufacturing establishments must register and provide additional information regarding manufactured products to the FDA upon their initial participation in the manufacturing process for a commercial product, as well as periodically during the year. The information that must be submitted to FDA regarding manufactured products was expanded through the Coronavirus Aid, Relief, and Economic Security, or CARES, Act to include the volume of drugs produced during the prior year.

Establishments may be subject to periodic, unannounced inspections by government authorities to ensure compliance with cGMP requirements and other laws. Discovery of problems may result in a government entity placing restrictions on a product, manufacturer or holder of an approved NDA or BLA, and may extend to requiring withdrawal of the product from the market among other consequences further described in this filing. Accordingly, manufacturers must continue to expend time, money and effort in the area of production and quality control to maintain compliance with cGMP and other aspects of regulatory compliance. The FDA may take into account results of inspections performed by certain counterpart ex-U.S. regulatory agencies in assessing compliance cGMPs. The FDA has entered into international agreements with ex-U.S. agencies, including the EU, in order to facilitate this type of information sharing.

We rely, and expect to continue to rely, on third parties for the production of clinical and commercial quantities of most of our product and product candidates. However, in 2021, we began cGMP manufacturing of clinical material at the Hopewell Facility for certain of our gene therapy product candidates other than PTC-AADC. Future FDA inspections may identify compliance issues at our facilities or at the facilities of our contract manufacturers that may disrupt production or distribution, or require substantial resources to correct. In addition, discovery of problems with a product or the failure to comply with applicable requirements may result in restrictions on a product, manufacturer or holder of an approved NDA, including withdrawal or recall of the product from the market or other voluntary, FDA-initiated or judicial action, among other consequences further described in this filing, that could delay or prohibit further marketing.

Once approval is granted, the FDA may withdraw the approval if compliance with regulatory requirements is not maintained or if issues bearing on the product's safety or efficacy are discovered. Newly discovered or developed safety or effectiveness data or other information may also require changes to a product's approved labeling, including the addition of new warnings and contraindications, and also may require the implementation of other risk management measures. Such actions may include refusal to approve pending applications, license or approval suspension or revocation, imposition of a clinical hold or termination of clinical trials, warning letters, untitled letters, cyber letters, modification of promotional materials or labeling, provision of corrective information, imposition of post-market requirements including the need for

additional testing, imposition of distribution or other restrictions under a REMS, product recalls, product seizures or detentions, refusal to allow imports or exports, total or partial suspension of production or distribution, FDA debarment, injunctions, fines, consent decrees, corporate integrity agreements, suspension and debarment from government contracts, and refusal of orders under existing government contracts, exclusion from participation in federal and state healthcare programs, restitution, disgorgement, or civil or criminal penalties, including fines and imprisonment, and adverse publicity, among other adverse consequences. New government requirements, including those resulting from new legislation, may be established that could delay or prevent FDA approval of our products under development or negatively impact the marketing of any future approved products.

FDA post-approval requirements are continually evolving. For example, in March 2020, the U.S. Congress passed the Coronavirus Aid, Relief, and Economic Security Act, or CARES Act, which includes various provisions regarding FDA drug shortage and manufacturing volume reporting requirements, as well as provisions regarding supply chain security, such as risk management plan requirements, and the promotion of supply chain redundancy and domestic manufacturing. As part of the CARES Act implementation, the FDA recently issued a guidance on the reporting of the volume of drugs produced, which reporting will require additional administrative efforts by drug manufacturers.

Additional controls for biologics

To help reduce the risk of the introduction of adventitious agents or of causing other adverse events with the use of biologic products, the PHSA emphasizes the importance of manufacturing control for products whose attributes cannot be precisely defined. The PHSA also provides authority to the FDA to immediately suspend licenses in situations where there exists a danger to public health, to prepare or procure products in the event of shortages and critical public health needs, and to authorize the creation and enforcement of regulations to prevent the introduction or spread of communicable diseases in the United States and between states.

After a BLA is approved, the product may also be subject to official lot release as a condition of approval. As part of the manufacturing process, the manufacturer is required to perform certain tests on each lot of the product before it is released for distribution. If the product is subject to official release by the FDA, the manufacturer submits samples of each lot of product to the FDA together with a release protocol showing the results of all of the manufacturer's tests performed on the lot. The FDA may also perform certain confirmatory tests on lots of some products before releasing the lots for distribution by the manufacturer.

In addition, the FDA conducts laboratory research related to the regulatory standards on the safety, purity, potency, and effectiveness of biological products.

Orphan drug designation.

We have received orphan drug designation from the FDA for Translarna for the treatment nmDMD, PTC-AADC for the treatment of AADC deficiency, Evrysdi for the treatment of SMA, PTC-FA for the treatment of Friedreich ataxia, PTC-AS for the treatment of Angelman syndrome, PTC923 for the treatment of hyperphenylalaninemia, including hyperphenylalaninemia caused by PKU, emvododstat for the treatment of AML and unesbulin for the treatment of LMS and DIPG. The FDA may grant orphan drug designation to drugs and biologics intended to treat a "rare disease or condition," which is defined as a disease or condition that affects fewer than 200,000 individuals in the United States, or more than 200,000 individuals in the United States and for which there is no reasonable expectation that the cost of developing and making available in the United States a product for this type of disease or condition will be recovered from sales in the United States for that product. Additionally, sponsors must present a plausible hypothesis for clinical superiority to obtain orphan designation if there is a product already approved by the FDA that that is considered by the FDA to be the same as the already approved product and is intended for the same indication. This hypothesis must be demonstrated to obtain orphan exclusivity. Orphan drug designation must be requested before submitting an application for marketing approval. Orphan drug designation does not convey any advantage in, or shorten the duration of, the regulatory review and approval process. Orphan drug designation can provide opportunities for grant funding towards clinical trial costs, tax advantages and FDA user-fee benefits. The tax advantages, however, were limited in 2017 Tax Cuts and Jobs Act. In addition, if a product which has an orphan drug designation subsequently receives the first FDA approval for the indication for which it has such designation, the product is entitled to orphan drug exclusivity, which means the

FDA may not approve any other application to market the same drug or biologic for the same indication for a period of seven years, except in limited circumstances, such as a showing of clinical superiority to the product with orphan exclusivity or the same drug or biologic for different indications. However, competitors may receive approval of different drugs or biologics for the indications for which the orphan product has exclusivity. The FDA awarded an orphan drug designation to Emflaza for the treatment of patients five years and older with DMD and approved Emflaza on February 9, 2017, as the first corticosteroid approved in the United States for the treatment of patients with DMD, granting Emflaza orphan drug exclusivity for this disease as of the date of approval. The FDA also approved the use of Emflaza for the treatment of patients 2 years to up to 5 years old with DMD on June 7, 2019, granting orphan drug exclusivity as of the date of this second approval.

Orphan product sameness decisions are an evolving space. The FDA recently issued a final guidance document on how the agency will determine the "sameness" of gene therapy products. Pursuant to the guidance, "sameness" will depend on the products' transgene expression, viral vectors groups and variants, and other product features that may have a therapeutic effect. Generally, minor differences between gene therapy products will not result in a finding that two products are different. Any FDA sameness determinations could impact our ability to receive approval for our product candidates and to obtain or retain orphan drug exclusivity.

Rare Pediatric Disease Voucher Program

Under the FDCA, the FDA awards priority review vouchers to sponsors of rare pediatric disease products that meet certain criteria. To qualify, the rare disease must be serious or life-threatening in which the serious or life-threatening manifestations primarily affect individuals aged from birth to 18 years. Also, the product must contain no active ingredient (including any ester or salt of the active ingredient) that has been previously approved in any other application and the application must meet certain additional qualifying criteria, including eligibility for FDA priority review. If FDA determines that a product is for a rare pediatric disease and the qualifying application criteria are met, upon a sponsor's request, FDA may award the sponsor a priority review voucher. This voucher may be redeemed to receive priority review (i.e., a review time of 6 months as compared to 10 months for standard review) of a subsequent marketing application for a different product. Use of a priority review voucher is subject to an FDA user fee. These vouchers are transferable. Accordingly, sponsors may sell these vouchers for substantial sums of money. Vouchers may also be revoked by FDA under certain circumstances and sponsors of approved rare pediatric disease products must submit certain reports to FDA.

Changes to the FDCA, however, have limited the future use of pediatric priority review vouchers. Under the law's sunset provision, the drug or biologic must be designated by FDA for a rare pediatric disease no later than September 30, 2024, and approved no later than September 30, 2026, unless the law is reauthorized by Congress. Accordingly, while PTC-AADC currently has a rare pediatric disease designation, if we cannot secure FDA BLA approval prior to September 30, 2026, we may not be able to receive the benefit of such designation.

Hatch-Waxman Act for Drugs.

Section 505 of the FDCA describes three types of drug marketing applications that may be submitted to the FDA to request marketing authorization for a new drug. A Section 505(b)(1) NDA is an application that contains full reports of investigations of safety and efficacy. A 505(b)(2) NDA is an application that contains full reports of investigations of safety and efficacy but where at least some of the information required for approval comes from investigations that were not conducted by or for the applicant and for which the applicant has not obtained the right of reference or use from the person by or for whom the investigations were conducted. This regulatory pathway enables the applicant to rely, in part, on the FDA's prior findings of safety and efficacy for an existing product, or published literature, in support of its application. Section 505(j) establishes an abbreviated approval process for a generic version of approved drug products through the submission of an Abbreviated New Drug Application, or ANDA. An ANDA provides for marketing of a generic drug product that generally has the same active ingredients, dosage form, strength, route of administration, labeling, performance characteristics and intended use, among other things, to a previously approved product, called the reference listed drug. Certain differences, however, between the reference listed drug and ANDA product may be permitted pursuant to a suitability petition. Certain labeling differences may also be permitted if information in the reference listed drug's label is protected by patent or exclusivities. ANDAs are termed "abbreviated" because they are generally not required to include preclinical (animal) and clinical (human) data to establish safety and efficacy. Instead, generic

applications must scientifically demonstrate that their product is bioequivalent to, or performs in the same manner as, the innovator drug through in vitro, in vivo, or other testing. The generic version must deliver the same amount of active ingredients to the site of action in the same amount of time as the innovator drug and can often be substituted by pharmacists under prescriptions written for the reference listed drug. In seeking approval for a drug through an NDA, applicants are required to list with the FDA each patent with claims that cover the applicants drug or a method of using the drug. Upon approval of a drug, each of the patents listed in the application for the drug is then published in the FDA's list of Approved Drug Products with Therapeutic Equivalence Evaluations, commonly known as the Orange Book. Drugs listed in the Orange Book can, in turn, be cited by potential competitors in support of approval of an ANDA or 505(b)(2) NDA. In an effort to clarify which patents must be listed in the Orange Book, in January 2021, Congress passed the Orange Book Transparency Act of 2020, which largely codifies FDA's existing practices into the FDCA.

Upon submission of an ANDA or 505(b)(2) NDA, an applicant must certify to the FDA that (1) no patent information has been submitted to the FDA; (2) such patent has expired; (3) the date on which such patent expires; or (4) such patent is invalid or will not be infringed upon by the manufacturer, use or sale of the drug product for which the application is submitted. The applicant may also elect to submit a "section viii" statement certifying that its proposed label does not contain (or carves out) any language regarding the patented method-of-use rather than certify to a listed method-of-use patent. Generally, the ANDA or 505(b)(2) NDA approval cannot be made effective until all listed patents have expired, except where the ANDA or 505(b)(2) NDA applicant challenges a listed patent through the last type of certification, also known as a paragraph IV certification.

If the ANDA or 505(b)(2) NDA applicant has provided a paragraph IV certification to the FDA, the applicant must send notice of the certification to the NDA and patent holders. The NDA and patent holders may then initiate a patent infringement lawsuit in response to the notice of the paragraph IV certification, in which case the FDA may not make an approval effective until the earlier of 30 months from the patent or application owner's receipt of the notice of the paragraph IV certification, the expiration of the patent, when the infringement case concerning each such patent is favorably decided in the applicant's favor or settled, or such shorter or longer period as may be ordered by a court. This prohibition is generally referred to as the 30-month stay. In instances where an ANDA or 505(b)(2) NDA applicant files a paragraph IV certification, the NDA holder or patent owner(s) regularly take action to trigger the 30-month stay. Thus, approval of an ANDA or 505(b)(2) NDA could be delayed for a significant period of time depending on the patent certification the applicant makes and the reference drug sponsor's decision to initiate patent litigation.

Market and data exclusivity provisions under the FDCA can delay the submission or the approval of certain applications for competing products. The FDCA provides a five-year period of non-patent data exclusivity within the United States to the first applicant to gain approval of an NDA for a new chemical entity. A drug is a new chemical entity if the FDA has not previously approved any other new drug containing the same active moiety, which is the molecule or ion responsible for the therapeutic activity of the drug substance. During the exclusivity period, the FDA generally may not accept for review an ANDA or a 505(b)(2) NDA submitted by another company that contains the new chemical entity. However, an ANDA or 505(b)(2) NDA may be submitted after four years if it contains a certification of patent invalidity or non-infringement.

The FDCA also provides a shorter three-year period of market exclusivity for an NDA, 505(b)(2) NDA, or supplement to an existing NDA or 505(b)(2) NDA if new clinical investigations, other than bioavailability studies, that were conducted or sponsored by the applicant are deemed by the FDA to be essential to the approval of the application. Three-year exclusivity may be granted for example, for new indications, dosages, strengths or dosage forms of an existing drug. This three-year exclusivity covers only the conditions of use associated with the new clinical investigations and, as a general matter, does not prohibit the FDA from approving ANDAs or 505(b)(2) NDAs for generic versions of the original, unmodified drug product. Five-year and three-year exclusivity will not delay the submission or approval of a full NDA; however, an applicant submitting a full NDA would be required to conduct or obtain a right of reference to all of the preclinical studies and adequate and well-controlled clinical trials necessary to demonstrate safety and effectiveness.

BPCIA Exclusivity

The 2010 Patient Protection and Affordable Care Act included the BPCIA as a subtitle. The BPCIA established a regulatory scheme authorizing the FDA to approve biosimilars and interchangeable biosimilars. The FDA has issued a

number of guidance documents outlining an approach to review and approval of biosimilars, including guidance documents on the demonstration of interchangeability and the licensure of biosimilar and interchangeable products for fewer than all of the reference product's licensed conditions of use.

Under the BPCIA, a manufacturer may submit an application for licensure of a biologic product that is "biosimilar to" or "interchangeable with" a previously approved biological product or "reference product." In order for the FDA to approve a biosimilar product, it must find that there is a high degree of similarity to the reference product, notwithstanding minor differences in clinically inactive components, and that there are no clinically meaningful differences between the reference product and proposed biosimilar product in terms of safety, purity and potency. Biosimilarity must be shown through analytical studies, animal studies, and at least one clinical trial, absent a waiver by the FDA. There must be no difference between the reference product and a biosimilar in mechanism of action, conditions of use, route of administration, dosage form, and strength. For the FDA to approve a biosimilar product as interchangeable with a reference product, the FDA must find that the biosimilar product can be expected to produce the same clinical results as the reference product, and (for products administered multiple times) that the biologic and the reference biologic may be switched after one has been previously administered without increasing safety risks or risks of diminished efficacy relative to exclusive use of the reference biologic.

Under the BPCIA, an application for a biosimilar product may not be submitted to the FDA until four years following the date of approval of the reference product. The FDA may not approve a biosimilar product until 12 years from the date on which the reference product was approved. However, certain changes and supplements to an approved BLA, and subsequent applications filed by the same sponsor, manufacturer, licensor, predecessor in interest, or other related entity do not qualify for the 12 year exclusivity period. Even if a product is considered to be a reference product eligible for exclusivity, another company could market a competing version of that product if the FDA approves a full BLA for such product containing the sponsor's own preclinical data and data from adequate and well-controlled clinical trials to demonstrate the safety, purity and potency of their product. The BPCIA also created certain exclusivity periods for biosimilars approved as interchangeable products.

The BPCIA also includes provisions to protect reference products that have patent protection. The biosimilar product sponsor and reference product sponsor may exchange certain patent and product information for the purpose of determining whether there should be a legal patent challenge. Based on the outcome of negotiations surrounding the exchanged information, the reference product sponsor may bring a patent infringement suit and injunction proceedings against the biosimilar product sponsor. The biosimilar applicant may also be able to bring an action for declaratory judgment concerning the patent.

The FDA maintains a publicly-available online database of licensed biological products, which is commonly referred to as the "Purple Book." The Purple Book lists product names, dates of licensure, and applicable periods of exclusivity. Further, pursuant to a recently enacted statute to enable biological product patent transparency, the reference product sponsor must provide patent information and patent expiry dates to FDA following the exchange of patent information between biosimilar and reference product sponsors. This information is then published in the Purple Book.

In an effort to increase competition in the drug and biologic product marketplace, Congress, the executive branch, and FDA have taken certain legislative and regulatory steps. For example, measures have been proposed and implemented to facilitate product importation. Moreover, the 2020 Further Consolidated Appropriations Act included provisions requiring that sponsors of approved drug and biologic products, including those subject to REMS, provide samples of the approved products to persons developing 505(b)(2) NDA or ANDA drug products, or biosimilar products within specified timeframes, in sufficient quantities, and on commercially reasonable market-based terms. Failure to do so can subject the approved product sponsor to civil actions, penalties, and responsibility for attorney's fees and costs of the civil action. This same bill also includes provisions with respect to shared and separate REMS programs for reference and generic drug products.

Patent Term Restoration

If approved, drug and biologic products may also be eligible for periods of U.S. patent term restoration. If granted, patent term restoration extends the patent life of a single unexpired patent, that has not previously been extended, for a maximum

of five years. The total patent life of the product with the extension also cannot exceed fourteen years from the product's approval date. Subject to the prior limitations, the period of the extension is calculated by adding half of the time from the effective date of an IND to the initial submission of a marketing application, and all the time between the submission of the marketing application and its approval. This period may also be reduced by any time that the applicant did not act with due diligence.

Pediatric exclusivity

Pediatric exclusivity is another type of non-patent market exclusivity in the United States and, if granted, provides for the attachment of an additional six months of market protection to the term of any existing Orange Book- listed patents or regulatory exclusivity, including the non-patent exclusivity periods described above. This six-month exclusivity may be granted based on the voluntary completion of a pediatric study or studies in accordance with an FDA-issued "Written Request" for such a study or studies within a specified timeframe prior to the expiration of the underlying patent or market exclusivity period to be extended.

Emergency Use Authorizations

While, in most cases, a therapeutic must be approved by the FDA pursuant to an NDA, an ANDA, or a BLA, before the product may be sold, when there is a public health emergency involving chemical, biological, radiological, or nuclear agents, including infectious diseases like COVID-19, new therapeutics may be distributed pursuant to an Emergency Use Authorization, or EUA. Under an EUA, the FDA may authorize the emergency use of an unapproved medical product or an unapproved use of an approved product for certain emergency circumstances to diagnose, treat, or prevent serious or life-threatening diseases or conditions when certain statutory criteria have been met, and after the Secretary of the Department of Health and Human Services has issued a declaration of emergency or threat justifying emergency use. EUAs are intended to address serious or life threatening diseases or conditions caused by a chemical, biological, radiological, or nuclear agent, including emerging infectious disease threats, such as the COVID-19 pandemic. To receive an EUA, the product sponsor must demonstrate that the product "may be effective" in the prevention, diagnosis, or treatment of an applicable disease or condition. Additionally, the FDA must determine that the product's known and potential benefits outweigh the known and potential risks. Further there must be no adequate, approved, and available alternative product for the indication. Potential alternative products may be unavailable if there are insufficient supplies to meet the emergency need. The FDA may establish additional conditions on an EUA that are necessary to protect public health, including conditions related to information that must be disseminated to healthcare providers and patients, the monitoring and reporting of adverse events, and record keeping. Conditions may also relate to how a product is distributed and administered and how a product is advertised. Importantly, EUAs are not full marketing approvals. Rather, EUAs are only effective for the duration of the applicable EUA declaration. Full approval of the product under applicable standards established under the FDCA would be necessary to continue to distribute the product absent an EUA. EUAs may also be revised or revoked by the FDA at any time.

Regulation outside the United States

In order to market any product outside of the United States, we would need to comply with numerous and varying regulatory requirements of other countries regarding safety and efficacy and governing, among other things, clinical trials, marketing authorization, commercial sales and distribution of our products. Whether or not we obtain FDA approval for a product, we would need to obtain the necessary approvals by the comparable regulatory authorities of ex-U.S. countries before we can commence clinical trials or marketing of the product in those countries. The approval process varies from country to country and can involve additional product testing and additional administrative review periods. The time required to obtain approval in other countries might differ from and be longer than that required to obtain FDA approval. Regulatory approval in one country does not ensure regulatory approval in another, but a failure or delay in obtaining regulatory approval in one country may negatively impact the regulatory process in others. And, even if regulatory approval is granted, it may be withdrawn or limited under certain circumstances or post-approval requirements may be imposed by the applicable regulatory authority. Because biologically sourced raw materials are subject to unique contamination risks, their use may be restricted in some countries.

Regulation in the European Union

We have obtained an orphan medicinal product designation from the European Commission, following an evaluation by the EMA's Committee for Orphan Medicinal Products, for Translarna for the treatment of nmDMD, Becker muscular dystrophy and aniridia – but have only received marketing authorization for Translarna for the treatment of nmDMD. The European Commission can grant orphan medicinal product designation to products for which the sponsor can establish that it is intended for the diagnosis, prevention, or treatment of (1) a life-threatening or chronically debilitating condition affecting not more than five in 10,000 people in the EU, or (2) a life threatening, seriously debilitating or serious and chronic condition in the EU and that without incentives it is unlikely that sales of the drug in the EU would generate a sufficient return to justify the necessary investment. In addition, the sponsor must establish that there is no other satisfactory method approved in the EU of diagnosing, preventing or treating the condition, or if such a method exists, the proposed orphan drug will be of significant benefit to patients. Orphan drug designation is not a marketing authorization. It is a designation that provides a number of benefits, including fee reductions, regulatory assistance, and, in the event of a successful application for a centralized EU marketing authorization, 10 years of EU market exclusivity. During this market exclusivity period, neither the EMA, nor the European Commission nor any EU member states can accept an application or grant a marketing authorization for a "similar medicinal product." A "similar medicinal product" is defined as a medicinal product containing a similar active substance or substances as contained in an authorized orphan medicinal product, and which is intended for the same therapeutic indication. The market exclusivity period for the authorized therapeutic indication may be reduced to six years if, at the end of the fifth year, it is established that the orphan designation criteria are no longer met, including where it is shown that the product is sufficiently profitable not to justify maintenance of market exclusivity. In addition, a competing similar medicinal product may in limited circumstances be authorized prior to the expiration of the market exclusivity period, including if it is shown to be safer, more effective or otherwise clinically superior to our product. Our product candidates can lose orphan designation, and the related benefits, prior to us obtaining a marketing authorization if it is demonstrated that the orphan designation criteria are no longer met.

Clinical Trial Developments. The structure and general regulation of clinical trials for both small molecule and biological medicines in the EU is similar to that in the United States. Separately, a new regulation, (EU) No.536/2014, regarding clinical trials of medicinal products for humans is included in the European regulatory framework and fills a series of regulatory gaps in the clinical trials regime through the creation of a uniform framework for the authorization of clinical trials by all interested EU member states with a single assessment of the results. The regulation (which came into effect on January 31, 2022) is thus intended to facilitate cross-border cooperation through streamlining of the rules on clinical trials across the EU, including by requiring the submission of clinical trial authorization applications via a new electronic EU portal.

Alongside the portal, a database is being created that will contain information on clinical trial data. The information on the database will be publicly accessible unless the trial data's confidentiality can be justified on the basis of protection of commercially confidential information, protection of personal data, protection of confidential communication between EU countries, or ensuring effective supervision of the conduct of clinical trials by EU countries. A sponsor of a trial conducted in the EU under the new regulation will be required to submit a summary of the clinical trial results to the EU database within a year of the end of the trial. In addition, where the trial was intended to be used for obtaining a marketing authorization (whether through the centralized procedure or via the national authorities), the applicant must submit the clinical study report within 30 days after the marketing authorization has been granted (or refused or withdrawn).

Overview of application process. To obtain regulatory approval of a drug under the EU's regulatory systems and authorization procedures, an applicant may submit marketing authorization applications under a centralized, decentralized, or national procedure. The centralized procedure is compulsory for certain medicinal products, including orphan medicinal products, like Translarna for the treatment of nmDMD, and medicinal products produced by certain biotechnological processes, and optional for certain other innovative products. The centralized procedure enables applicants to obtain a marketing authorization that is valid in all EU member states based on a single application. Under the centralized procedure, the EMA's Committee for Human Medicinal Products, or CHMP, is required to adopt an opinion on a valid application within 210 days, excluding clock stops, when additional written or oral information is to be provided by the applicant in response to questions.

More specifically, on day 120 of the procedure, once the CHMP has received the preliminary assessment reports and opinions from the rapporteur and co-rapporteur, it prepares a list of potential outstanding issues, referred to as "other concerns" or "major objections". These are sent to the applicant together with CHMP's recommendation. In addition, in relation to advanced therapy medicinal products, or ATMPs, which are medicines based on genes, cells or tissues, the Committee for Advanced Therapies, or CAT, EMA's committee responsible for assessing the quality, safety and efficacy of ATMPs, prepares a draft opinion on the ATMP application that is submitted to EMA before the CHMP adopts a final opinion on the marketing authorization of the applicable medicine. The CHMP can make one of two recommendations: (1) the marketing authorization could be granted provided that satisfactory answers are given to the "other concerns" and/or "major objections" identified and that all conditions outlined in the list of outstanding issues are implemented and complied with; or (2) the product is not approvable since there are "major objections".

Applicants have three months from the date of receiving the potential outstanding issues to respond to the CHMP, and can request a three-month extension if necessary. The granting of a marketing authorization will depend on the recommendations and potential major objections identified by the CHMP as well as the ability of the applicant to adequately respond to these findings. An accelerated assessment can be granted by the CHMP in exceptional cases, when a medicinal product is expected to be of a major public health interest, in particular from the viewpoint of therapeutic innovation. In this circumstance, the EMA ensures that the opinion of the CHMP is given within 150 days. After the adoption of the CHMP opinion, a decision on the marketing authorization application must be adopted by the European Commission, after consulting the EU member states, which in total can take more than 60 days.

An applicant for a marketing authorization application may request a re-examination in the event of a negative opinion, in connection with which CHMP appoints new rapporteurs. Within 60 days of receipt of the negative opinion, the applicant must submit a document explaining the basis for its request for re-examination. The CHMP has 60 days to consider the applicant's request for re-examination. The applicant may request an oral explanation before the CHMP, which is routinely granted, following which CHMP will adopt a final opinion. The final opinion, whether positive or negative, is published by the CHMP shortly following the CHMP meeting at which the oral explanation takes place. The EMA publishes a European Public Assessment Report, or EPAR, for every medicine granted a central marketing authorization by the European Commission following an assessment by the CHMP. EPARs are full scientific assessment reports of medicines authorized by the EMA.

Conditional marketing authorizations. In specific circumstances, as with Translarna for the treatment of nmDMD, EU legislation enables applicants to obtain a marketing authorization on a conditional basis prior to obtaining the comprehensive clinical data required for an application for a full marketing authorization. Such conditional approvals may be granted for products designated as orphan medicinal products, if (1) the benefit-risk balance of the product is positive, (2) it is likely that the applicant will be in a position to provide the required comprehensive clinical trial data, (3) the product fulfills unmet medical needs, and (4) the benefit to public health of the immediate availability on the market of the medicinal product concerned outweighs the risk inherent in the fact that additional data are still required. A conditional marketing authorization may contain specific obligations to be fulfilled by the marketing authorization holder, including obligations with respect to the completion of ongoing or new studies, and with respect to the collection of pharmacovigilance data. Conditional marketing authorizations are valid for one year, and may be renewed annually, if the benefit-risk balance remains positive, and after an assessment of the need for additional or modified conditions and/or specific obligations. The timelines for the centralized procedure described above also apply with respect to the review by the CHMP of applications for a conditional marketing authorization. The granting of a conditional marketing authorization will depend on the applicant's ability to fulfill the conditions imposed within the agreed upon deadline.

For important information about matters that may adversely affect our ability to renew our conditional marketing authorization for Translarna, see "Item 1A. Risk Factors-Risks Related to the Development and Commercialization of our Product and our Product Candidates" and "Risks Related to Regulatory Approval of our Product and our Product Candidates."

Variations to conditional marketing authorizations. After the granting of a conditional marketing authorization, the marketing authorization holder may submit an application to vary the conditional marketing authorization under a variation procedure. In the case of the introduction of an additional therapeutic indication, the timeframe for the variation procedure for the initial assessment of the dossier is generally 90 days (plus up to 20 days for validation).

However, in the framework of a variation application assessment procedure, the EMA may send one or more requests for supplementary information to the marketing authorization holder, requiring that additional information be provided by the marketing authorization holder to support its variation application. Such supplementary requests will be sent together with a timetable stating the date by when the marketing authorization holder must submit the requested data and, where appropriate, the extended evaluation period to be applied to such variation procedure. The 90-day variation procedure may be suspended for up to three months for the marketing authorization holder to submit its responses to such supplementary requests. The marketing authorization holder will be notified of the outcome of the CHMP's assessment of the variation procedure within 15 days from the adoption of the CHMP opinion. If unfavorable, the CHMP opinion may be subject to a re-examination procedure upon the marketing authorization holder's request. This may imply an additional minimum two-month procedure. If the CHMP opinion is favorable, the European Commission will usually vary the marketing authorization to introduce the additional therapeutic indication within approximately two months from the receipt of the final CHMP opinion.

Exceptional Circumstances. Similarly, certain of our product candidates may be eligible for a marketing authorization under exceptional circumstances. Such an authorization may be granted where the applicant can demonstrate in its application that it is unable to provide comprehensive data on efficacy and safety under normal conditions of use, because: 1) the indications for which the product in question is intended are encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence; 2) in the present state of scientific knowledge, comprehensive information cannot be provided; or 3) it would be contrary to generally accepted principles of medical ethics to collect such information. Authorizations under exceptional circumstances are annually reassessed and granted subject to a requirement for the applicant to implement certain procedures, in particular, competent authority notification in the event of any safety issue. After 5 years, the authorization is renewed under exceptional circumstances for an unlimited period, unless European Medicines Agency decides, on justified grounds relating to pharmacovigilance, to proceed with one additional five-year renewal. A marketing authorization under exceptional circumstances will not be granted when a conditional marketing authorization is more appropriate. Orphan products are further eligible for approval under exceptional circumstances only if the criteria considered for the approval under exceptional circumstances are fulfilled.

Additional requirements and considerations. Prior to obtaining a marketing authorization in the EU, applicants have to demonstrate compliance with all measures included in an EMA-approved Pediatric Investigation Plan, or PIP, covering all subsets of the pediatric population, unless the EMA has granted (1) a product-specific waiver, (2) a class waiver, or (3) a deferral for one or more of the measures included in the PIP. In the case of orphan medicinal products, completion of an approved PIP can result in an extension of the aforementioned market exclusivity period from ten to twelve years.

In the EU there is also a procedure which allows member states to authorize the distribution of an unauthorized medicinal product in response to the spread of pathogens. The UK (but no EU countries) used this procedure with two COVID-19 vaccines during December 2020. Notwithstanding the UK's subsequent full departure from the EU, the EU provision is mirrored in UK medicines legislation.

In the EU, for a period of eight years from the grant of a marketing authorization of an innovative product (the "reference medicinal product"), competent authorities may not accept marketing authorization applications from applicants seeking to market "generic medicinal products" where such applications rely on the data in the marketing authorization dossier of the reference product. Moreover, generic medicinal products that rely on the independently generated data of the reference product may not be placed on the market for 10 years from the granting of the initial marketing authorization for that reference medicinal product. This is extended to a maximum of 11 years if, during the first eight years of those 10 years, the marketing authorization holder obtains an authorization for one or more new therapeutic indications considered to offer a significant clinical benefit in comparison with existing therapies. These periods of data exclusivity do not prevent other companies from obtaining a marketing authorization based on their own independently generated data.

If a marketing authorization is granted in the EEA for a medicinal product, such as the marketing authorization granted for Translarna for the treatment of nmDMD by the European Commission, the marketing authorization holder is required to comply with a range of requirements applicable to the manufacturing, marketing, promotion and sale of the medicinal products that are in addition to the other conditions of the marketing authorization described above. The marketing authorization holder must, for example, comply with the EU's stringent pharmacovigilance or safety reporting rules, pursuant to which post- authorization studies and additional monitoring obligations can be imposed. Other requirements

relate to, for example, the manufacturing of products and active pharmaceutical ingredients in accordance with good manufacturing practice standards. Competent authorities of EU member states may conduct inspections to verify compliance with applicable requirements, and the marketing authorization holder will have to continue to expend time, money and effort to remain compliant. Non-compliance with EU requirements regarding safety monitoring or pharmacovigilance, and with requirements related to the development of products for the pediatric population, can also result in significant financial penalties in the EU Similarly, failure to comply with the EU's requirements regarding the protection of individual personal data can also lead to significant penalties and sanctions. Individual EU member states may also impose various sanctions and penalties in case we do not comply with locally applicable requirements. The CAT is involved in any procedure regarding the provision of advice on the conduct of efficacy follow-up, pharmacovigilance and risk management systems of ATMPs as provided for in ATMP legislation.

Off-label promotion of medicinal products is prohibited in the EU. The applicable laws at EU level and in the individual EU member states also prohibit the direct-to-consumer advertising of prescription-only medicinal products. Violations of the rules governing the promotion of medicinal products in the EU could be penalized by administrative measures, fines and imprisonment. These laws may further limit or restrict our promotional activities with healthcare professionals. In addition, legislation adopted at the EU level and by individual EU member states require that promotional materials and advertising in relation to medicinal products comply with the product's Summary of Product Characteristics, or SmPC, as approved by the competent authorities. The SmPC is the document that provides information to physicians concerning the safe and effective use of the medicinal product. Promotion of indications not covered by the SmPC is specifically prohibited. ATMP legislation lays down certain minor extra labelling requirements for ATMPs.

The EMA is responsible for coordinating inspections to verify compliance with the principles of GCP, good manufacturing practice, or GMP, GLP, and good pharmacovigilance practice. These inspections are also intended to verify compliance with other aspects of the supervision of authorized medicinal products in use in the EU. The EMA coordinates any inspection by the relevant member state regulatory authority as requested by the CHMP in connection with the assessment of marketing authorization applications or matters referred to these committees. Inspections may be routine or triggered by issues arising during the assessment of the dossier or by other information, such as previous inspection experience. Inspections usually are requested during the initial review of a marketing authorization application, but could arise post-authorization.

Inspectors are drawn from the regulatory authorities of member states of the EU and the EEA. Following an inspection, the inspectors provide a written inspection report to the inspected site or applicant and provide an opportunity for response. Some inspection reports require follow-up and may result in additional adverse consequences due to critical or major findings. The inspectors and the CHMP will comment on any response from an inspected site or applicant and may monitor future compliance with any proposed corrective action plan.

In the GCP area, inspectors grade their findings according to the following scale:

- Critical: Conditions, practices or processes that adversely affect the rights, safety or well-being of the subjects or the quality and integrity of data. Observations classified as critical may include a pattern of deviations classified as major.
- Major: Conditions, practices or processes that might adversely affect the rights, safety or well-being of the subjects and/or the quality and integrity of data. Observations classified as major may include a pattern of deviations or numerous minor observations.
- Minor: Conditions, practices or processes that would not be expected to adversely affect the rights, safety or wellbeing of the subjects or the quality and integrity of data. Minor observations indicate the need for improvement of conditions, practices and processes.
- Comments: Suggestions on how to improve quality or reduce the potential for a deviation to occur in the future.

Possible consequences of critical and major findings include rejection of clinical trial data, causing significant delays in obtaining final marketing authorization, or other direct action by national regulatory authorities.

Falsified Medicines Directive – As of February 2019, new legislation required manufacturers of marketed prescription medicines to place safety features on all medicines and contribute financially to the establishment of a verification system

allowing the authenticity of a medicine to be assessed at the time of supply to the patient. Under the legislation, all packages of prescription medicines placed on the market in Europe have to bear two safety features: a unique identifier in the form of a two-dimensional data matrix (barcode) and an anti-tamper device. In addition, ATMP legislation requires a procedure for tracing the product and its starting and raw materials from its source to the site where the product is used.

Early access programs

Many jurisdictions allow the supply of unauthorized medicinal products in the context of strictly regulated and exceptional EAP programs, and some countries may provide reimbursement for drugs provided in the context of such programs. In the EU, the legal basis for EAP programs, also referred to as named-patient and compassionate use programs, is set out in the EU legislation regulating the authorization, manufacture, distribution and marketing of medicinal products. Detailed regulatory requirements applicable to EAP programs have been adopted and implemented by EU member states in their national laws. The promotion, advertising and marketing of unauthorized medicinal products is generally prohibited, and authorization for EAP programs must generally be obtained from national competent authorities, which might not grant such authorization. Obtaining authorization for an EAP program in one country does not ensure that authorization will be obtained in another country.

U.S. law permits "expanded access" (also known as compassionate use and treatment use) for certain patients with serious diseases who have no comparable alternative treatment options. The potential patient benefit must justify the potential risks of the treatment use and those potential risks must not be unreasonable in the context of the disease or condition to be treated. Moreover, providing the investigational drug or biologic for the requested use must not interfere with the initiation, conduct, or completion of clinical investigations that could support marketing approval of the expanded access use or otherwise compromise the potential development of the expanded access use. Additional requirements apply depending on the size of the expanded access population. To provide expanded access, sponsors, including individual physicians, must submit detailed regulatory information to the FDA and receive the agency's approval for the use. However, if there is an emergency that requires that a patient be treated before a written submission can be made, the FDA may authorize the expanded access use by telephone. In such a case, a written expanded access submission must be submitted to the FDA within fifteen working days of the FDA's authorization. Following approval for expanded access use, both the sponsor of the use and the investigator (i.e., physician) must comply with certain FDA requirements. Sponsors may not promote products as safe or effective for expanded-access uses.

U.S. law further permits access to investigational drugs or biologics for treatment use under the federal Right to Try legislation. Under this law, patients diagnosed with a life-threatening disease or condition, who have exhausted all approved treatment options, may be able to obtain access, with the agreement of the product manufacturer and the patient's physician to certain investigational drugs and biologics. The patient must further be unable to participate in a clinical trial involving the investigational drug or biologic and must provide informed consent. If all of the statutory criteria are satisfied, FDA approval of the use of the investigational drug or biologic for patient treatment is not required but certain reports must be submitted to the agency annually. Individual states also have their own Right to Try statutes.

Pharmaceutical Pricing and Reimbursement

The containment of healthcare costs has become a priority of federal, state and ex-U.S. governments, and the prices of pharmaceuticals have been a focus of this effort. Ex-U.S. governments, the U.S. government, and state legislatures have shown significant interest in implementing cost-containment programs to limit the growth of government-paid healthcare costs, including price controls, increases in rebates paid, restrictions on reimbursement and requirements for substitution of generic products for branded prescription drugs.

In some countries, particularly the countries of the EU, the pricing of prescription pharmaceuticals is subject to governmental control. In these countries, pricing and reimbursement negotiations with governmental authorities can take considerable time after the receipt of marketing approval for a product and there is only limited EU-level control over the decision-making autonomy of the government authorities including in relation to timing, justification and the ability to challenge such decisions. In addition, there can be considerable pressure by governments and other stakeholders on prices and reimbursement levels, including as part of cost containment measures. In some countries, governments can set conditions that must be satisfied for prices to be set at a certain value. Political, economic and regulatory developments

may further complicate pricing and reimbursement negotiations, and pricing negotiations may continue after reimbursement has been obtained. Reference pricing used by various EU member states, and parallel distribution (arbitrage between low-priced and high- priced member states), can further reduce prices. In some countries we may be required to conduct a clinical trial or other studies that compare the cost-effectiveness of our product or product candidate to other available therapies in order to obtain reimbursement or pricing approval.

In the United States, federal price reporting laws require manufacturers to calculate and report complex pricing metrics used to determine prescription rebates paid under the Medicaid Drug Rebate Program and amounts reimbursed pharmacies and other providers by the Medicaid and Medicare programs. Various state healthcare programs similarly obligate us to report drug pricing information that is used as the basis for their reimbursement of pharmacies and other healthcare providers and the negotiation of supplemental rebates. Payment for a manufacturer's drugs by these programs is conditioned on submission of this pricing information. Some government healthcare programs impose penalties if drug price increases exceed specified percentages or inflation rates, and these penalties can result in mandatory penny prices for certain federal and 340B program customers. States, such as California, have also enacted transparency laws that require manufacturers to report price increases and related information, and may cap price increases, or require negotiation of supplemental rebates for new drugs entering the market at price points determined to be high. Refusal to negotiate supplemental rebates can negatively affect market access and provider reimbursement. Failure to comply with the rules for calculating and submitting pricing information or otherwise overcharging the government or its beneficiaries may result in criminal, civil, or administrative sanctions or enforcement actions, and expose us to federal civil False Claims Act, or the False Claims Act, liability.

The Veterans Health Care Act of 1992 requires, as a condition of payment by certain federal agencies and the Medicaid program, that manufacturers of "covered drugs" (including all drugs approved under an NDA) enter into a Master Agreement and Federal Supply Schedule (FSS) contract with the Department of Veterans Affairs through which their covered drugs must be offered for sale at a mandatory ceiling price to certain federal agencies, including the VA and Department of Defense. FSS contracts require compliance with applicable federal procurement laws and regulations, including disclosure of commercial prices during contract negotiations and maintenance of price relationships during the term of the contract, and subject manufacturers to contractual remedies as well as administrative, civil, and criminal sanctions. The Veterans Health Care Act also requires manufacturers to enter into pricing agreements with the Department of Health and Human Services to charge no more than a different ceiling price (derived from the Medicaid rebate percentage) to covered entities participating in the 340B drug discount program. Failure to provide the mandatory discount may subject the manufacturer to specific civil monetary penalties. Termination of either of these agreements also jeopardizes payment by Medicaid and Medicare for the manufacturer's drugs in an outpatient setting.

Coverage policies, third-party reimbursement rates and drug pricing regulation may change at any time. For example, in the United States, healthcare reform measures under the Affordable Care Act, contain provisions that may affect the profitability of drug products. However, since its passage, Congress has repealed and amended certain provisions of the Affordable Care Act, repeal efforts may occur again, and legal challenges to the Affordable Care Act may contribute to the uncertainty of the ongoing implementation and impact of the Affordable Care Act and underscore the potential for additional reform going forward. Certain provisions of enacted or proposed legislative changes may negatively impact coverage and reimbursement of, or rebates paid by manufacturers for, healthcare items and services. We cannot assure that the Affordable Care Act, as currently enacted or as amended in the future, will not adversely affect our business and financial results and we cannot predict how future federal or state legislative or administrative changes relating to healthcare reform will affect our business.

Legislators and regulators at both the federal and state level are increasingly focused on containing the cost of drugs, and there has been increasing legislative and enforcement interest in the United States with respect to specialty drug pricing practices. Specifically, there have been recent U.S. Congressional inquiries and proposed bills designed to, among other things, bring more transparency to drug pricing, penalize companies that do not agree to cap prices paid for certain drugs, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for drugs. For example, in 2016, the Centers for Medicare and Medicaid Services, or CMS, issued a final rule regarding the Medicaid drug rebate program, which among other things, revises the manner in which the "average manufacturer price" or AMP is to be calculated by manufacturers participating in the program and implements certain amendments to the Medicaid rebate statute created under the Affordable Care Act, or ACA. More recently,

Congress amended the Medicaid statute, effective October 1, 2019, to exclude prices paid by secondary manufacturers for an authorized generic drug (but not a product approved under the BLA process) from the NDA holder's AMP for the brand, thereby increasing the rebate amount and the 340B price for the brand. This was implemented by CMS in a final rule issued December 31, 2020. The rule also expanded the definition of products identified as "line extensions" and, in certain circumstances, required inclusion of patient copay assistance in Medicaid best price (effective January 1, 2023), thereby potentially increasing Medicaid rebates paid by manufacturers for such drugs. 340B program guidance regulations on civil monetary penalties for statutory violations, which had been finalized in early 2017 but deferred, also recently went into effect. On November 27, 2020, CMS issued an interim final rule implementing a Most Favored Nation payment model under which reimbursement for certain Medicare Part B drugs and biologicals will be based on a price that reflects the lowest per capita Gross Domestic Product-adjusted (GDP-adjusted) price of any non-U.S. member country of the Organisation for Economic Co-operation and Development (OECD) with a GDP per capita that is at least sixty percent of the U.S. GDP per capita. This rule now has been rescinded, but similar programs have been described in recent legislative proposals. These and any additional healthcare reform measures could further constrain our business or limit the amounts that federal and state governments will pay for healthcare products and services, which could result in additional pricing pressures.

Any regulatory approval of a product is limited to specific diseases and indications for which such product has been deemed safe and effective by the FDA. Coverage by federal healthcare programs, however, may be more limited than the indications for which a drug is approved by the FDA or comparable ex-U.S. regulatory authorities' coverage of the same products. Sales of any products for which we may receive regulatory approval for commercial sale will depend in part on the extent to which the costs of the products will be covered and reimbursed by third-party payors, including government healthcare programs (such as, in the United States, Medicare and Medicaid), private health insurers and other organizations. Obtaining reimbursement for orphan drugs may be particularly difficult because of the significant research and development challenges and costs and resulting pricing considerations typically associated with drugs developed to treat conditions that affect a small population of patients. In addition, third-party payors are likely to impose strict requirements for reimbursement in connection with drugs that are perceived as having high costs. Net prices for products may be reduced by mandatory discounts or rebates required by government healthcare programs or private payors.

The process for determining whether a payor will provide coverage for a product may be separate from the process for setting the price or reimbursement rate that the payor will pay for the product once coverage is approved. Third- party payors may limit coverage to specific products on an approved list, or formulary, which might not include all of the approved products for a particular indication. Third-party payors are increasingly challenging the price and examining the cost-effectiveness of medical products and services. We may need to conduct expensive pharmacoeconomic studies in order to demonstrate the cost-effectiveness of our product or product candidates or conduct direct head-to-head studies to demonstrate clinical superiority and cost-effectiveness. Our products and product candidates may not be considered clinically superior and cost-effective to competitor products.

The marketability of any products for which we receive regulatory approval for commercial sale may suffer if the government and other third-party payors fail to provide adequate coverage and reimbursement.

For important information regarding certain pricing and reimbursement matters see "Item 1. Business-Commercial Matters-Market Access Considerations" and "Item 1A. Risk Factors," including the risk factor titled "*Commercialization of Translarna has been in, and is expected to continue to take place in, countries that tend to impose strict price controls, which may adversely affect our revenues. Failure to obtain and maintain acceptable pricing and reimbursement terms for Translarna for the treatment of nmDMD in the EEA and other countries where Translarna is available would delay or prevent us from marketing our product in such regions, which would adversely affect our business, results of operations, and financial condition."*

Freedom of Information Requests and Affirmative Disclosures

We are also subject, in the U.S. and many other countries, to various regulatory schemes that require disclosure of clinical trial data or allow access to our data via freedom of information requests. We have been and may, from time to time, be notified by regulators, such as the EMA or the competent authorities of EU member states that they have received a freedom of information request for documents that they hold relating to our company, including information related to our

product or our product candidates. For example, in 2015, we were notified by the EMA that it had received from another pharmaceutical company a request under Regulation (EC) No 1049/2001 seeking access to aspects of our marketing authorization application for Translarna for the treatment of nmDMD. Following the decision of the EMA to release such documentation with only minimal redactions we initiated litigation before the General Court of the EU to prevent disclosure of this information. In the first quarter of 2018, the Court ruled in favor of the EMA, allowing the EMA to release the documentation. We appealed the General Court's decision to the Court of Justice of the EU, or CJEU, but the CJEU dismissed our appeal in January 2020 and released the information to the requester. In addition, under policies recently adopted in the EU, clinical trial data submitted to the EMA in MAAs that were traditionally regarded as confidential commercial information is now subject to automatic public disclosure. Further, under the Clinical Trials Regulation 536/2014, the sponsor of an EU trial must submit a summary of the results to an EU database within a year of the end of the trial. In addition, where the trial was intended to be used for obtaining a marketing authorization the applicant must submit the clinical study report 30 days after MA has been granted, refused or withdrawn. Subject to our limited ability to review and redact a narrow sub-set of confidential commercial information, these new EU policies will result in the EMA's public disclosure of certain of our clinical study reports, clinical trial data summaries and clinical overviews for recently completed and future MAA submissions. The move toward public disclosure of development data could adversely affect our business in many ways, including, for example, resulting in the disclosure of our confidential methodologies for development of our products, preventing us from obtaining intellectual property right protection for innovations, requiring us to allocate significant resources to prevent other companies from violating our intellectual property rights, adding even more complexity to processing health data from clinical trials consistent with applicable data privacy regulations, and enabling competitors to use our data to gain approvals for their own products.

Fraud and Abuse Laws

Any present or future arrangements or interactions with third-party payors, healthcare providers and professionals, hospital and healthcare organizations, patients and customers may expose us to broadly applicable fraud and abuse and other healthcare laws and regulations that may restrict certain marketing and contracting practices. These laws include, and are not limited to, anti-kickback and false claims statutes.

Both the federal Foreign Corrupt Practices Act, or FCPA, and the UK Bribery Act of 2010, or Bribery Act are broad in scope and will require companies to make and keep books and records that accurately and fairly reflect the transactions of the company and to devise and maintain an adequate system of internal accounting controls. The FCPA prohibits the offering, promising, giving, or authorizing others to give anything of value, either directly or indirectly, to a non-U.S. government official, political party or candidate for public office in order to improperly influence any act or decision, secure any other improper advantage, or obtain or retain business. The FCPA also prohibits any U.S. person from corruptly acting outside the U.S. in furtherance of such offer, promise or payment. Under the UK Bribery Act, companies which carry on a business or part of a business in the United Kingdom may be held liable for bribes given, offered or promised to any person, including non-UK government officials and private persons, by employees and persons associated with the company in order to obtain or retain business or a business advantage for the company. Similar statutes have been adopted, or may be adopted in the future, by other countries in which we operate and with which we are or may be required to comply.

The federal Anti-Kickback Statute prohibits, among other things, knowingly and willfully offering, paying, soliciting or receiving remuneration, directly or indirectly, in cash or kind, to induce or reward either the referral of an individual for, or the purchase, or order or recommendation of, any good or service, for which payment may be made in whole or in part under federal and state healthcare programs such as Medicare and Medicaid. This statute imposes criminal penalties and has been broadly interpreted to apply to manufacturer arrangements with prescribers, purchasers and formulary managers, among others. Although a number of statutory exemptions and regulatory safe harbors exist to protect certain common activities from prosecution, the exemptions and safe harbors for this statute are narrow, and practices that involve compensation intended to induce prescriptions, purchases, or recommendations may be subject to scrutiny if they do not qualify for an exemption or safe harbor. HHS recently promulgated a regulation that is effective in two phases. First, the regulation excludes from the definition of "remuneration" limited categories of (a) PBM rebates or other reductions in price to a plan sponsor under Medicare Part D or a Medicaid Managed Care Organization plan reflected in point-of sale reductions in price and (b) PBM service fees. Second, the regulation expressly provides that rebates to plan sponsors under Medicare Part D either directly to the plan sponsor under Medicare Part D, or indirectly through a pharmacy benefit

manager will not be protected under the anti-kickback discount safe harbor. Recent legislation delayed implementation of this portion of the rule until January 1, 2026, and further proposed legislation would permanently prohibit implementation of the rule beginning in 2026. Our practices may not always meet all of the criteria for safe harbor protection. A person or entity need not have knowledge of the statutes or the specific intent to violate it in order to have committed a violation. In addition, the government may assert that a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the federal civil False Claims Act. Many states have adopted laws similar to the federal Anti-Kickback Statute, which apply to items and services reimbursed under Medicaid and other state programs; furthermore, in several states, these statutes and regulations apply regardless of the payor. Sanctions under these federal and state laws may include civil monetary penalties, exclusion of a manufacturer and its products from participation in federal healthcare programs, debarment from federal government procurement and non-procurement programs, criminal fines, and imprisonment. Several other countries, including the United Kingdom, have enacted similar anti-kickback, fraud and abuse laws and regulations.

The federal civil False Claims Act imposes civil liability and penalties on individuals or entities for knowingly presenting, or causing to be presented, to the federal government, claims for payment that are false or fraudulent, knowingly making, using, or causing to be made or use a false record or statement material to a false or fraudulent claim, or making a false statement to avoid, decrease or conceal an obligation to pay money to the federal government. Claims under the federal civil False Claims Act may be initiated by whistleblowers, who receive substantial financial incentives to come forward, through qui tam actions and pursued even if the government declines to intervene. Intent to deceive is not necessary to establish civil liability, which may be predicated on deliberate indifference or reckless disregard for the truth. The federal government continues to use the False Claims Act, and the accompanying threat of significant liability, in investigations against pharmaceutical and healthcare companies. These investigations have involved, for example, allegations of improper financial relationships with referral sources, providing free product to customers with the expectation that the customers would bill federal programs for the free product, as well as the promotion of products for unapproved uses and reporting false pricing information. A violation of the federal Anti-Kickback Statute is a per se violation of civil False Claims Act. Potential liability under the federal civil False Claims Act includes treble damages and significant per claim penalties. The criminal federal False Claims Act imposes criminal fines or imprisonment against individuals or entities who make or present a claim to the government knowing such claim to be false, fictitious or fraudulent. Conviction or civil judgment for violation of the False Claims Act can also result in debarment from federal government procurement and non-procurement programs and exclusion from participation in federal healthcare programs. The majority of states also have statutes or regulations similar to the federal False Claims Act, which apply to items and services reimbursed under Medicaid and other state programs.

The Affordable Care Act authorized the imposition of civil monetary penalties on manufactures participating in the 340B program for failure to charge the statutory ceiling price, and required HHS to promulgate regulations establishing the standards for implementing this Civil Monetary Penalty, or CMP, authority. CMS' final CMP rule went into effect January 1, 2019.

The Affordable Care Act included a provision requiring certain providers and suppliers of items and services to federal healthcare programs to report and return overpayments within sixty days after they are "identified" (the "Overpayment Statute"), after which the recipient of the overpayment incurs federal civil False Claims Act liability. The law prohibits a recipient of a payment from the government from keeping an overpayment when the government mistakenly pays more than the amount to which the recipient is entitled even if the overpayment is not caused by any conduct of the recipient. In 2014 and 2016, the CMS released regulatory guidance (in the form of final rules) to Medicare providers, suppliers and managed care and prescription drug plans regarding how to comply with the Overpayment Statute. Although these Medicare providers, suppliers and plans have faced federal False Claims Act liability since 2010 for failures to comply with the Overpayment Statute, these final rules interpreting the Overpayment Statute provide guidance regarding how to comply with applicable obligations, and guidance to government regulators and enforcement authorities regarding monitoring and prosecuting suspected violations. These final rules are not directly applicable to manufacturers, except if a manufacturer is a direct recipient of payment by an agency such as a research grant but may impact their customers and potential customers who are Medicare providers, suppliers, and plans.

The federal Physician Payments Sunshine Act, enacted as part of the Affordable Care Act, and its implementing regulations, require manufacturers of drugs, devices, biologics and medical supplies for which payment is available under

Medicare, Medicaid, or the Children's Health Insurance Program (with certain exceptions) to report annually to CMS information related to certain payments and other transfers of value made to or at the request of covered recipients, such as, but not limited to, physicians, physician assistants, nurse practitioners, clinical nurse specialists, certified registered nurse anesthetists and certified nurse midwives licensed in the United States and to teaching hospitals, as well as ownership and investment interests held by physicians and their immediate family. Payments made to physicians, other principal investigators and certain research institutions for research, including clinical trials are included within the ambit of this law. Such information is made publicly available by CMS in a searchable format, with data collected in each calendar year published the following June. Failure to submit required information may result in civil monetary penalties, with increased penalties for "knowing failures," for each payment, transfer of value or ownership or investment interest not timely and accurately reported in an annual submission. If not preempted by this federal law, several states currently require pharmaceutical companies to report expenses relating to the marketing and promotion of pharmaceutical products and to report gifts and payments to healthcare professionals in those states. Depending on the state, legislation may prohibit various other marketing related activities, such as gift bans, or require the posting of information relating to clinical studies and their outcomes. In addition, certain states, such as California, Nevada, Connecticut and Massachusetts, require pharmaceutical companies to implement compliance programs or marketing codes and several other states are considering similar proposals. Manufacturers that fail to comply with these state laws can face civil penalties.

Statutory requirements to disclose publicly payments made to healthcare professionals and healthcare organizations have also been enacted in certain European Union member states. In addition, self-regulatory bodies of the pharmaceuticals industry, such as the European Federation of Pharmaceutical Industries and Associations, or EFPIA, have published codes of conduct to which its members have agreed to abide, that require the public disclosure of payments made to healthcare professionals and healthcare organizations. In some countries (including France, Denmark and Portugal) such requirements are enforceable by law.

The federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, also created federal criminal statutes that prohibit, among other actions, knowingly and willfully executing, or attempting to execute, a scheme to defraud or to obtain, by means of false or fraudulent pretenses, representations or promises, any of the money or property owned by, or under the custody or control of, a healthcare benefit program, regardless of whether the payor is public or private, in connection with the delivery of, or payment for, healthcare benefits, knowingly and willfully embezzling or stealing from a healthcare benefit program, willfully obstructing a criminal investigation of a healthcare offense and knowingly and willfully falsifying, concealing, or covering up by any trick or device a material fact or making any materially false statements in connection with the delivery of, or payment for, healthcare benefits, items, or services relating to healthcare matters. Additionally, the Affordable Care Act amended the intent requirement of certain of these criminal statutes under HIPAA so that a person or entity no longer needs to have actual knowledge of the statute, or the specific intent to violate it, to have committed a violation. HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act of 2009, or HITECH Act, and similar state laws also impose obligations on certain entities with respect to safeguarding the privacy, security and transmission of individually identifiable health information, known as protected health information. Among other things, the HITECH Act and its implementing regulations make HIPAA's security and certain privacy standards directly applicable to "business associates," defined as persons or organizations of covered entities, other than members of the covered entity's workforce, that create, receive, maintain or transmit protected health information on behalf of a covered entity for a function or activity regulated by HIPAA. The HITECH Act also strengthened the civil and criminal penalties that may be imposed against covered entities, business associates and individuals, and gave state attorneys general new authority to file civil actions for damages or injunctions in federal courts to enforce the federal HIPAA laws and seek attorneys' fees and costs associated with pursuing federal civil actions. In addition, other federal and state laws, such as the California Consumer Privacy Act, may regulate the privacy and security of information that we maintain, many of which may differ from each other in significant ways and may not be preempted by HIPAA.

Outside of the U.S., additional privacy and data protection laws may apply to our operations. For example, the European General Data Protection Regulation, or GDPR, United Kingdom's implementation of the GDPR and equivalent Swiss legislation may apply to some or all of the clinical or other protected data obtained, transmitted, or stored from those territories. These laws require specific, freely given and fully informed consent to be obtained from patients or clinical study participants. There are also other requirements for lawful processing, including transparency obligations, data minimization requirements, data transfer restrictions and compliance obligations with individuals' stringent rights to

access their personal data and to otherwise control the processing of their personal data. There are data breach notification obligations, to supervisory authorities and to individuals, where there are potential risks to them arising from the data breach. These laws impose high regulatory fines in the event of breach of processing requirements of up to 4% of global annual turnover or EUR 20 million (whichever is the higher amount). The European, UK and Swiss legislation only permits data export to countries where there is adequate protection or where other controls are in place such as data export agreements. In July 2020, the European Court declared the EU-US data 'Privacy Shield' invalid meaning that data transfers to the United States require other guarantees such as standard contractual clauses. Further certain privacy laws and genetic testing laws may apply directly to our operations and/or those of our collaborators and may impose restrictions on our use and dissemination of individuals' health information.

Any continuing efforts to modify, repeal, or otherwise invalidate all, or certain provisions of, the Affordable Care Act, could have an impact on fraud and abuse provisions and other requirements, including the Physician Payments Sunshine Act, that were authorized and enacted under the Affordable Care Act.

The foregoing discussion should be read in conjunction with the information appearing under "Item 1A. Risk Factors-*Our relationships with customers, healthcare providers and professionals, patients, patient organizations, and third-party payors are or will be subject to applicable anti-kickback, fraud and abuse, transparency and other healthcare laws and regulations, which could expose us to criminal sanctions, civil penalties, contractual damages, reputational harm and diminished profits and future earnings."* which contains important information regarding some of the risks to our business arising as a result fraud and abuse laws.

Human Capital Resources

As of December 31, 2021, we had 1,177 employees, of whom 1,167 were employed on a full-time basis, and 96 consultants and contractors, of whom 85 were full-time. None of our U.S. based employees are represented by labor unions or covered by collective bargaining agreements, although certain international employees are covered by collective labor agreements established under local law. We consider our relationship with our employees to be good.

We believe that our growth and success is dependent on the contributions of our employees, as led by our executive officers. We focus significant attention on attracting, retaining, engaging and further developing talented and experienced individuals to manage and support our operations. In particular, recruiting and retaining qualified scientific, clinical, manufacturing, commercial, marketing and support personnel is critical to our success. Competition for these skilled personnel is high. We believe that our strong culture of teamwork and desire to be ever better helps us to attract and retain employees. To continue to build upon our culture, we have partnered with Gallup, Inc., or Gallup, a global analytics and advice firm with approximately 35 million respondents within its employee engagement database, to conduct employee engagement surveys from time to time. Our executive team reviews these Gallup employee engagement surveys to monitor employees' needs, individual contribution, teamwork and growth. Results allow target action plans to be created if needed. Our employees also complete Gallup's CliftonStrengths talent assessment and attend related training sessions. These tools have been implemented to help our employees identify their core strengths and learn how to use these strengths to become more engaged and productive at work as well as to lead an overall more satisfied and healthier lifestyle. In 2021, we received the Don Clifton Strength-Based Culture Award, an award granted by Gallup to recognize organizations with workplace cultures that put the strengths of leaders, managers and employees at the core of how they work every day.

Based on external benchmarks, we offer employees a number of additional resources and tools to help in their personal and professional development, including career coaching, targeted leadership development for identified current and emerging leaders, internal and external development programs, professional assessment tools, a paid subscription to a digital on-demand career and management learning solutions platform and a wellness website through which employees may access information regarding scheduled healthy lifestyle activities, articles and other beneficial resources. To help newly hired employees, our global onboarding team conducts monthly surveys and focus groups and each newly hired employee is paired with a "buddy" to assist in their transition. Additionally, we require specialized leadership training for all employees that are responsible for the management of others within our organization. Our executive team routinely reviews employee turnover throughout the organization to monitor employee satisfaction.

We believe that we provide a competitive total rewards offering to our employees, with market competitive cash compensation, equity, and industry competitive company-paid benefits, including subsidized medical, and dental insurance and retirement plans, as well as group vision insurance, tuition reimbursement, fitness reimbursement and benefits and policies to support parental leave, family planning and child bonding. Total rewards offerings are established by employee positions, skill levels, experience, knowledge, and geographic location. In addition, to assist our employees during times of personal disasters that impact them and their families, we have established an employee relief program that is funded by our employees with corporate matches.

We are committed to hiring, developing and supporting a diverse and inclusive workplace, and continue to focus on extending our equality, diversity and inclusion initiatives across our workforce. All of our employees are required to adhere to our Code of Business Conduct and Ethics, and all relevant country regulations which sets forth the high level of integrity, legal compliance and patient-centric focus expected of all our employees. We have a Chief Culture and Community Officer who is responsible for maintaining and building upon our culture, ensuring a strong and engaged workforce, and organizing outreach to our external communities. A core element of these responsibilities includes overseeing an equality, diversity and inclusion, or ED&I, program which is managed by an ED&I professional, who routinely meets with our executive committee. Our ED&I program uses awareness and education, talent development, employee resource groups and targeted focus groups with employees to present the opinions of our employees at all levels to our executive team. In addition, we completed our inaugural global Talent Pipeline Program, or the TPP, which was originally established in 2020 to benefit students that graduated during the COVID-19 pandemic, and in January 2022, we announced the launch of our 2022 TPP. The TPP is a one-year global fellowship program aimed at providing recent diverse graduates real-world experience in the biopharmaceutical industry and related professions, including research, clinical, finance, commercial, marketing, compliance, quality, legal, information technology, human resources, government affairs, and communications. Participants are recruited form a global diverse group of institutions and networks and are provided mentorship, job coaching, career counseling, and leadership training.

In response to the continued COVID-19 pandemic and related mitigation efforts, we have maintained a COVID-19 task force, which consists of senior leaders from various departments within our organization and is responsible for the safety of our employees, consultants and contractors throughout the world and for the maintenance of our business continuity. Our COVID-19 task force continues to monitor and evaluate safety protocols and procedures to protect our workers as well as business essential operations. Our COVID-19 task force periodically provides updates to our executive team and our board of directors and provides timely communications to our employees. We have encouraged and, where possible, required all employees to be fully vaccinated against COVID-19.

Our Corporate Information

Our principal executive offices are located at 100 Corporate Court, South Plainfield, New Jersey 07080. Our telephone number is (908) 222-7000. We maintain a website at www.ptcbio.com.

Additional Information

We make available, free of charge on our website, www.ptcbio.com, our annual reports on Form 10-K, quarterly reports on Form 10-Q, current reports on Form 8-K, and all amendments to those reports filed or furnished pursuant to Section 13(a) or 15(d) of the Securities Exchange Act of 1934, as amended, or the Exchange Act, as soon as reasonably practicable after we electronically file those reports with, or furnish them to, the Securities and Exchange Commission, or SEC. We also make available, free of charge on our website, the reports filed with the SEC by our executive officers, directors and 10% stockholders pursuant to Section 16 under the Exchange Act as soon as reasonably practicable after copies of those filings are provided to us by those persons. Such reports, proxy statements and other information may be obtained through the SEC's website (www.sec.gov). The information contained on, or that can be accessed through, our website is not a part of or incorporated by reference in this Annual Report on Form 10-K.

Item 1A. Risk Factors

The following risk factors and other information included in this Annual Report on Form 10-K should be carefully considered. The risks and uncertainties described below are not the only ones we face. Additional risks and uncertainties

not presently known to us or that we presently deem less significant may also impair our business operations. Please see page 1 of this Annual Report on Form 10-K for a discussion of some of the forward-looking statements that are qualified by these risk factors. If any of the following risks occur, our business, financial condition, results of operations and future growth prospects could be materially and adversely affected.

Risks Related to the COVID-19 Pandemic

We face risks related to health epidemics and other widespread outbreaks of contagious disease, which are, and may continue to, delay our ability to complete our ongoing clinical trials and initiate future clinical trials, disrupt regulatory activities and have other adverse effects on our business and operations, including the novel coronavirus (COVID-19) pandemic, which has disrupted, and may continue to disrupt, our operations and may significantly impact our operating results. In addition, the COVID-19 pandemic has caused substantial disruption in the financial markets and economies, which could result in adverse effects on our business and operations.

Significant outbreaks of contagious diseases, and other adverse public health developments, could have a material impact on our business operations and operating results. In December 2019, a strain of novel coronavirus, COVID-19, causing respiratory illness emerged in the city of Wuhan in the Hubei province of China. Since that time, multiple other countries throughout the world, including the United States, have been affected by the spread of the virus. To date, responsive measures such as social distancing, vaccine mandates, travel bans and quarantines have been put into place in many countries throughout the world, including the United States. These responsive measures have had a significant impact, both direct and indirect, on business and commerce worldwide, as worker shortages have occurred, supply chains have been disrupted and facilities and production have been suspended or curtailed.

The spread of COVID-19 and the responsive measures taken to date have limited our access to our facilities, the access of trial participants to clinical sites and caused the majority of our employees to work from home. We continue to monitor the global spread and response of international, national and local authorities of COVID-19 and have put in place and will continue to put in place measures as appropriate and necessary for our business and the safety of our employees. While we expect the pandemic to continue to have an adverse effect on our business and operations, and the pandemic may have an adverse effect on our financial condition and results of operations, we are unable to predict the extent or nature of the future progression of the COVID-19 pandemic or its effects on our business, operations, financial condition and results of operations at this time.

Furthermore, we have clinical trial sites located in countries that have been affected by COVID-19 that have been and may continue to be disrupted, including the United States. The disruption of our clinical trial sites has had an adverse impact on our clinical trial plans and timelines. The COVID-19 pandemic has also adversely affected our ability to timely enroll patients for our clinical trials which may delay the completion of clinical trials. For example, we have experienced delays in enrolling our registration-directed Phase 2/3 randomized, placebo-controlled trial of vatiquinone in children with mitochondrial disease associated seizures as some patients have been unable or hesitant to travel to clinical trial sites due to the COVID-19 pandemic and we now anticipate results from this trial to be available in the fourth quarter of 2022. Such disruptions could result in significant delays or could require us to abandon a clinical trial altogether. For additional information, see the risk factor under "Risks Related to the Development and Commercialization of our Products and our Product Candidates" titled, *"If we experience delays or difficulties in the enrollment of patients in our clinical trials, our receipt of necessary regulatory approvals could be delayed or prevented."*

Our ability to market and promote our products, as well as patient demand for our products may also be impacted. Because access to healthcare providers and institutions has been limited in certain regions of the world, we have had to transition to virtual and online promotion to reach existing and potential customers in those areas. Healthcare provider and institution restrictions and closures, as well as patient reticence to visit their physicians may also result in a decrease in product prescribing.

Significant suppliers and manufacturing located in countries that have been affected by COVID-19 may also be disrupted, which may affect our ability to procure items that are essential for our research and development activities and may cause disruptions or delays in our sales and commercialization efforts of approved products and clinical trials with respect to product candidates. For example, in response to the COVID-19 pandemic, China has at times imposed complete lockdowns

of cities that have experienced a high number of COVID-19 cases. We contract with third-party manufacturers located in China that may be forced to shut down for an unknown amount of time if the Chinese government determines that there is a COVID-19 outbreak where they are located. Additionally, we have experienced delays in certain of our preclinical programs due to a shortage in non-human primates. Many manufacturers have also experienced shortages of key equipment and ingredients needed for product manufacturing. Our business and operations may be disrupted as resources, components and materials that are essential for our research and development, commercialization and manufacturing activities may be diverted towards the ongoing efforts to rapidly diagnose, find and distribute treatments or vaccines for COVID-19 and may not be readily available. The response to the COVID-19 pandemic may also redirect resources with respect to regulatory matters in a way that would adversely impact our ability to progress to regulatory approval. For instance, certain of the third-party development and manufacturing organizations that we contract with for analytical testing had previously prioritized materials and testing kits to support COVID-19 testing, diverted employees to support COVID-19 related programs and reduced their workforce to comply with social distancing requirements imposed in connection with the COVID-19 pandemic. As a result of this shift in resources in 2020, we experienced a delay in generating analytical data needed to respond to questions sent by the EMA regarding our MAA for PTC-AADC for the treatment of AADC deficiency in the EEA. Following a clock stop extension, we submitted responses to the EMA's questions. We may also choose to redirect our own resources in a way that may adversely impact or delay certain of our programs. For additional information, see the risk factor under "Risks Related to the Development and Commercialization of our Products and our Product Candidates" titled, *"We contract with third parties for the manufacture and distribution of our products and certain of our product candidates, which may increase the risk that we will not have sufficient quantities of our products or product candidates, such quantities may not meet the applicable regulatory quality standards, or such quantities at an acceptable cost, which could delay, prevent or impair our commercialization or development efforts. For certain of our product candidates, we may also directly engage in manufacturing, which will require significant expenditures and compliance with FDA's manufacturing requirements."*

Furthermore, we may face impediments to regulatory meetings and approvals due to measures intended to limit in-person interactions. For example, due to delays related to responsive measures to the COVID-19 pandemic taken in Europe, including travel bans and quarantines, the CHMP required additional time to complete its pre-approval inspections and imposed a clock stop extension with respect to our MAA for the treatment of AADC deficiency in the EEA. To the extent that inspections of facilities by governmental authorities are required, the review of our marketing applications or supplements may further be delayed as regulatory authorities, such as FDA, have significantly limited facility inspections during the pandemic.

Our own relationships with commercial customers and suppliers could be affected if the government places rated or allocation orders under the Defense Production Act, directly or through higher tier contractors, either with respect to our products or our partners' supplies or products that may be related to the COVID-19 pandemic. Specifically, the Defense Production Act provides the U.S. President with authority to direct private sector production in, among other circumstances, national emergencies. Once the Defense Production Act is invoked, federal agencies can use it to direct companies to prioritize the sale of goods to the federal government. On March 18, 2020, former U.S. President Donald Trump issued an executive order authorizing use of the Defense Production Act to acquire "health and medical resources needed to respond to the spread of COVID-19." President Biden has also directed that executive agencies consider whether further use of the Defense Production Act is appropriate in support of the COVID-19 response effort. Invocation of the Defense Production Act to prioritize orders can result in diversion of Company products intended for our commercial customers to the government or interfere with our ability to obtain supplies and services necessary to our business.

We cannot foresee if and when the COVID-19 pandemic will be effectively contained, nor can we predict the severity and duration of its impact. If the COVID-19 pandemic is not effectively and timely controlled, we may experience further or prolonged disruption of our clinical trials, third-party suppliers or contract manufacturers, extended closures of facilities, such as clinical trial sites, suppliers, manufacturers and distributors, including single source suppliers, and further delays with respect to regulatory approvals or the commercialization of any current or future products. Such events may materially and adversely affect our business operations and financial condition. Additionally, the COVID-19 pandemic has caused significant disruptions in the financial markets, and may continue to cause such disruptions, which could impact our ability to raise additional funds and has also impacted, and may continue to impact, the volatility of our stock price and trading in our stock. Moreover, the COVID-19 pandemic has significantly impacted economies worldwide, which could result in adverse effects on our business and operations. We cannot be certain what the overall impact of the COVID-19 pandemic

will be on our business and it has the potential to materially adversely affect our business, financial condition, results of operations, and prospects.

Risks Related to Our Gene Therapy Platform

We may fail to obtain regulatory approval for PTC-AADC for the treatment of AADC deficiency within our expected timeline or at all.

In July 2017, an end-of-phase 2 meeting was held with the United States Food and Drug Administration, or FDA, and the clinical data from two completed PTC-AADC clinical trials, and non-clinical and manufacturing data available to date were reviewed. The FDA provided feedback indicating that the clinical and non-clinical data available to date were sufficient to support a submission for a biologics license application, or BLA, without undertaking additional trials at this time. In late 2019, the FDA requested additional information concerning the use of the commercial delivery system for PTC-AADC in young patients. Based on the FDA input, including with respect to manufacturing, we are preparing a BLA for PTC-AADC for the treatment of AADC deficiency in the United States, which we anticipate submitting to the FDA in the second quarter of 2022. In April 2018, Agilis held a protocol assistance meeting with the Scientific Advice Working Party of the European Medicines Agency, or EMA, in anticipation of the expected submission of a Marketing Authorization Application, or MAA, in the European Union, or EU and received feedback indicating the clinical and non-clinical data available to date were sufficient to support a submission for an MAA without undertaking additional trials or studies at this time. In January 2020, we submitted an MAA to the EMA for PTC-AADC for the treatment of AADC deficiency in the EEA. However, certain of the third-party development and manufacturing organizations that we contract with for analytical testing have prioritized materials and testing kits to support COVID-19 testing, diverted employees to support COVID-19 related programs and reduced their workforce to comply with social distancing requirements imposed in connection with the COVID-19 pandemic. As a result of this shift in resources, we experienced a delay in generating analytical data needed to respond to questions sent by the EMA regarding our MAA for PTC-AADC for the treatment of AADC deficiency. Following a clock stop extension, we submitted responses to the EMA's questions. Subsequently, due to delays related to responsive measures to the COVID-19 pandemic taken in Europe, including travel bans and quarantines, the CHMP required additional time to complete its pre-approval inspections and imposed a clock stop extension with respect to our MAA for the treatment of AADC deficiency in the EEA. We expect an opinion from the CHMP in April 2022. There is no guarantee that we will be able to make our BLA submissions, or respond to the EMA's additional data requests in support of our manufacturing process, within our expected timelines or that the FDA, upon making our BLA submission, or the EMA would not have additional comments or requirements with respect to the respective submissions that we would be required to address before such applications would be accepted for regulatory review or before obtaining regulatory approval, or that the FDA or the EMA will approve PTC-AADC for the treatment of AADC deficiency at all. Any delays in obtaining regulatory approval from either the FDA and/or the EMA, or if we never obtain regulatory approval from either the FDA and/or the EMA, could have a material adverse effect on our business, financial condition and results of operations.

Gene therapies are novel, complex and difficult to manufacture. We could experience manufacturing problems that result in delays in the development or commercialization of our gene therapy product candidates or otherwise harm our business.

The manufacture of gene therapy products and our other gene therapy product candidates, such as PTC-AADC, is technically complex and necessitates substantial expertise and capital investment. Production difficulties caused by unforeseen events, including the COVID-19 pandemic, may delay the availability of material for clinical studies and commercial product for any of our gene therapy product candidates that may receive regulatory approval in the future. We presently contract a third party manufacturer to provide sufficient quantities of our PTC-AADC program materials to meet anticipated clinical trial and commercial scale demands. In 2021, we began cGMP manufacturing of clinical material at the Hopewell Facility for certain of our gene therapy product candidates other than PTC-AADC. We still rely on third-party manufacturers to complete product testing for all of our gene therapy product candidates that we manufacture at the Hopewell Facility as well as to provide sufficient quantities of certain program materials that we have not yet transitioned to the Hopewell Facility. To the extent we rely on contract manufacturers, we have personnel with manufacturing and quality experience to oversee our contract manufacturers.

To meet our projected needs for commercial manufacturing, we or the third party from whom we currently obtain our commercial supply of PTC-AADC may need to increase the scale of production and confirm with the applicable regulatory authorities that the commercial material is comparable to the material used in clinical trials in addition to satisfying other regulatory obligations, or we will need to secure alternate suppliers. In general, gene therapy products have only in limited cases been manufactured at scales sufficient for pivotal trials and commercialization. Few pharmaceutical contract manufacturers specialize in gene therapy products and those that do are still developing appropriate processes, controls and facilities for large-scale production. While we believe that there are alternate sources of supply that can satisfy our clinical and commercial requirements, we cannot be certain that we will be able to identify and establish relationships with such sources, if necessary, in a timely manner or at all, and what the terms and costs of such new arrangements would be, or that such alternate suppliers would be able to supply our potential commercial needs. To the extent that we decide to manufacture our own clinical and commercial supply as an alternative source of supply, there is no guarantee that we will be able to cost-effectively produce sufficient quantities of our program materials. Any switch from our current manufacturer would result in a significant delay, would require FDA approval, and cause material additional costs.

As further described in these risks, the manufacturers of pharmaceutical products must comply with strictly enforced cGMP requirements, state and federal regulations, as well as ex-U.S. requirements when applicable. Any failure by us or our contract manufacturing organizations to adhere to or document compliance to such regulatory requirements could lead to a delay or interruption in the availability of our program materials for clinical studies or commercial use, among other consequences. If we or our manufacturers fail to comply with the requirements set forth by the FDA, EMA, or other regulatory authorities, it could result in sanctions being imposed on us, including fines, injunctions, civil penalties, delays, suspension or withdrawal of approvals, clinical holds or termination of clinical studies, warning or untitled letters, regulatory communications warning the public about safety issues with a product, import or export refusals, license revocation, seizures, detentions, or recalls of product candidates or product, operating restrictions, criminal prosecutions or debarment, suits under the civil False Claims act, corporate integrity agreements, or consent decrees any of which could significantly and adversely affect supplies of our product candidates and our business, results of operations and financial condition could be materially adversely affected.

Due to the potential impact of the COVID-19 pandemic on the manufacture of gene therapy products, the FDA issued guidance concerning how sponsors and investigators may address these challenges. This included recommendations regarding the conduct of risk assessments to identify, evaluate, and mitigate factors that may allow for the transmission of the COVID-19 virus by gene therapy products.

Any dependence upon others for the manufacture of our product candidates may also adversely affect our business, results of operations, financial condition and prospects, and our ability to commercialize any product candidates that receive regulatory approval on a timely and competitive basis.

We have limited experience manufacturing gene therapy products or product candidates on our own and could encounter problems and delays in operating our biologics manufacturing facility that could adversely affect our business.

In 2021, we began cGMP manufacturing of clinical material at the Hopewell Facility for certain of our gene therapy product candidates other than PTC-AADC. The Hopewell Facility requires substantial investment and significant expertise, and our management devotes substantial time to its operation. While some of our employees have experience with gene therapy manufacturing, we have previously never manufactured gene therapy product materials as a company and we may encounter unforeseen delays, equipment failure, labor shortages, natural disasters, power failures, transportation difficulties, quality control or other issues, including those resulting from compliance with regulatory requirements, as further described in these risks, that could prevent us from realizing the intended benefits of our manufacturing strategy. In addition, competition for skilled personnel within gene therapy manufacturing is intense and we may not be able to attract and retain these personnel on acceptable terms. Moreover, operating a manufacturing facility may cost more than we currently anticipate. If we experience any problems or delays with the Hopewell Facility, we may need to rely on contract manufacturers for the manufacturing of program materials that we intended to produce ourselves, which may cause additional timing delays due to the availability of contract manufacturers, and our business, financial condition and results of operations could be materially and adversely affected. We presently contract a third party

manufacturer to provide sufficient quantities of our PTC-AADC program materials to meet anticipated clinical trial and commercial scale demands.

Additionally, while we expect to use the Hopewell Facility in the production of research and cGMP quality plasmid DNA and AAV vectors for gene therapy applications for potential external customers, we have never produced gene therapy product materials for third parties and we have yet to manufacture cGMP gene therapy product materials for our own clinical trials or commercialization. If we are unable to manufacture these product materials to the required specifications for the third parties we contract with, our business, financial condition, and results of operations could be materially adversely affected and we may become subject to regulatory actions. Similarly, if we experience a reduced product yield for our manufactured materials, due to manufacturing issues or otherwise, we may expend significant time and cost to remedy these issues and we may be delayed in our ability to supply product materials to our customers in an efficient manner, all of which could cause us to forgo sales, incur liabilities or lose customers, and materially adversely affect our business, financial condition and results of operations. Furthermore, we may be unable to identify and retain potential customers and we may encounter unforeseen delays that could prevent us from realizing the intended benefits of our third party manufacturing business. For additional information, see the risk factor under "Risks Related to Our Business" titled, "*We contract with third parties for the manufacture and distribution of our products and certain of our product candidates, which may increase the risk that we will not have sufficient quantities of our products or product candidates, such quantities may not meet the applicable regulatory quality standards, or such quantities at an acceptable cost, which could delay, prevent or impair our commercialization or development efforts. For certain of our product candidates, we may also directly engage in manufacturing, which will require significant expenditures and compliance with FDA's manufacturing requirements.*"

The process for administering PTC-AADC is complex and includes specific specialized requirements that could delay or prevent the regulatory approval of PTC-AADC for the treatment of AADC deficiency, limit its commercial potential or result in significant negative consequences following any potential marketing approval.

PTC-AADC is administered directly to the putamen in the brain using stereotactic surgery, a brain surgery requiring significant skill and training. There is little experience with such surgeries being used to deliver drugs and for such surgeries being performed on children. Delivery of PTC-AADC to the putamen also requires certain medical devices, which may result in our product candidate being deemed to be a combination product by FDA. This would potentially require additional development work and collaboration with medical device manufacturers, which may delay the submission of product candidate marketing applications and approval. It may also require compliance with certain of the FDA's medical device regulations. If we are unable to engage with and train sufficient brain surgeons to perform the procedure properly, the availability of PTC-AADC for the treatment of AADC deficiency could be substantially diminished. The need to train brain surgeons to perform the procedures may also expose us to additional regulatory risks as our interactions with such healthcare providers must comply with all applicable laws and regulations. For example, if PTC-AADC receives approval in the United States, such interactions would need to comply with FDA's laws and regulations on product promotion, as well as laws and regulations related to healthcare fraud and abuse. As a result, we will need to invest significant resources to ensure all personnel and contractors are adequately trained on these requirements and to monitor their conduct.

Any contamination in our manufacturing process, shortages of raw materials or failure of any of our key suppliers to deliver necessary components could result in delays in our clinical development or marketing schedules and adversely affect our ability to meet our supply obligations.

Given the nature of biologics manufacturing, there is a risk of contamination. Any contamination could materially adversely affect our ability to produce our gene therapy product candidates on schedule and could, therefore, harm our results of operations and cause reputational damage.

Some of the raw materials and other components required in our manufacturing process are derived from diverse biologic sources. Such raw materials are difficult to procure and may be subject to contamination or recall. A material shortage, supply chain disruption, including disruptions caused by the COVID-19 pandemic, contamination, recall or restriction on the use of biologically derived substances in the manufacture of our product candidates could adversely impact or disrupt the production of clinical material, which could materially and adversely affect our development and commercialization

timelines, including with respect to PTC-AADC for the treatment of AADC deficiency, and our business, financial condition and results of operations.

Regulatory requirements governing gene therapy products have changed frequently and may continue to change in the future. Such requirements may lengthen the regulatory review process, require us to perform additional studies, and increase our development costs, or may force us to delay, limit, or terminate certain of our programs.

We may experience development problems related to our gene therapy programs that cause significant delays, changes in plans or unanticipated costs, or that cannot be solved. Although numerous companies are currently advancing gene therapy product candidates through clinical trials, to date, the FDA has only approved a limited number of gene therapy treatments, including vector-based gene therapies. In addition, there are also only limited gene therapy products for genetic diseases approved to date in the EU**.** As a result, it is difficult to determine how long it will take or how much it will cost to obtain regulatory approvals for PTC-AADC for the treatment of AADC deficiency or our other gene therapy product candidates in any jurisdiction, if at all. Regulatory requirements governing gene therapy products are still evolving and may continue to change in the future. For example, the FDA has issued a number of guidance documents on human gene therapy development. The FDA will likely continue to issue new guidance and replace existing guidance. The European Commission may also issue new guidelines concerning the development and marketing authorization for gene therapy medicinal products and require that we comply with these new guidelines. Regulatory review agencies and the new requirements and guidelines they promulgate may lengthen the regulatory review process, require us to perform additional or larger studies, increase our development costs, lead to changes in regulatory positions and interpretations, delay or prevent approval and commercialization of our product candidates or lead to significant post-approval studies, limitations or restrictions. Moreover, while there are significant risks that accompany all development programs, because gene therapy products are a relatively new development, less is known about such products and product candidates. Accordingly, there is an increased risk that such products and product candidates may not perform in clinical or preclinical trials as we expect. Additionally, because gene therapy products are complex, the manufacture of such products and product candidates is more difficult and costly. We may not be able to reliably manufacture such products in accordance with the applicable regulatory requirements in sufficient quantities to support our development programs and, if ultimately approved, commercial supply. Delay, failure or unexpected costs in obtaining, the regulatory approval necessary to bring our product candidates to market, as well as manufacturing difficulties or challenges, could have a material adverse effect on our business, results of operations, financial condition and prospects. Even if we do obtain regulatory approval, ethical, social and legal concerns about gene therapy arising in the future could result in additional regulations restricting or prohibiting sale of our products.

In addition, the clinical trial requirements of the FDA, the EMA and other regulatory authorities and the criteria these regulators use to determine the safety and efficacy of a product candidate vary substantially according to the type, complexity, novelty and intended use and market of such product candidates. The regulatory approval process for novel product candidates such as ours can be more expensive and take longer than for other, better known or more extensively studied product candidates.

The FDA has established the Office of Tissues and Advanced Therapies within the Center for Biologics Evaluation and Research, or CBER, to consolidate the review of gene therapy and related products, and has established the Cellular, Tissue and Gene Therapies Advisory Committee to advise the CBER in its review; other international regulatory agencies have also dedicated personnel and/or offices to review gene therapy programs and products.

These regulatory review committees and advisory groups and any new guidelines they promulgate, as well as any unexpected results or manufacturing difficulties, may lengthen the regulatory review process, require us to perform additional studies, increase our development costs, lead to changes in regulatory positions and interpretations, delay or prevent approval and commercialization of our product candidates or lead to significant post-approval limitations or restrictions. As we advance our gene therapy product candidates, we will be required to consult with these regulatory and advisory groups and comply with applicable laws, regulations and guidelines. If we fail to do so, we may be required to delay or discontinue development of certain of our product candidates. These additional requirements may result in a review and approval process that is longer than we otherwise would have expected.

For our gene therapy product candidates, we may also pursue alternative approval pathways. For instance, in the EU, we may pursue an exceptional circumstances marketing authorization. If a product candidate is eligible for the grant of a marketing authorization under exceptional circumstances, the authorization would be subject to a requirement for the applicant to implement specific procedures, in particular related to notification of the competent authorities of any safety issue. Such exceptional circumstance marketing authorizations are annually reassessed and after five years, the authorization may be renewed under exceptional circumstances for an unlimited period, or the EMA may decide, on justified grounds relating to pharmacovigilance, to proceed with one additional five-year renewal. If any product we have is approved under the exceptional circumstances process, there is no guarantee that we will be able to maintain such approval. Moreover, our product candidates may not be eligible for exceptional circumstances marketing authorization. By example, the product candidate may not fulfill the qualifying criteria or the EMA may determine that the marketing authorization under exceptional circumstances may not be granted because a conditional marketing authorization is more appropriate. Orphan products are further eligible for approval under exceptional circumstances only if the criteria considered for the approval under exceptional circumstances are fulfilled.

Delays as a result of lengthier regulatory approval process and further restrictions on development or the approval of our gene therapy product candidates can be costly and could negatively impact our or our collaborators' ability to complete clinical trials and commercialize our current and future product candidates in a timely manner, if at all, any of which could have a material adverse effect on our business, results of operations, financial condition and prospects.

Our gene therapy product candidates and the process for administering such product candidates may cause undesirable side effects or have other properties that could delay or prevent their regulatory approval, limit their commercial potential or result in significant negative consequences following any potential marketing approval.

The goal of gene therapy is to be able to correct an inborn genetic defect through one-time administration of therapeutic genetic material containing non-defective gene copies. The gene copies are designed to reside permanently in a patient, allowing the patient to produce an essential protein or ribonucleic acid, or RNA, molecule that a healthy person would normally produce. There is a risk, however, that the new gene copies will produce too much or too little of the desired protein or RNA. There is also a risk that production of the desired protein or RNA will increase or decrease over time. Because the treatment is irreversible, there may be challenges in managing side effects, particularly those caused by overproduction. Adverse effects would not be able to be reversed or relieved by stopping dosing and might require us to develop additional clinical safety procedures. Furthermore, because the new gene copies are designed to reside permanently in a patient, there is a risk that they will disrupt other normal biological molecules and processes, including other healthy genes, and we may not learn the nature and magnitude of these side effects until long after clinical trials have been completed. Accordingly, long-term patient and clinical study subject follow up and associated regulatory reporting may be required for gene therapies to assess delayed adverse events.

There have been several significant adverse side effects in gene therapy treatments in the past, including reported cases of leukemia, immune- and complement-mediated responses, and death seen in other trials using other vectors. While new recombinant vectors have been developed to potentially reduce these side effects, gene therapy is still a relatively new approach to disease treatment and additional adverse side effects could develop. Accordingly, depending on the vector that is used, additional manufacturing, clinical, and preclinical testing may be required, as well as additional analyses, assessments, and potential long-term patient and clinical study subject monitoring and sample testing and associated regulatory reporting. There also is the potential risk of delayed adverse events following exposure to gene therapy products due to persistent biologic activity of the genetic material or other components of products used to carry the genetic material.

Possible adverse side effects that could occur with treatment with gene therapy products include an immunologic or complement-mediated reactions early after administration which, while not necessarily adverse to the patient's health, could substantially limit the effectiveness of the treatment.

In addition to any potential side effects caused by any gene therapy product candidate, the administration process or related procedures also can cause adverse side effects. If any such adverse events occur, our clinical trials could be suspended, modified, or terminated or we may be required to interrupt or cease commercial sales of any product candidates that may receive regulatory approval. If in the future we are unable to demonstrate that such adverse events were caused by the administration process or related procedures, the FDA, the European Commission, the EMA or other regulatory authorities

could order us to cease further development of, or deny approval of, our product candidates for any or all targeted indications. Even if we are able to demonstrate that all future serious adverse events are not product-related, such occurrences could affect patient recruitment or the ability of enrolled patients to complete the trial, as well as the receptivity of patients and physicians to try any approved gene therapy products. Moreover, if we elect, or are required, to delay, suspend or terminate any clinical trial of any of our product candidates, the commercial prospects of such product candidates may be harmed and our ability to generate product revenues from any of these product candidates may be delayed or eliminated. Any of these occurrences may harm our ability to develop other product candidates, and may have a material adverse effect on our business, results of operations, financial conditions and prospects.

Furthermore, if we or others later identify undesirable side effects caused by any of our gene therapy product candidates, several potentially significant negative consequences could result, including:

- regulatory authorities may suspend or withdraw approvals of any product candidate that may receive regulatory approval, thereby preventing or delaying its commercialization;
- regulatory authorities may require additional warnings or limitations of use in product labeling;
- we may be required to change the way a product candidate is administered or conduct additional clinical trials;
- we could be sued and held liable for harm caused by our products to patients; and
- our reputation may suffer.

Any of these events could prevent us from achieving or maintaining market acceptance of our gene therapy assets for which we receive marketing approval and could materially harm our business, financial condition, results of operations and prospects.

Our gene therapy approach utilizes vectors derived from viruses, which may be perceived as unsafe or may result in unforeseen adverse events. Negative public opinion and increased regulatory scrutiny of gene therapy may damage public perception of the safety of PTC-AADC for the treatment of AADC deficiency or our other gene therapy product candidates and adversely affect our ability to conduct our business or obtain regulatory approvals for PTC-AADC or our other gene therapy product candidates.

Because gene therapy remains a novel technology, we face uncertainty as to whether gene therapy will gain the acceptance of the public or the medical community. Even if we obtain regulatory approval for our product candidates, the commercial success of our product candidates will depend, in part, on the acceptance of physicians, patients and healthcare payers of gene therapy products in general, and of our product candidates in particular, as medically necessary, cost-effective and safe. Public perception may be influenced by claims that gene therapy is unsafe, and gene therapy may not gain the acceptance of the public or the medical community. In particular, our success will depend in part upon physicians who specialize in the treatment of genetic diseases targeted by our product candidates, if approved, prescribing treatments that involve the use of our product candidates, if approved, in lieu of, or in addition to, existing treatments, if any, with which they are familiar and for which greater clinical data may be available. Even if a product candidate displays a favorable efficacy and safety profile in clinical trials and is ultimately approved, market acceptance of the product candidate will not be fully known until after it is commercialized. More restrictive government regulations or negative public opinion would have an adverse effect on our business, financial condition, results of operations and prospects and may delay or impair the development and commercialization of our product candidates or demand for any product candidates that receive regulatory approval. For example, earlier gene therapy trials conducted by other organizations have led to several well-publicized adverse events, including cases of leukemia, immune- and complement-mediated adverse events, and death seen in other such organizations' trials using other vectors. A significant negative development in any other gene therapy program or our failure to satisfy any post-marketing regulatory commitments and requirements to which we may become subject may adversely impact the commercial results and potential of our product candidates. Serious adverse events in our clinical trials, or other clinical trials involving gene therapy products or our competitors' products, even if not ultimately attributable to the relevant product candidates, and the resulting publicity, could result in increased government regulation, unfavorable public perception, potential regulatory delays in the testing or approval of our product candidates, stricter labeling requirements for those product candidates that are approved and a decrease in demand for any gene therapy products for which we obtain marketing approval. Any of the foregoing could have a material adverse effect on our business, results of operations, financial condition and prospects.

The insurance coverage and reimbursement status of newly approved products is uncertain. Failure to obtain or maintain adequate coverage and reimbursement for our products candidates, if approved, could limit our ability to market those products and decrease our ability to generate product revenue.

We expect the cost of a single administration of gene therapy products, including PTC-AADC for the treatment of AADC deficiency, to be substantial. We expect that coverage and reimbursement by government and private payers will be essential for most patients to be able to afford these treatments. Accordingly, sales of any product candidates, if approved, will depend substantially, both domestically and abroad, on the extent to which the prices of such product candidates will be paid by health maintenance, managed care, pharmacy benefit and similar healthcare management organizations, or will be reimbursed by government authorities, private health coverage insurers and other third-party payers. Coverage and reimbursement by a third-party payer may depend upon several factors, including the availability of alternative therapies or a third-party payer's determination that use of a product is:

- a covered benefit under its health plan;
- safe, effective and medically necessary;
- appropriate for the specific patient;
- cost-effective; and
- neither experimental nor investigational.

Obtaining coverage and reimbursement for a product from third-party payers is a time-consuming and costly process that could require us to provide to the payer supporting scientific, clinical and cost-effectiveness data. We may not be able to provide data sufficient to gain acceptance with respect to coverage and reimbursement.

There is significant uncertainty related to third-party coverage and reimbursement of newly approved products, including potential one-time gene therapies, such as PTC-AADC for the treatment of AADC deficiency. In the United States, third-party payers, including government payers such as the Medicare and Medicaid programs, play an important role in determining the extent to which new drugs and biologics will be covered and reimbursed. Expensive specialty drugs in particular are often subject to restriction. The Medicare and Medicaid programs increasingly are used as models for how private payers and government payers develop their coverage and reimbursement policies. Currently, there is limited experience with Centers for Medicare and Medicaid Services', or CMS, coverage of gene therapy products. We cannot be assured that Medicare or Medicaid will cover our product candidates that may be approved or provide reimbursement without restriction and at adequate levels to realize a sufficient return on our investment. Our rebate payments may increase or our prices be adjusted under value-based purchasing arrangements based on evidence-based measures or outcomes-based measures for a patient or beneficiary based on use of our drug. Moreover, reimbursement agencies in the EU may be more conservative than CMS. It is difficult to predict what third-party payers will decide with respect to the coverage and reimbursement for our products for which we obtain marketing approval. Additionally, within Europe, each country has its own reimbursement regime employing various health technology assessment approaches to assess the cost-effectiveness of the product (in the United Kingdom a HTA assessment is conducted by NICE) which may significantly affect the effective access to the market.

We may face competition from biosimilars approved through an abbreviated regulatory pathway or from separate full applications for approval.

Biologics, including our gene therapy product candidates are regulated by the FDA under the Federal Food, Drug and Cosmetics Act, or FDCA, and the Public Health Service Act, or PHSA. Biologics require the submission of a BLA and approval by the FDA prior to being marketed in the United States. Historically, a biologic product approved under a BLA was not subject to the generic drug review and approval provisions of the FDCA. However, the Biologics Price Competition and Innovation Act of 2009, or BPCIA, created a regulatory pathway under the PHSA for the abbreviated approval of biological products that are demonstrated to be "biosimilar" or "interchangeable" with an FDA approved biological product. To demonstrate biosimilarity, the biosimilar sponsor must show that the product candidate is highly similar to the reference product, notwithstanding minor differences in clinically inactive components, and that there is no clinically meaningful difference between the biosimilar product and the reference product in terms of safety, purity, and potency. In order to meet the standard of interchangeability, a sponsor must demonstrate that the biosimilar product can be expected to produce the same clinical result as the reference product, and for a product that is administered more than

once, that the risk of switching between the reference product and biosimilar product is not greater than the risk of maintaining the patient on the reference product.

Such biosimilars would reference biological products approved in the United States. The BPCIA, however, establishes certain protections for reference biologic products. For example, the BPCIA sets up a complex and involved framework for reference and biologic product sponsors to bring patent infringement actions and actions for declaratory judgment. If another company pursues approval of a product that is biosimilar to any biologic product for which we receive FDA approval, we may need to pursue costly and time-consuming patent infringement actions, which may include certain statutorily specified regulatory steps before an infringement action may be brought. We may also need to spend time and money defending an action for declaratory judgement that is brought by the biosimilar product sponsor.

Another protection established by the BPCIA is a period of 12 years of exclusivity for reference products that begins on the date that the reference product was first licensed by FDA. During this time, FDA may not make the licensure of a biosimilar product effective. Biosimilar applications can, however, be submitted for FDA review beginning four years after the date of the reference product's first licensure. Any of our product candidates that may be approved under BLAs in the future could be reference products for biosimilar marketing applications. As a result, any of our product candidates that may receive regulatory approval may face competition from other biological products that receive regulatory approval pursuant to an abbreviated pathway, which may have a material adverse effect on our results of operations, business, financial condition or prospects.

In addition, the biologic exclusivity period has certain limitations that may limit its ability to protect our product candidates, if approved, from biosimilar or interchangeable product competition. For example, certain changes and supplements to an approved BLA, and certain subsequent applications filed by the same sponsor, manufacturer, licensor, predecessor in interest, or other related entity do not qualify for the 12-year exclusivity period. Moreover, there have been legislative efforts to decrease this period of exclusivity to a shorter timeframe. Future proposed budgets, international trade agreements and other arrangements or proposals may affect periods of exclusivity. Further, even if our biologic product candidates qualify for the BPCIA's 12-year period of exclusivity, there is a risk that the FDA will not consider our product candidates to be reference products for competing products, potentially creating the opportunity for biosimilar competition sooner than anticipated. Additionally, this period of regulatory exclusivity does not apply to companies pursuing regulatory approval via their own traditional BLA, rather than via the abbreviated pathway. Accordingly, another company could market a competing version of a biological product if the FDA approves a full BLA for such product containing the sponsor's own preclinical data and data from adequate and well-controlled clinical trials to demonstrate the safety, purity and potency. Moreover, the extent to which a biosimilar, once approved, will be substituted for any one of our reference products in a way that is similar to traditional generic substitution for non-biological products is not yet fully clear, and will depend on a number of marketplace and regulatory factors that are still developing. It is also possible that payers will give reimbursement preference to biosimilars, even over reference biologics, absent a determination of interchangeability.

Similarly, in the EU, another company could gain approval for a competing product based on an MAA with a completely independent data package that includes pharmaceutical tests, preclinical tests and clinical trials.

To the extent we do not receive any anticipated periods of regulatory exclusivity or to the extent the FDA or ex-U.S. regulatory authorities approve any biosimilar, interchangeable, or other competing products, our business would be adversely impacted. Competition that our products may face from biosimilar, interchangeable, or other competing products could materially and adversely impact our future revenue, profitability, and cash flows and substantially limit our ability to obtain a return on the investments we have made in those product candidates. In the United States, this risk has increased in recent years as the FDA and the U.S. government have taken steps to encourage increased biosimilar competition in the market, in an effort to bring down the cost of biologic products.

Risks Related to the Development and Commercialization of our Products and our Product Candidates

If we are unable to continue to execute our commercial strategy for our products, fail to obtain renewal of, or satisfy the conditions of our marketing authorization for our products, or if we experience significant delays in accomplishing such goals, our business will be materially harmed.

We have invested a significant portion of our efforts and financial resources to bring our products to market through research and development, collaborations and acquisitions. Our ability to continue to generate product revenues will depend heavily on the successful commercialization of our products.

As we presently have no patent rights to protect the approved use of Emflaza, we rely on the market exclusivity periods currently available to us under the Orphan Drug Act to commercialize Emflaza for DMD in the United States. Failure to maintain the market exclusivity period, maintain our marketing authorization for Emflaza in the United States, or timely execute our commercialization plans for Emflaza, would have a material adverse effect on our business, financial position and results of operations.

While we have obtained marketing authorization for Translarna for the treatment of nmDMD in the EEA, such authorization is subject to annual review and renewal by the European Commission following the annual EMA reassessment as well as the specific obligation to conduct and submit the results of Study 041. For a review of recent developments that have had, and may continue to have, a material adverse effect on our ability to commercialize Translarna for the treatment of nmDMD, please review the risk factor titled, "*ACT DMD did not meet its primary efficacy endpoint, and there is substantial risk that regulators will not agree with our interpretation of the results of ACT DMD and the totality of clinical data from our trials in Translarna for the treatment of nmDMD, which would have a material adverse effect on our business, financial performance and results of operations.*"

We and our collaborators are currently pursuing further clinical development efforts for our products for other indications. Each genetic disorder has unique genetic and pathophysiological characteristics and we believe that regulators, including the FDA and the EMA, will evaluate the effectiveness of such products for any given indication based on the merits of the clinical efficacy evidence available for such indication. However, because we are developing products for the treatment of multiple indications, there is a risk that negative results in a clinical or pre-clinical trial of a product for one indication, could adversely affect the perception of such product in a different indication. There can be no assurance that regulators, including the FDA and the EMA, will not consider such results when making determinations with respect to our ongoing or future regulatory submissions for marketing authorization of our products for any indication, including the FDA's Complete Response Letter to our NDA for Translarna for the treatment of nmDMD and the EMA's annual reassessment of our marketing authorization for Translarna for the treatment of nmDMD, which could have an adverse effect on the outcome of the applicable regulatory review. There can be no assurance that regulators will agree with our interpretation of data from our clinical trials.

If we do not successfully maintain our marketing authorizations for our products, our ability to generate additional revenue will be jeopardized and, consequently, our business will be materially harmed. The success of our products will depend on a number of additional factors, including the following:

- our ability to negotiate, secure and maintain adequate pricing, coverage and reimbursement terms on a timely basis, or at all;
- the timing, scope and outcome of commercial launches;
- the maintenance and expansion of a commercial infrastructure capable of supporting product sales, marketing and distribution;
- the implementation and maintenance of marketing and distribution relationships with third parties in territories where we do not pursue direct commercialization;
- our ability to establish and maintain commercial manufacturing arrangements with third-party manufacturers;
- our ability or the ability of our third-party manufacturers to successfully produce commercial and clinical supply of drug on a timely basis sufficient to meet the needs of our commercial and clinical activities;
- successful identification of eligible patients;

- acceptance of the drug as a treatment for the approved indication by patients, the medical community and third-party payors;
- effectively competing with other therapies;
- global trade policies;
- a continued acceptable safety profile of the drug;
- the costs, timing and outcome of post-marketing studies and trials required for our products, including, with respect to Translarna, Study 041;
- protecting our rights in our intellectual property portfolio, obtaining and maintaining regulatory exclusivity and, including with respect to Emflaza, whether we are able to maintain market exclusivity periods under the Orphan Drug Act;
- whether, with respect to Translarna, we are able to continue to satisfy our obligations under, and maintain, the marketing authorization in the EEA for Translarna for the treatment of nmDMD, including whether the EMA determines on an annual basis that the benefit-risk balance of Translarna supports renewal of our marketing authorization in the EEA, on the current approved label;
- whether, and within what timeframe, we are able to advance Translarna for the treatment of nmDMD in the United States, including, whether we will be required to perform additional clinical trials, non-clinical studies or CMC assessments or analyses at significant cost which, if successful, may enable FDA review of an NDA submission by us and, ultimately, may support approval of Translarna for nmDMD in the United States;
- our ability to obtain additional and maintain existing reimbursed named patient and cohort EAP programs for our products on adequate terms;
- our ability to successfully prepare and advance regulatory submissions for marketing authorizations for our products in additional territories and for additional or expanded indications and whether and in what timeframe we may obtain such authorizations;
- the ability and willingness of patients and healthcare professionals to access our products through alternative means if pricing and reimbursement negotiations in the applicable territory do not have a positive outcome; and
- protecting our rights in our intellectual property portfolio.

If we do not achieve one or more of these factors in a timely manner or at all, we could experience significant delays or an inability to continue to commercialize our products, either of which would have a material adverse effect on our business, results of operations and financial condition.

The marketing authorization granted by the European Commission for Translarna for the treatment of nmDMD is limited to ambulatory patients aged two years and older located in the EEA, which significantly limits an already small treatable patient population, which reduces our commercial opportunity and is also subject to annual reassessment of the benefit-risk balance by the EMA as well as the specific obligation to conduct Study 041, and may be varied, suspended or withdrawn by the European Commission if we fail to satisfy those requirements.

We have obtained orphan drug designations from the EMA and from the FDA for Translarna for the treatment of nmDMD because the number of patients who could benefit from treatment with Translarna is small. The marketing label approved by the European Commission further limits the currently treatable patient population to ambulatory nmDMD patients aged two years and older who have been identified through genetic testing as having a nonsense mutation in the dystrophin gene. Prevalence estimates for rare diseases are uncertain due to the uncertainties associated with the methodologies used to derive estimates, such as epidemiology assumptions. It can take many years of experience in rare disease market places before prevalence becomes well characterized. Our estimates of both the number of people who have DMD caused by a nonsense mutation, as well as the subset of people with nmDMD who are ambulatory and at least two years old (and, therefore, satisfy the conditions for treatment under our current product label in the EEA), are based on our beliefs and estimates derived from a variety of sources and may prove to be either incorrect or subject to additional refinement or characterization on a country specific basis over the coming years. Prevalence estimates vary given some degree of variation in the incidence of live male births, the incidence of DMD, the incidence of nonsense mutations and other factors. Information concerning the eligible patient population is generally limited to certain geographies and may not employ definitive measures capable of establishing with precision the actual number of nmDMD patients in such geography. If the market opportunities for Translarna for the treatment of nmDMD are smaller than we believe they are, our business and anticipated revenues will be negatively impacted. If we decide to seek to expand the approved product label of

Translarna for the treatment of nmDMD in the future, the timing of, and our ability to generate, the necessary data or results required to obtain expanded regulatory approval is currently uncertain. Given the small number of patients who have nmDMD, and the smaller number of patients who meet the criteria for treatment under our current marketing authorization, our commercial opportunity is limited. It is critical to the commercial success of Translarna for nmDMD that we successfully identify and treat these patients.

In order to continue to generate revenue from Translarna, we must maintain our marketing authorizations in the EEA and Brazil for Translarna for the treatment of nmDMD in ambulatory patients aged two years and older, maintain our marketing authorization for Translarna in Russia for the treatment of nmDMD in patients aged two years and older and we also may need to receive or maintain marketing authorizations in other territories. The marketing authorization in the EEA is conditional and subject to annual review and renewal by the European Commission following reassessment by the EMA of the benefit-risk balance of the authorization, which we refer to as the annual EMA reassessment, as well as the specific obligation to complete and report the results of Study 041 to the EMA. We expect that as part of the annual EMA assessment, the EMA will consider the ongoing status of Study 041. We expect results from the placebo-controlled trial of Study 041 to be available in mid-2022. We then expect to submit a report on the placebo-controlled trial and the open-label extension data from Study 041 that has been collected to date to the EMA by the end of the third quarter of 2022, as required. The marketing authorization was last renewed in June 2021 and is effective, unless extended, through August 5, 2022. In February 2022, we submitted a marketing authorization renewal request to the EMA.

If the EMA determines in any annual renewal cycle that the balance of benefits and risks of using Translarna for the treatment of nmDMD has changed materially or that we have not or are unable to comply with any conditions that have been or may be placed on the marketing authorization, the European Commission could, at the EMA's recommendation, vary, suspend, withdraw or refuse to renew the marketing authorization for Translarna or require the imposition of other conditions or restrictions. As such, there is ongoing risk to our ability to maintain our marketing authorization in the EEA.

If we are unable to renew our marketing authorization in the EEA during any annual renewal cycle, or if our product label is materially restricted, we would lose all, or a significant portion of, our ability to generate revenue from sales of Translarna, whether pursuant to a commercial or an EAP program, and in all territories, which would have a material adverse effect on our business, results of operations and financial condition. See "Risks Related to Regulatory Approval of our Products and our Product Candidates" below for further detail regarding conditional marketing authorizations in the EEA.

Delays or failures in obtaining regulatory approval in the United States, may prevent us from commercializing Translarna for nmDMD in that territory and our ability to generate revenue will be materially impaired. In the event that the FDA requires us to conduct additional clinical trials in nmDMD which, if successful, may enable FDA review of an NDA submission by us, we would expect to incur significant costs, which may have a material adverse effect on our business and results of operations.

In the first quarter of 2017, we filed our Translarna NDA for nmDMD with the FDA via the "file over protest" process that allows a company to have its NDA filed and reviewed when there is a disagreement with regulators over the acceptability of the NDA submission. In October 2017, the Office of Drug Evaluation I of the FDA issued a Complete Response Letter for the NDA, stating that it was unable to approve the application in its current form. In response, we filed a formal dispute resolution request with the Office of New Drugs of the FDA. In February 2018, the Office of New Drugs of the FDA denied our appeal of the Complete Response Letter. In its response, the Office of New Drugs recommended a possible path forward for the ataluren NDA submission based on the accelerated approval pathway. This would involve a re-submission of an NDA containing the current data on effectiveness of ataluren with new data to be generated on dystrophin production in nmDMD patients' muscles. We followed the FDA's recommendation and collected, using newer technologies via procedures and methods that we designed, such dystrophin data in a new study, Study 045, and announced the results of Study 045 in February 2021. Study 045 did not meet its pre-specified primary endpoint. We expect results from the placebo-controlled trial of Study 041 to be available in mid-2022, and subject to a positive outcome in that study, we expect to re-submit the NDA.

There is significant risk that we will be unable to obtain FDA approval of Translarna for nmDMD, on a timely basis or at all, and we may be required to perform additional clinical trials, non-clinical studies or CMC assessments or analyses at

significant cost. Even if we are able to enroll and fund any such additional trials or studies or complete such assessments or analyses, there is substantial risk that the results would not ultimately support the approval of a re-submission of an NDA in the United States for Translarna for nmDMD. In addition, any such requirement for additional trials would most likely result in our inability to sell Translarna in the United States for a significant period of time, which would have a material adverse effect on our ability to generate revenue from the sales of Translarna for the treatment of nmDMD.

We may pursue the accelerated approval pathway for Translarna, pending the results of Study 041. However, the FDA may determine that Translarna does not qualify for accelerated approval. Moreover, even if we do ultimately receive approval for Translarna in the United States, if such approval is via the accelerated approval pathway, we will need to complete a post-approval study confirming Translarna's clinical benefit. This study would likely require substantial time, effort, and funds. Furthermore, if Translarna is ultimately approved through the accelerated approval pathway, we would be subject to additional regulatory requirements, such as the pre-submission of promotional materials to FDA and potential restrictions, such as distribution restrictions, to assure the product's safe use. Accelerated approval would also subject us to the risk of expedited FDA withdrawal procedures if we do not conduct required post-approval studies, such studies do not meet FDA's standards, such studies do not confirm the product's clinical benefit, or FDA finds that any post market restrictions are inadequate to assure the safe use of the product, among other circumstances. In recent years, the accelerated approval pathway has come under significant FDA and public scrutiny. Accordingly, depending on the results of our studies, the FDA may be more conservative in granting accelerated approval or, if granted, may be more apt to withdrawal approval if clinical benefit is not confirmed. Due to these and other uncertainties, we are unable to estimate the timing or potential for a launch of Translarna for the treatment of nmDMD in the United States or the cost or effort required to receive FDA approval for Translarna and meet FDA's regulatory requirements both before and after approval. Even if we receive approval for Translarna, there is no guarantee that we would be able to maintain such approval.

The FDA has repeatedly disagreed with our interpretation of the study results for Translarna. In 2010, we filed a NDA for ataluren based on our Phase 2b clinical data, which the FDA refused to file. We filed a formal dispute resolution request concerning this decision in 2011 and, in 2012, the FDA reaffirmed its previous decision to refuse to file the 2010 NDA.

In October 2015, we announced that the primary efficacy endpoint in the ITT population did not achieve statistical significance in ACT DMD. On the basis of our position that the totality of clinical data from ACT DMD and our prior Phase 2b trial support the clinical benefit of Translarna for the treatment of nmDMD, in December 2015, we submitted our analyses of the ACT DMD data and meta-analysis of the combined ACT DMD and Phase 2b subgroup data to the FDA, as part of our NDA, after commencing our submission on a rolling basis in December 2014.

On February 22, 2016, we received a Refuse to File letter from the FDA stating that our NDA was not sufficiently complete to permit a substantive review in particular because, in the view of the FDA, both the Phase 2b and Phase 3 ACT DMD trials were negative and do not provide substantial evidence of effectiveness and that our NDA does not contain adequate information regarding the abuse potential of Translarna. Additionally, the FDA stated that we had proposed a post-hoc adjustment of ACT DMD that eliminates data from a majority of enrolled patients. In addition, the FDA noted that our NDA does not contain adequate information regarding the abuse potential of Translarna. While other comments and requests were noted in the letter as items to be addressed if the NDA were to be resubmitted, the FDA specified that they were not related to its refusal to file our NDA.

Following the refusal to file of our NDA, we initiated dialogue with the FDA to discuss and clarify the matters set forth in the letter and determine our best path forward. In accordance with the formal dispute resolution process that exists within the Center for Drug Evaluation and Research of the FDA, we filed a formal appeal of the Refuse to File letter, which was denied in October 2016. In the first quarter of 2017, we filed our Translarna NDA for nmDMD via the FDA's file over protest regulations. We included additional retrospective and post hoc analyses from our clinical trials with the NDA filed in 2017, including analyses of the 6-minute walk test using alternative statistical and analytical methods and new analyses from the North Star Ambulatory Assessment test, a functional scale designed for boys affected by DMD. Filing over protest is a procedural path permitted by FDA regulations that allows a company to have its NDA filed and reviewed when there is a disagreement with regulators over the acceptability of the NDA submission.

In its 2016 Refuse to File letter and in its 2017 Complete Response Letter and its denial of our appeal to the Complete Response Letter, the FDA referenced its prior refusal to file relative to the Phase 2b data and our early discussions with the FDA, reiterating the views previously expressed.

ACT DMD did not meet its primary efficacy endpoint, and there is substantial risk that regulators will not agree with our interpretation of the results of ACT DMD and the totality of clinical data from our trials in Translarna for the treatment of nmDMD, which would have a material adverse effect on our business, financial performance and results of operations.

In October 2015, we announced that the primary efficacy endpoint in the ITT population did not achieve statistical significance in ACT DMD. We submitted our analyses of the ACT DMD data and meta-analyses of the combined ACT DMD and Phase 2b subgroup data to the EMA to support continuation of our marketing authorization in the EEA, which is subject to annual review and renewal by the European Commission following reassessment by the EMA of the benefit-risk balance of the authorization. The EMA and European Commission did not approve our request for full marketing authorization of Translarna for the treatment of nmDMD and, instead, approved the annual renewal of our marketing authorization with the specific obligation to confirm the efficacy and safety of Translarna for the treatment of nmDMD in ambulatory patients age 5 years or older via Study 041.

Enrolling, conducting and reporting a clinical trial is a time-consuming, expensive and uncertain process that takes years to complete, and we have incurred and expect to continue to incur material costs related to the implementation and conduct of Study 041. We expect that conducting a placebo-controlled trial in nmDMD of this size will be challenging and we have enrolled patients in countries with a different standard of care for nmDMD patients and at clinical trial sites that are inexperienced with nmDMD clinical trials, which may affect our ability to accurately evaluate the study and maintain compliance with applicable regulatory requirements and laws. In addition, we may experience unknown complications with Study 041 and may not achieve the pre-specified endpoint with statistical significance, which would have a material adverse effect on our ability to maintain our marketing authorization in the EEA.

There is substantial risk that other regulators in regions where we have not yet sought or are currently seeking marketing authorization will not agree with our interpretation of the results of ACT DMD and the totality of clinical data from our trials in Translarna for the treatment of nmDMD, which would have a material adverse effect on our ability to generate revenue from the sales of Translarna for the treatment of nmDMD in those applicable territories. In addition, we may not be able to maintain or obtain marketing authorizations in areas where such authorizations are contingent upon decisions of the EMA with respect to our marketing authorization in the EEA.

For additional information, see "Risks Related to Regulatory Approval of our Products and our Product Candidates" below.

If clinical trials of our products or our product candidates fail to demonstrate safety and efficacy to the satisfaction of the EMA, the FDA or other regulators, or do not otherwise produce favorable results, we may experience delays in completing, or ultimately be unable to complete, the development and commercialization of our products or product candidates.

In connection with seeking marketing authorization from regulatory authorities for the sale of any product candidate, we must complete preclinical development and then conduct extensive clinical trials to demonstrate the safety and efficacy of our product candidates in humans. Clinical and preclinical testing is expensive, difficult to design and implement, can take many years to complete and is uncertain as to outcome. This is especially true for rare and/or complicated diseases. A failure of one or more clinical or preclinical trials can occur at any stage of testing. Preclinical and clinical studies may reveal unfavorable product candidate characteristics, including safety concerns, or may not demonstrate product candidate efficacy. In some instances, there can be significant variability in safety or efficacy results between different clinical trials of the same product candidate due to numerous factors, including changes in trial procedures set forth in protocols, differences in the size and type of the patient populations, changes in and adherence to the clinical trial protocols and the rate of dropout among clinical trial participants. The outcome of preclinical testing and early clinical trials may not be predictive of the success of later clinical trials, and interim results of a clinical trial do not necessarily predict final results. Moreover, preclinical and clinical data are often susceptible to varying interpretations and analyses, and many companies

that have believed their product candidates performed satisfactorily in preclinical studies and clinical trials have nonetheless failed to obtain marketing authorization of their products.

With respect to Translarna, the primary efficacy endpoint in the intent to treat, or ITT, population did not achieve statistical significance in the Phase 2b (completed in 2009) or Phase 3 ACT DMD (completed in 2015) clinical trials of Translarna for the treatment of nmDMD. For a review of recent developments that have had, and may continue to have, a material adverse effect on our ability to commercialize Translarna for the treatment of nmDMD, please review the risk factor titled, "*ACT DMD did not meet its primary efficacy endpoint, and there is substantial risk that regulators will not agree with our interpretation of the results of ACT DMD and the totality of clinical data from our trials in Translarna for the treatment of nmDMD, which would have a material adverse effect on our business, financial performance and results of operations.*"

If the FDA, the EMA and other regulators do not agree with our interpretation of the results of the clinical data from our trials, and, when and if completed, Study 041 and related analyses, or otherwise do not view the results of these trials as favorable; if we are required to conduct additional clinical trials or other testing of our products or product candidates that we develop beyond those that we contemplate; if we are unable to successfully complete our clinical trials or other testing; if the results of these trials or tests are not positive or are only modestly positive; or if there are safety concerns, we may, among other things:

- be unable to successfully maintain our marketing authorization in the EEA for Translarna for the treatment of nmDMD, which is subject to annual review and renewal following reassessment of the benefit-risk balance of the authorization by the EMA;
- be unable to successfully maintain our marketing authorization in Brazil or Russia for Translarna for the treatment of nmDMD;
- be unable to successfully maintain our marketing authorization in other countries that we have received approval for Translarna for the treatment of nmDMD;
- be delayed in or unable to obtain marketing approval in the United States for Translarna or any other product candidates, including supplemental application approvals for any products that receive approval;
- be delayed in obtaining additional marketing authorizations, or not obtain additional marketing authorizations at all, for Translarna for the treatment of nmDMD;
- be delayed in obtaining marketing authorizations, or not obtain marketing authorizations at all, for our other product candidates;
- obtain approval for indications, uses or patient populations that are not as broad as intended or desired;
- obtain approval with labeling that includes significant use or distribution restrictions or safety warnings, including boxed warnings;
- obtain approval with labeling that does not include claims that are necessary or desirable for the successful commercialization of the product or product candidate;
- be subject to additional post-marketing requirements or restrictions, such as post-approval studies or REMS;
- have the product removed from markets after obtaining applicable marketing authorizations; or
- not be permitted to sell Translarna under some or any reimbursed EAP programs.

If we or our collaborators experience any of a number of possible unforeseen events in connection with clinical trials related to our products or our product candidates, maintenance of our existing marketing authorization for our products and any additional potential marketing authorization or commercialization of our products or our product candidates could be delayed or prevented.

We or our collaborators may experience numerous unforeseen events during, or as a result of, clinical trials that could delay or prevent our ability to receive marketing authorization or commercialize our products or our product candidates, including:

- clinical trials of our products or our product candidates may produce negative or inconclusive results for the necessary study endpoints, our studies may fail to reach the necessary level of statistical significance, and we may decide, or regulators may require us, to conduct additional clinical trials or abandon product development programs;

- there may be flaws in our clinical trials' design that may not become apparent until the clinical trials are well advanced or regulators may not agree with the design of our studies or our analysis of the resulting data;
- the number of patients required for clinical trials of our product and product candidates may be larger than we anticipate, enrollment in these clinical trials may be slower than we anticipate or participants may drop out of these clinical trials or be lost to follow-up at a higher rate than we anticipate;
- clinical trial sites or enrolled patients may be negatively affected by the COVID-19 pandemic, resulting in delays and disruptions in completing clinical trials, such as the delays we have experienced in enrolling our registration-directed Phase 2/3 placebo-controlled trial of vatiquinone in children with mitochondrial disease associated seizures trial as some patients have been unable or hesitant to travel to clinical trial sites due to the COVID-19 pandemic;
- patients that enroll in our studies may misrepresent their eligibility or may otherwise not comply with the clinical trial protocol, resulting in the need to drop the patients from the study, increase the needed enrollment size for the study or extend the study's duration;
- we may be unable to enroll a sufficient number of patients in our clinical trials to ensure adequate statistical power to detect any statistically significant treatment effects;
- we may enroll patients at clinical trial sites in countries that are inexperienced with clinical trials in general, or with the indication that is the subject of the trial;
- we may enroll patients at clinical trial sites in countries that have a different standard of care for patients in general, or with respect to the indication that is the subject of the trial. Regulatory authorities, such as the FDA, may also not accept data generated at international clinical trial sites;
- our third-party contractors may fail to comply with regulatory requirements or meet their contractual obligations to us in a timely manner, or at all, or we may be required to engage in additional clinical trial site monitoring;
- regulators, institutional review boards, institutional biosafety committees, or independent ethics committees may not authorize us or our investigators to commence a clinical trial or conduct a clinical trial at a prospective trial site or may require us to submit additional data, conduct additional studies or amend our investigational new drug application, or IND, or comparable application or protocols prior to commencing a clinical trial;
- we may fail to reach an agreement with regulators, institutional review boards, institutional biosafety committees, or independent ethics committees regarding the scope, design, or implementation of our clinical trials. For instance, the FDA or comparable ex-U.S. regulatory authorities may require changes to our study design that make further study impractical or not financially prudent;
- we may have delays in reaching or may fail to reach agreement on acceptable clinical trial contracts or clinical trial protocols with prospective trial sites and contract research organizations;
- we may have delays in adding new investigators or clinical trial sites, or we may experience a withdrawal of clinical trial sites;
- we may have to suspend or terminate clinical trials of our products or our product candidates for various reasons, including a finding that the participants are being exposed to unacceptable health risks;
- regulators, institutional review boards, institutional biosafety committees, or independent ethics committees may require that we or our investigators suspend or terminate clinical research for various reasons, including noncompliance with regulatory requirements or a finding that the participants are being exposed to unacceptable health risks;
- the cost of clinical trials of our products or our product candidates may be greater than we anticipate or we may have insufficient funds for a clinical trial or to pay the substantial user fees required by the FDA upon the filing of a marketing application;
- the supply or quality of our products or our product candidates or other materials necessary to conduct clinical trials of our products or our product candidates may be insufficient or inadequate;
- our products or our product candidates may have undesirable side effects or other unexpected characteristics, causing us or our investigators, regulators, institutional review boards, institutional biosafety committees or independent ethics committees to suspend or terminate the trials;
- regulators may require us to perform additional or unanticipated clinical or preclinical trials, develop additional manufacturing information, or make changes to our manufacturing process to obtain approval or we may be subject to additional post-marketing testing, surveillance, or REMS requirements to maintain regulatory approval;
- there may be changes in the applicable regulatory authorities' approval policies or review, statutes, or regulations, which may render our data insufficient to obtain marketing approval;

- we may decide that it is no longer in our business interest to continue a development program;
- there may be regulatory questions or disagreements regarding interpretations of data and results, or new information may emerge regarding our product candidates;
- the FDA or comparable ex-U.S. regulatory authorities may disagree with our study design, including endpoints, or our interpretation of data from preclinical studies and clinical trials or find that a product candidate's benefits do not outweigh its safety risks;
- the FDA or comparable regulatory authorities may disagree with our intended indications;
- the FDA or comparable ex-U.S. regulatory authorities may fail to approve or subsequently find fault with the manufacturing processes for clinical and future commercial supplies, the Hopewell Facility or our contract manufacturer's manufacturing facility;
- the data collected from clinical trials of our product candidates may not be sufficient to the satisfaction of the FDA or comparable ex-U.S. regulatory authorities to support the submission of a marketing application, or other comparable submission in ex-U.S. jurisdictions or to obtain regulatory approval in the United States or elsewhere;
- the FDA or comparable regulatory authorities may take longer than we anticipate to make a decision on our product candidates; or
- we may not be able to demonstrate that a product candidate provides an advantage over current standards of care or current or future competitive therapies in development.

For example, the Phase 2 Moonfish study, which was evaluating the safety and efficacy of RG7800 under our SMA collaboration, was terminated in December 2016 following a suspension and clinical hold in the first half of 2015 to investigate an eye finding in a 39-week study in cynomolgus monkeys. The suspension and termination of Moonfish resulted in unanticipated delays in the advancement of the SMA program.

Our product development costs will increase if we experience delays in testing or marketing authorizations, and we may not have sufficient funding to complete the testing and approval process for any of our product candidates. We may be required to obtain additional funds to complete clinical trials and prepare for possible commercialization of our products and product candidates. We do not know whether any preclinical tests or clinical trials will begin as planned, will need to be restructured or will be completed on schedule, or at all. Significant preclinical or clinical trial delays also could shorten any periods during which we may have the exclusive right to commercialize our products or our product candidates and allow our competitors to bring products to market before we do, or impair our ability to successfully commercialize our products or our product candidates, and so may harm our business, results of operations and financial condition.

Our conclusions regarding the activity and potential efficacy of Translarna in nmDMD are primarily based on retrospective, subgroup and meta-analyses of the results of our Phase 2b and ACT DMD clinical trials of Translarna for the treatment of nmDMD. Other than with respect to certain of our meta-analyses, results of our analyses are expressed as nominal p-values, which are generally considered less reliable indicators of efficacy than adjusted p-values. In addition, retrospective analyses are generally considered less reliable than pre-specified analyses.

After determining that we did not achieve the primary efficacy endpoint with the pre-specified level of statistical significance in our completed ACT DMD and Phase 2b clinical trials of Translarna for the treatment of nmDMD, we performed subgroup, retrospective, and meta-analyses. We submitted these analyses to the FDA as part of our NDA, taking the position that the totality of clinical data from these trials support the clinical benefit of Translarna for the treatment of nmDMD. In addition, after determining that the primary efficacy endpoint did not achieve statistical significance in ACT DMD or our Phase 2b clinical trial of Translarna for the treatment of nmDMD, we performed retrospective and subgroup analyses that we believe provide sufficient support for concluding that Translarna was active and showed clinically meaningful improvements over placebo in these trials.

We believe that our reliance upon the additional analyses of the results of these trials was warranted, but the FDA typically does not find a retrospective analysis performed after unblinding trial results to be persuasive because it can result in the introduction of bias if the analysis is inappropriately tailored or influenced by knowledge of the data and actual results.

Some of our favorable statistical data from these trials also are based on nominal p-values that reflect only one particular comparison when more than one comparison is possible. Typically, a trial result is interpreted as being statistically significant if the chance of the same result occurring with the placebo is less than one in 20, resulting in a p-value of less

than 0.05. Nominal p-values cannot be compared to the typical significance level (p-value less than 0.05) to determine statistical significance without adjusting for the testing of multiple dose groups, end points or analyses of subgroups. Because of these limitations, regulatory authorities typically give greater weight to results from pre-specified analyses and adjusted p-values and less weight to results from post-hoc, retrospective analyses and nominal p-values. A p-value is considered nominal if it is the result of one particular comparison prior to any pre-specified multiplicity adjustment, such as when two active treatments are compared to placebo or when two or more subgroups are analyzed. For example, the p-values in ACT DMD for change from baseline at week 48 in the 6-minute walk test, or 6MWT (which we also refer to as 6-minute walk distance, or 6MWD) and each secondary end point timed function test in the pre-specified subgroup of patients with a baseline 300-400 meter 6MWD had p-values of less than 0.05. The FDA considered these p-values to be nominal because of the sequential testing method we used.

On February 22, 2016, we received a Refuse to File, or RTF, letter from the FDA stating the FDA's opinion that both the Phase 2b and Phase 3 ACT DMD trials were negative and did not provide substantial evidence of effectiveness and that our NDA did not contain adequate information regarding the abuse potential of Translarna. Additionally, the FDA stated that we had proposed a post-hoc adjustment of ACT DMD that eliminates data from a majority of enrolled patients. Our reliance on nominal p-values for some of our statistical data and our use of retrospective analyses had a negative impact on the FDA's interpretation of the results of our Phase 2b trial, ACT DMD and the totality of the data from our clinical trials. The FDA reiterated this view in the Complete Response Letter that it sent to us in October 2017 and its denial of our appeal of that letter.

Our reliance on nominal p-values for some of our statistical data and our use of retrospective analyses has also had a negative impact on the EMA's evaluation of a prior application for continued marketing authorization for Translarna for the treatment of nmDMD, including delays in timing of the CHMP's opinion with respect to the annual renewal of our marketing authorization, and could negatively impact regulatory determinations by regulators in other territories with respect to new or existing authorizations.

An unfavorable view of our data and analyses by the FDA and EMA for Translarna has and could continue to negatively impact our ability to obtain or maintain authorizations to market Translarna for the treatment of nmDMD. An inability to obtain new marketing authorizations or maintain our current marketing authorization in the EEA would have a material adverse effect on our revenue from Translarna and would materially harm our business, financial results and results of operations.

Because we are developing products and product candidates for the treatment of diseases in which there is little clinical experience and, in some cases, using new endpoints or methodologies, there is increased risk that the outcome of our clinical trials will not be favorable.

There are no marketed therapies approved to treat the underlying cause of nmDMD. In addition, there has been limited historical clinical trial experience generally for the development of drugs to treat nmDMD and other diseases that we are studying or have studied. As a result, the design and conduct of clinical trials for these diseases, particularly for drugs to address the underlying nonsense mutations causing these diseases in some subsets of patients, is subject to increased risk.

For example, on March 2, 2017, we announced that the primary and secondary endpoints were not achieved in ACT CF, our Phase 3 clinical trial for Translarna in nmCF. As a result, we discontinued our clinical development of Translarna for nmCF at that time.

Prior to the Phase 2b clinical trial of Translarna for nmDMD, there was no precedent of an established trial design to evaluate the efficacy of Translarna in nmDMD over a 48 week duration. In addition, clinical understanding of the methodologies used to analyze the resulting data were also limited. The study design and enrollment criteria for ACT DMD were based on available natural history data of the disease, including third-party data and results from our Phase 2b clinical trial. An evolving understanding in the DMD community has led to a greater appreciation of the optimal window for the 6MWT in assessing physical function. We believe that this factor may have led to the primary efficacy endpoint in the intent to treat population not achieving statistical significance in ACT DMD.

Additionally, following the FDA's recommendation to collect dystrophin data using validated quantification methods, we initiated Study 045 to evaluate the ability of ataluren to increase dystrophin protein levels in boys with nmDMD. Study 045 did not meet its pre-specified primary endpoint.

We faced similar challenges in connection with the designs of our study of Translarna in nonsense mutation aniridia, which did not meet statistical significance, our study of Translarna in nonsense mutation Dravet syndrome/CDKL5, which did not meet its primary endpoint and our study in Emflaza in limb-girdle 2I. In each case, there was limited historical clinical trial experience for the development of drugs to treat the underlying cause of these disorders. Our program for Emflaza in limb-girdle 2I was discontinued in 2019 and our programs for Translarna in nonsense mutation aniridia and Translarna in nonsense mutation Dravet syndrome/CDKL5 were each discontinued in 2020.

If we experience delays or difficulties in the enrollment of patients in our clinical trials, our receipt of necessary regulatory approvals could be delayed or prevented.

We may not be able to initiate or continue clinical trials for our product candidates, including clinical trials related to our splicing, gene therapy, Bio-e, metabolic and oncology programs and studies of emvododstat for COVID-19 as well as studies in our products for maintaining authorizations, label extensions and additional indications.

Many of the indications we are currently pursuing for our products and product candidates are characterized by relatively small patient populations, which could result in slow enrollment of clinical trial participants. In addition, our competitors have ongoing clinical trials for product candidates that could be competitive with our product candidates. As a result, potential clinical trial sites may elect to dedicate their limited resources to participation in our competitors' clinical trials and not ours, and patients who would otherwise be eligible for our clinical trials may instead enroll in clinical trials of our competitors' product candidates. For example, there is significant competition, including from other companies and governmental organizations, to find treatments for COVID-19 which may affect the patient enrollment of our studies of emvododstat for COVID-19.

Patient enrollment is affected by other factors including:

- severity of the disease under investigation;
- eligibility criteria for the study in question;
- perceived benefits and risks of the product candidate under study;
- disruptions caused by the COVID-19 pandemic;
- the willingness of potential patients to enroll in a clinical trial during the COVID-19 pandemic;
- efforts to facilitate timely enrollment in clinical trials;
- patient referral practices of physicians;
- the ability to monitor patients adequately during and after treatment; and
- proximity and availability of clinical trial sites for prospective patients.

For example, we have experienced delays in enrolling our registration-directed Phase 2/3 randomized, placebo-controlled trial of vatiquinone in children with mitochondrial disease associated seizures as some patients have been unable or hesitant to travel to clinical trial sites due to the COVID-19 pandemic and we now anticipate results from this trial to be available in the fourth quarter of 2022.

Enrollment delays in our clinical trials may result in increased development costs for our product candidates. Our inability to enroll, timely or at all, a sufficient number of patients in our clinical trials for our splicing, gene therapy, Bio-e, metabolic and oncology programs and studies of emvododstat for COVID-19 as well as studies in our products for maintaining authorizations, label extensions and additional indications, or any of our, or our collaboration partners', other clinical trials would result in significant delays or may require us to abandon one or more clinical trials altogether.

If serious adverse side effects are identified during the development or further development of any product candidate or for any product for which we have or may obtain marketing approval, including Translarna and Emflaza, we may need to abandon or limit our development and/or marketing of that product or product candidate.

Our products and product candidates are in clinical or preclinical development, or further development, and their risk of failure is high. It is impossible to predict when or if any of our product candidates will prove effective or safe in humans or will receive regulatory approval. If our products or our product candidates are associated with undesirable side effects or have characteristics that are unexpected, regulatory authorities, institutional review boards, institutional biosafety committees, or independent ethics committees may place our studies on clinical hold, withdraw or suspend study approvals, or require that we modify our protocols. We may also need to abandon their development or limit development to certain uses or subpopulations in which the undesirable side effects or other characteristics are less prevalent, less severe or more acceptable from a benefit-risk perspective. Adverse events or side effects may also result in regulatory authorities denying approval of any applications we may submit for marketing approval, limitations on the indicated use of a product, the inclusion of warnings, contraindications, or precautions on the label of any approved products, or significant conditions imposed on any approval, including the requirement of a REMS, costly post-marketing studies or clinical trials and surveillance to monitor the safety of the product. Many compounds that initially showed promise in clinical or earlier stage testing have later been found to cause side effects that prevented further development of the compound.

For example, although we did not observe a pattern of liver enzyme elevations in our Phase 2 or Phase 3 clinical trials of Translarna, we did observe modest elevations of liver enzymes in some subjects in one of our Phase 1 clinical trials. These elevated enzyme levels did not require cessation of Translarna administration, and enzyme levels typically normalized after completion of the treatment phase. We did not observe any increases in bilirubin, which can be associated with serious harm to the liver, in the Phase 1 clinical trial.

In addition, in Study 009, our first Phase 3 clinical trial of Translarna for the treatment of nmCF, five adverse events in the Translarna arm of the trial that involved the renal system led to discontinuation. As compared to the placebo group, the Translarna treatment arm also had a higher incidence of adverse events of creatinine elevations, which can be an indication of impaired kidney function. In the Translarna treatment arm, more severe clinically meaningful creatinine elevations were reported in conjunction with cystic fibrosis pulmonary exacerbations. These creatinine elevations were associated with concomitant treatment with antibiotics associated with impaired kidney functions, such as aminoglycosides or vancomycin. This led to the subsequent prohibition of concomitant use of Translarna and these antibiotics, which was successful in addressing this issue in the clinical trial.

In addition, we may be obligated to perform certain FDA post-marketing requirements in connection with any product approvals that we may receive. If we or others identify previously unknown side effects, whether pursuant to these post-marketing requirements, or otherwise, and in particular if such side-effects are severe, or if known side effects are more frequent or severe than in the past then our marketing authorizations may be restricted or withdrawn, changes may be required to the product's label, sales may be adversely impacted, we may be required to undertake additional studies or trials, and government investigations or litigation, including product liability claims, may be brought against us. Additionally, if the safety warnings in our product labels are not followed, adverse medical situations in patients may arise, resulting in negative publicity and potential lawsuits, even if our products worked as we described. Any of these occurrences would limit or prevent us from commercializing our products, which would have a material adverse effect on our business, financial results and operations.

Our product candidates, including our gene therapy product candidates, may be subject to marketing and distribution restrictions that could limit our ability to successfully market and distribute those products, and limit the ability of physicians to prescribe and administer such products.

Our product candidates, including our gene therapy product candidates, if approved, may be subject to restrictions on product labeling, marketing, distribution, prescribing, and use, which could increase our cost to commercialize such products and decrease our ability to generate product revenue. One such restriction may be risk evaluation and mitigation strategies, or REMS. A REMS may be required to include various elements, such as a medication guide or patient package insert, a communication plan to educate healthcare providers of the product's risks, limitations on who may prescribe or dispense the product, or other measures that the FDA deems necessary to assure the safe use of the product. Several gene

therapy products that have been approved by FDA have required substantial REMS. If any of our product candidates are subject to REMS, it may require a significant investment in time and funds to implement such REMS and may harm our results of operation.

Any of our products or any other product candidate that receives marketing authorization, if any, may fail to achieve the degree of market acceptance by physicians, patients, third-party payors and others in the medical community necessary for commercial success.

Although Translarna is currently authorized by the EMA for marketing for the treatment of nmDMD, such marketing authorization is subject to the specific obligation to conduct and submit the results of Study 041 to the EMA and is also subject to annual review and renewal by the European Commission following reassessment of the benefit-risk balance of the authorization by the EMA. Even if our marketing authorization in the EEA and other territories where we currently have approval for Translarna for the treatment of nmDMD is maintained, or we are successful in obtaining marketing authorization for Translarna for other indications or territories, such product may nonetheless fail to gain sufficient market acceptance by physicians, patients, third-party payors and others in the medical community. In addition, Emflaza for the treatment of DMD in the United States or any of our other products or product candidates that receive marketing authorization, may fail to gain sufficient market acceptance by physicians, patients, third-party payors and others in the medical community. Third-party payors may require prior authorizations or failure on another type of treatment before covering a particular drug, particularly with respect to higher-priced drugs. Decreases in third-party reimbursement for a product or a decision by a third-party payor to not cover a product could reduce physician usage of the product, including Emflaza or Translarna. If these products do not achieve an adequate level of acceptance, we may not generate significant product revenues or any profits from operations.

The degree of market acceptance of our products or product candidates, if approved for commercial sale, will depend on a number of factors, including:

- the efficacy and potential advantages compared to alternative treatments;
- the prevalence and severity of any side effects;
- the limitations or warnings contained in the product's FDA-approved labeling;
- the claims we may make for a product, based on the approved label;
- distribution and use restrictions imposed by the FDA with respect to such product candidates or to which we agree as part of a REMS or voluntary risk management plan;
- the ability to offer our products or product candidates for sale at competitive prices;
- convenience and ease of administration compared to alternative treatments;
- the willingness of the target patient population to try new therapies and of physicians to prescribe these therapies;
- the strength of marketing and distribution support;
- sufficient third-party coverage or reimbursement;
- adverse publicity about our products or product candidates or favorable publicity about competitive products or product candidates; and
- any restrictions on concomitant use of other medications.

In addition, because we are developing Translarna for the treatment of different indications, negative results in a clinical trial evaluating the efficacy of Translarna for one indication, could have a negative impact on the perception of the efficacy of Translarna in a different indication, which could have an adverse effect on our commercialization efforts and financial results.

Our ability to negotiate, secure and maintain third-party coverage and reimbursement may be affected by political, economic and regulatory developments in the United States, the EU, Latin America and other jurisdictions. Governments continue to impose cost containment measures, and third-party payors are increasingly challenging prices charged for medicines and examining their cost effectiveness, in addition to their safety and efficacy. These and other similar developments could significantly limit the degree of market acceptance of our products or any of our other product candidates that receive marketing authorization.

We face risks related to the development of emvododstat as a potential treatment for COVID-19 and we may ultimately be unsuccessful in developing a treatment for the virus in a timely manner or at all. Even if we are able to produce a drug that successfully treats the virus, there is significant competition in the search for a treatment for COVID-19 and our product would not be the only commercially available treatment.

In June 2020, the FDA authorized the initiation of a Phase 2/3 clinical trial evaluating emvododstat as a potential treatment for COVID-19 and we expect results from this trial to be available in the first half of 2022. Our clinical trial for emvododstat may reveal unfavorable characteristics, including safety concerns, and may not demonstrate efficacy. We cannot be certain that the Phase 2/3 clinical trial will be sufficient to enable us to obtain marketing approval of emvododstat for the treatment of COVID-19, and we may need to conduct additional clinical trials before we are able to apply for marketing approval. Additionally, the FDA and other regulators may not agree with our interpretation of the results of the clinical data from the trial. If we are unable to successfully complete the clinical trial, if the results of the clinical trial are not positive or are only modestly positive, or if there are safety concerns, we may be unable to produce a drug that successfully treats COVID-19 and receives regulatory approval in a timely manner, if at all.

The timing and success of our clinical trial of emvododstat for the treatment of patients with COVID-19 will depend on our ability to enroll patients in the trial. Our inability to enroll a sufficient number of patients could result in significant delays or could require us to abandon the trial and development of emvododstat for the treatment of COVID-19 altogether. Patient enrollment may be affected by the availability of commercially available treatments and vaccines and other ongoing clinical trials. There is significant competition, including from other companies and governmental organizations, to find a treatment for COVID-19. For example, the FDA has approved the use of the Pfizer and Moderna COVID-19 vaccines and authorized the use of the Johnson & Johnson COVID-19 vaccine in the United States. The FDA has approved Gilead's antiviral drug Velkury (remdesivir) for the treatment of COVID-19. The FDA has also granted emergency use authorizations to Merck's molnupiravir, Pfizer's Paxlovid (nirmatrelvir tablets and ritonavir tablets, co-packaged for oral use) and monoclonal antibodies, among other products, for the treatment and prevention of COVID-19. As a result, even if we are able to sufficiently enroll our clinical trial and produce an effective treatment for COVID-19, there is no guarantee that we will be able to successfully commercialize our product. For additional information, see the risk factor under "Risks Related to the Development and Commercialization of our Products and our Product Candidates" titled, *"If we experience delays or difficulties in the enrollment of patients in our clinical trials, our receipt of necessary regulatory approvals could be delayed or prevented."*

If we are unable to establish or maintain sales, marketing and distribution capabilities or enter into agreements with third parties to market, sell and distribute our products or product candidates, we may not be successful in our continuing efforts to commercialize our products or any other product candidate if and when they are approved.

Our ongoing commercial strategy for our products and any other product candidate that may receive marketing authorization involves the development of a commercial infrastructure that spans multiple jurisdictions and is heavily dependent upon our ability to continue to build an infrastructure that is capable of implementing our global commercial strategy. The establishment and development of our commercial infrastructure will continue to be expensive and time consuming, and we may not be able to develop our commercial organizations in all intended territories, including in the United States, in a timely manner or at all. Doing so will require a high degree of coordination and compliance with laws and regulations in numerous territories, including in the United States, each state, and other countries in which we do business, including restrictions on advertising practices, enforcement of intellectual property rights, restrictions on pricing or discounts, transparency laws and regulations, and unexpected changes in regulatory requirements and tariffs. If we are unable to effectively coordinate such activities or comply with such laws and regulations, our ability to commercialize our products or any other product candidates that may receive marketing authorization in the United States, the EEA, Latin America and other jurisdictions will be adversely affected. If we are unable to establish and maintain adequate sales, marketing and distribution capabilities, whether independently or with third parties, we may not be able to generate product revenue consistent with our expectations and may not become profitable.

There are risks involved with establishing our own sales and marketing capabilities and entering into arrangements with third parties to perform these services. For example, recruiting and training an internal commercial team is expensive and time consuming and could delay commercialization efforts. If a commercial launch for any product or product candidate for which we recruit a commercial team and establish marketing capabilities is delayed or does not occur for any reason,

we would have prematurely or unnecessarily incurred these commercialization expenses. This may be costly, and our investment would be lost if we cannot retain or reposition such personnel.

The arrangements that we have entered into, or may enter into, with third parties to perform sales and marketing services will generate lower product revenues or profitability of product revenues to us than if we were to market and sell any products that we develop ourselves. In addition, we may not be successful in entering into arrangements with third parties to sell and market our product candidates or may be unable to do so on terms that are favorable to us. We have little control over such third parties, and any of them may fail to devote the necessary resources and attention to sell and market our products effectively.

If we do not establish sales and marketing capabilities successfully, either on our own or in collaboration with third parties, we will not be successful in commercializing our products or product candidates.

Factors that may materially affect our efforts to commercialize our products include:

- our ability to recruit, train and retain adequate numbers of effective sales and marketing personnel;
- our ability to monitor the legal and regulatory compliance of sales and marketing personnel;
- an inability to secure adequate coverage and reimbursement by government and private health plans;
- reduced realization on government sales from mandatory discounts, rebates and fees, and from price concessions to private health plans and pharmacy benefit managers necessitated by competition for access to managed formularies;
- the clinical indications for which the products are approved and the claims that we may make for the products;
- limitations or warnings, including distribution or use restrictions, contained in the products' approved labeling;
- any distribution and use restrictions imposed by the FDA or to which we agree as part of a mandatory REMS or voluntary risk management plan;
- liability for sales or marketing personnel who fail to comply with the applicable legal and regulatory requirements;
- our ability to implement third-party marketing and distribution relationships on favorable terms, or at all, in territories where we do not pursue direct commercialization;
- the ability of our commercial team to obtain access to or persuade adequate numbers of physicians to prescribe our current or any future products;
- the lack of complementary products to be offered by our commercial team, which may put us at a competitive disadvantage relative to companies with more extensive product lines; and
- unforeseen costs and expenses associated with creating an independent commercial organization.

Any of these factors, individually or as a group, if not resolved in a favorable manner may have a material adverse effect on our business and results of operations. Similar risks apply in those territories where any of our products are available on a reimbursed basis under an EAP program.

A substantial portion of our commercial sales currently occurs in territories outside of the United States which subjects us to additional business risks that could adversely affect our revenue and results of operations.

We commercialize Translarna, Tegsedi and Waylivra outside of the United States. We have operations in multiple European countries, Latin America and other territories. We expect that we will continue to expand our international operations in the future, including in emerging growth markets, pending successful completion of the applicable regulatory processes. International operations inherently subject us to a number of risks and uncertainties, including:

- various effects and responsive measures relating to the COVID-19 pandemic;
- political, regulatory, compliance and economic developments that could restrict our ability to manufacture, market and sell our products;
- financial risks such as longer payment cycles, difficulty collecting accounts receivable and exposure to fluctuations in foreign currency exchange rates;
- difficulty in staffing and managing international operations;

- potentially negative consequences from changes in or interpretations of tax laws;
- changes in international medical reimbursement policies and programs;
- unexpected changes in healthcare policies of ex-U.S. jurisdictions;
- trade protection measures, including import or export licensing requirements and tariffs;
- our ability to develop relationships with qualified local distributors and trading companies;
- political and economic instability in particular ex-U.S. economies and markets, in particular in emerging markets, for example in Brazil;
- diminished protection of intellectual property in some countries outside of the United States;
- differing labor regulations and business practices; and
- regulatory and compliance risks that relate to maintaining accurate information and control over sales and distributors' and service providers' activities that may fall within the purview of the Foreign Corrupt Practices Act, UK Bribery Act or similar local regulation.

For example, as a result of the COVID-19 pandemic, the Brazilian Ministry of Health is continuing to experience significant delays processing centralized group purchase orders. Almost all of our product revenue for Translarna in Brazil is attributable to such purchase orders. These centralized group purchase order delays have caused, and may continue to cause, fluctuations in our ability to generate revenue in Brazil.

In addition, some countries in which a product candidate is not approved allow patients access to the product candidate through other legal mechanisms, including court intervention or EAP programs, if the product is approved in another jurisdiction. The price that is ultimately approved by governmental authorities in any country pursuant to commercial pricing and reimbursement processes may be significantly lower than the price we are able to charge for sales under such legal mechanisms and we may become obligated to repay such excess amount. For additional information, see also "Risks Related to the Regulation of our Products and our Product Candidates"-"*Commercialization of Translarna has been in, and is expected to continue to take place in, countries that tend to impose strict price controls, which may adversely affect our revenues. Failure to obtain and maintain acceptable pricing and reimbursement terms for Translarna for the treatment of nmDMD in the EEA and other countries where Translarna is available would delay or prevent us from marketing our product in such regions, which would adversely affect our anticipated revenue, growth and business.*"

Some of the countries in which our products are available for sale are in emerging markets. Some countries within emerging markets, including those in Latin America, may be especially vulnerable to periods of global or regional financial instability or may have very limited resources to spend on. We also may be required to increase our reliance on third-party agents within less developed markets. In addition, many emerging market countries have currencies that fluctuate substantially and if such currencies devalue and we cannot offset the devaluations, our financial performance within such countries could be adversely affected.

Furthermore, in some countries, including Russia, orders for named patient sales may be for multiple months of therapy, which can lead to an unevenness in orders which could result in significant fluctuations in quarterly net product sales. Other factors may also contribute to fluctuations in quarterly net product sales including a product's availability in any particular territory, government actions, economic pressures, political unrest and other factors. Net product sales are impacted by factors, such as the timing of decisions by regulatory authorities, in particular the FDA and the EMA with respect to our ability to market or sell Translarna for the treatment of nmDMD, and our ability to successfully negotiate favorable pricing and reimbursement processes on a timely basis in the countries in which we have or may obtain regulatory approval, including the United States, EEA and other territories.

Any of these factors may, individually or as a group, have a material adverse effect on our business and results of operations. As we continue to expand our existing international operations, we may encounter new risks.

Laws and regulations governing export restrictions and economic sanctions may preclude us from developing and selling certain products, generating revenue from such products, and manufacturing certain materials outside of the United States.

Many countries, including the United States, restrict the export or import of products to or from certain countries through, for example, bans, sanction programs, and boycotts. Such restrictions may preclude us from supplying products or generating revenue in certain countries or may require an export license prior to the export of the controlled item. Various laws, regulations and executive orders also restrict the use and dissemination outside of the United States, or the sharing with certain non-U.S. nationals, of information classified for national security purposes, as well as certain products and technical data relating to those products. Furthermore, if we, or third parties acting on our behalf, do not comply with these restrictions, we may be subject to substantial civil and criminal penalties and suspension or debarment from government contracting.

Our activities outside of the United States, require that we dedicate resources to comply with these laws. Many of our customers and suppliers are ex-U.S. entities or have significant ex-U.S. operations. Although these restrictions have not affected our operations in the past, there is a risk that they could do so in the future as additional geographic regions and entities may become subject to such restrictions. The imposition of new or additional economic and trade sanctions against our major customers or suppliers or financial counterparties or intermediaries could result in our inability to sell to, and generate revenue from such customers or purchase materials from such suppliers. For example, we make sales of Translarna through a distributor to the Ministry of Health of the Russian Federation to access Russian nmDMD patients. Our ability to generate and realize revenue in Russia may be materially and adversely impacted as many countries, including the United States, consider imposing enhanced export controls on certain products and sanctions on certain industry sectors and parties in Russia. We also contract with government-owned hospitals and third-party manufacturers located in China, which has recently been involved in political conflict with the United States. This conflict has increased the likelihood of restrictions that could materially and adversely affect our clinical trial sites located in China and our ability to obtain certain supplies. If our activities are affected because of these or other such restrictions, sanctions, or controls, our business, financial condition and results of operations could be materially and adversely affected. As a result of restrictive export laws, our customers may also seek to obtain a greater supply of similar or substitute products from our competitors that are not subject to these restrictions, which could materially and adversely affect our business, financial condition and results of operations.

We face substantial competition, which may result in others discovering, developing or commercializing products before or more successfully than we do.

The development and commercialization of new drug products is highly competitive. We face competition with respect to our current products and product candidates and any products we may seek to develop or commercialize in the future from major pharmaceutical companies, specialty pharmaceutical companies, and biotechnology companies worldwide. Other gene therapy companies may in the future decide to utilize existing technologies to address unmet needs that could potentially compete with our product candidates.

There is currently no marketed therapy, other than Translarna in the EEA, which has received approval for the treatment of the underlying cause of nmDMD. Sarepta recently received approval in the United States for two treatments (Exondys 51 (eteplirsen) and Vyondys 53 (golodirsen)) addressing the underlying cause of disease for different mutations in the DMD gene. Additionally, the FDA granted accelerated approval to Viltepso (viltolarsen) from NS Pharma for the treatment of DMD in patients with exon 53 skipping and Sarepta (Casimersen (SRP 4045) for the treatment of DMD in patients with exon 45 skipping. Viltepso (viltolarsen) from NS Pharma is also approved in Japan. Other biopharmaceutical companies are developing treatments for the underlying cause of disease for different mutations in the DMD gene, Daiichi Sankyo (DS-5141), Nippon Shinyaku (Viltolarsen (NS-065/NCNP-01) and NS-089/NCNP-02), and Astellas (AT-702). Other pharmaceutical companies are developing micro dystrophin gene therapies for patients with DMD regardless of genotype, including Sarepta (SRP-9001), Pfizer (PF-06939926) and Solid Biosciences (SGT-001).

Although the FDA has not approved a corticosteroid specifically for DMD in the United States other than Emflaza, we face competition in the U.S. DMD market from prednisone/prednisolone, which, while not approved for DMD in the United States, is generically available and has been prescribed off label for DMD patients. ReveraGen BioPharma and Santhera are developing a glucocorticoid antagonist (vamorolone) for DMD patients with anticipated NDA filing in 2022.

Evrysdi also faces competition. For example, in December 2016, the FDA approved Spinraza (nusinersen), a drug developed by Ionis and marketed by Biogen, to treat SMA. Zolgensma (onasemnogene abeparvovec), a gene therapy drug

developed by AveXis, Inc. (acquired by Novartis in 2018) is approved in the United States and Japan for the treatment of SMA in patients under 2 years of age and in Europe for babies and young children who weigh up to 21 kilograms. Other companies are also pursuing product candidates for the treatment of SMA, including Kowa (sodrium valproate), Catalyst Pharmaceuticals (amifampridine), Scholar Rock (SRK-015), Roche Pharmaceuticals (RO7204239) and Cytokinetics (reldesemtiv).

There are several pharmaceutical and biotechnology companies engaged in the development or commercialization of products against targets that are also targets of Tegsedi and Waylivra. For example, if approved, Waylivra could face competition from drugs like Myalept (metreleptin). Myalept, produced by Novelion Therapeutics, Inc., is currently approved for use in generalized lipodystrophy patients. Additionally, Ionis is developing AKCEA-APOCIII-LRx for the treatment of FCS. Tegsedi also faces competition from drugs like Onpattro (patisiran), which was launched by Alnylam in the United States in 2018 and received approval in Brazil for the treatment of hATTR amyloidosis in 2020. Vyndaqel (tafamidis meglumine) and Vyndamax (tafamidis) are commercialized in the United States, EU and some other countries in Latin America by Pfizer. Other companies are also pursing product candidates for the treatment of ATTR Amyloidosis with polyneuropathy including Alnylam (vutrisiran), BridgeBio Pharma (AG-10), Proclara Biosciences (NPT-189), Prothena (PRK-004) and SOM Biotech (tolcapone).

Further, Tegsedi and Waylivra are delivered by injection, which may render them less attractive to patients than non-injectable products offered by our current or future competitors. If Tegsedi or Waylivra cannot compete effectively with these and other products with common or similar indications, we may not be able to generate substantial revenue from our product sales.

Currently, no treatment options are available for the underlying cause of AADC deficiency, and care is limited to palliative options with significant burden on caregivers. Additionally, we are not aware of any late-stage development product candidates for AADC deficiency.

There are currently no drugs approved to delay the onset or slow the progression of Huntington's disease. However, Novartis (branaplam), uniQure (AMT-130), Roche and Ionis (tominersen) and Wave Life Sciences (WVE-003) are all developing product candidates for treatment of Huntington disease.

While there are currently no disease modifying treatment options available for Friedreich ataxia, omaveloxolone, which is being developed by Reata Pharmaceuticals and RT-001, which is being developed by Retrotope, are each late stage product candidates being investigated for the treatment of Friedreich ataxia.

There are no disease modifying drugs approved for the treatment of mitochondrial disease associated seizures and we are not aware of any late-stage development product candidates for mitochondrial disease associated seizures.

Current standard of care for ALS is Rilutek (riluzole), currently available as a generic and other formulations, and Radicava (edaravone). Amylyx Pharmaceuticals (AMX-0035) has submitted an NDA to the FDA and an MAA to EMA. There are multiple other late stage product candidates being developed for the treatment of ALS including Ionis (Jacifusen), Clene Nanomedicine (CNM-Au8), MediciNova (Ibudilast), AB Science (AB-1010 mastinib mesylate), and Prilenia Therapeutics (Pridopidine).

If approved, PTC923 could face competition from Kuvan (sapropterin dihydrochloride), including generic versions, and Palynziq (pegvaliase-pqpz), each of which is approved for the treatment of PKU. Furthermore, Homology (HMI-102) and BioMarin (BMN 307) each are developing gene therapy product candidates for the treatment of PKU.

If approved, emvododstat for COVID-19 could face significant competition as many other companies and governmental organizations have expended resources to find a treatment for COVID-19. The FDA has approved the use of the Pfizer and Moderna COVID-19 vaccines and authorized the use of the Johnson & Johnson COVID-19 vaccine in the United States. The FDA has approved Gilead's antiviral drug Velkury (remdesivir) for the treatment of COVID-19. The FDA has also granted emergency use authorizations to Merck's molnupiravir, Pfizer's Paxlovid (nirmatrelvir tablets and ritonavir tablets, co-packaged for oral use) and monoclonal antibodies, among other products, for the treatment and prevention of COVID-19.

First line treatment for LMS is surgery where appropriate and then chemotherapy options including doxorubicin, gemcitabine, dacarbazine and docetaxel for unresectable metastatic disease. For second line treatment, two drugs are approved for soft tissue sarcoma including LMS and these are Yondelis (trabectedin) and Votrient (pazopanib). Most LMS patients require multiple lines of therapy.

There is no approved treatment for DIPG and very little improvement have been observed over the past 40 years. The current standard of care is radiation therapy which can shrink the tumor, though response is transient.

Our competitors may develop products that are more effective, safer, more convenient or less costly than any that we are marketing or developing or that would render our products or product candidates obsolete or non-competitive. Our competitors may also obtain marketing authorization for their products more rapidly than we may obtain approval for our products and product candidates, which could result in our competitors establishing a strong market position before we are able to enter the market.

We believe that many competitors are attempting to develop therapeutics for the target indications of our products and product candidates, including academic institutions, government agencies, public and private research organizations, large pharmaceutical companies and smaller more focused companies.

Many of our competitors may have significantly greater financial resources and expertise in research and development, manufacturing, preclinical testing, conducting clinical trials, obtaining regulatory approvals and marketing approved products than we do. Mergers and acquisitions in the pharmaceutical and biotechnology industries may result in even more resources being concentrated among a smaller number of our competitors. Smaller and other early stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies. These third parties compete with us in recruiting and retaining qualified scientific and management personnel, establishing clinical trial sites and patient registration for clinical trials, as well as in acquiring technologies complementary to or necessary for our programs.

Our products or product candidates may become subject to unfavorable pricing regulations, third-party reimbursement practices or healthcare reform initiatives, which would harm our business.

We may not obtain adequate coverage or reimbursement for our products or we may be required to sell our products at an unsatisfactory price. In addition, obtaining pricing, coverage and reimbursement approvals can be a time consuming and expensive process. Our business would be materially adversely affected if we do not receive these approvals on a timely basis.

The regulations and practices that govern marketing authorizations, pricing, coverage and reimbursement for new drug products vary widely from country to country. Current and future legislation may significantly change the approval requirements in ways that could involve additional costs and cause delays in obtaining approvals. Some countries, including almost all of the member states of the EEA, require approval of the sale (list) price of a drug before it can be marketed. In many countries, the pricing review period begins after marketing or product licensing approval is granted. In some ex-U.S. markets, including the European market, prescription pharmaceutical pricing remains subject to continuing governmental control even after initial approval is granted. As a result, we might obtain marketing authorization for a product in a particular country, but then be subject to price regulations, in some countries at national as well as regional levels, that delay our commercial launch of the product, possibly for lengthy time periods, and negatively impact the revenues we are able to generate from the sale of the product in that country. Adverse pricing limitations may hinder our ability to recoup our investment in one or more products, including Emflaza and Translarna, or other product candidates, even following marketing authorization.

Our ability to successfully commercialize our products or product candidates that may receive marketing authorization will depend in large part on the extent to which coverage and reimbursement for these products and related treatments will be available from government health administration authorities, private health insurers, managed healthcare organizations and other third-party payors and organizations. Government authorities and other third-party payors, such as private health insurers and managed healthcare organizations, decide which medications they will pay for and establish reimbursement conditions and rates. A primary trend in the EU and U.S. healthcare industries and elsewhere is cost containment.

Government authorities, including the United States government and state legislatures, and other third-party payors have attempted to control costs by limiting coverage and the amount of reimbursement for particular medications. Prices at which our products are reimbursed can be subject to challenge, reduction or denial by the government and other payers. Increasingly, third-party payors are requiring that drug companies provide them with discounts off the products' sale (list) prices and are challenging the prices manufacturers charge for medical products. We cannot be sure that coverage will be available for any product or product candidate that we may commercialize and, if coverage is available, the level of reimbursement is also uncertain.

Reimbursement levels may impact the demand for, or the price of, any product or product candidate for which we obtain marketing authorization. Obtaining reimbursement for Emflaza and for Translarna has been and is expected to continue to be, particularly difficult due to price considerations typically associated with drugs that are developed to treat conditions that affect a small population of patients. In addition, third-party payors are likely to impose strict requirements for reimbursement of a higher priced drug, such as prior authorization and the requirement to try other therapies first, or high co-payments which can result in patient rejection. Decreases in third-party reimbursement for a product or a decision by a third-party payor to not cover a product could reduce physician usage of the product, including Emflaza or Translarna. If reimbursement is not available or is available only on a limited basis, we may not be able to successfully commercialize any product or product candidate for which we have obtained or may obtain marketing authorization, including Emflaza or Translarna.

There may be significant delays in obtaining coverage for newly approved drugs, and coverage may be more limited than the drug's approved indications as determined by the applicable regulatory authority. Moreover, eligibility for reimbursement does not imply that any drug will be paid for in all cases or at a rate that covers our costs, including research, development, manufacture, sale and distribution. Interim reimbursement levels for new drugs, if applicable, may also not be sufficient to cover our costs and may not be made permanent, and programs intended to provide patient assistance until coverage is established can be very costly. Reimbursement rates may vary according to the use of the drug and the clinical setting in which it is used, may be based on reimbursement levels already set for lower cost drugs, and may be incorporated into existing payments for other services. Further, coverage policies and third-party reimbursement rates may change at any time. Even if favorable coverage and reimbursement status is attained for one or more products for which we receive regulatory approval, less favorable coverage policies and reimbursement rates may be implemented in the future.

Net prices for drugs may be reduced by mandatory discounts or rebates required by government healthcare programs or private payors and by any future relaxation of laws, enforcement policies or administrative determinations with respect to the importation of drugs into the United States from other countries where they may be sold at lower prices.

In the United States, third-party payors include federal healthcare programs, such as Medicare, Medicaid, TRICARE, and Veterans Health Administration programs; managed care providers, private health insurers and other organizations. Several of the U.S. federal healthcare programs establish ceiling prices or require that drug manufacturers extend discounts or pay rebates to certain programs in order for their products to be covered and reimbursed. For example, the Medicaid Drug Rebate Program requires pharmaceutical manufacturers of covered outpatient drugs to enter into and have in effect a national rebate agreement with the federal government as a condition for coverage of the manufacturer's covered outpatient drug(s) by state Medicaid programs. The amount of the rebate for each product is based on a statutory formula and may be subject to an additional discount if certain pricing increases more than inflation. State Medicaid programs and Medicaid managed care plans can seek additional "supplemental" rebates from manufacturers in connection with states' establishment of preferred drug lists. A further requirement for Medicaid coverage is that manufacturers of single source and innovator multiple source drugs enter into a Master agreement and Federal Supply Schedule, or FSS, agreement with the Secretary for Veterans Affairs and charge no more than statutory ceiling prices to the Department of Veteran Affairs, the Department of Defense and certain other federal agencies.

Similarly, in order for a covered outpatient drug to receive federal reimbursement under the Medicare Part B and Medicaid programs, the manufacturer must extend discounts on the covered outpatient drug to entities that are enrolled and participating in the 340B drug pricing program, which is a federal program that requires manufacturers to provide discounts to certain statutorily-defined safety-net providers. The 340B discount for each product is calculated based on certain Medicaid Drug Rebate Program metrics that manufacturers are required to report to CMS.

Emflaza is also eligible for reimbursement under the Medicare Part D program. Under Part D, Medicare beneficiaries may enroll in prescription drug plans offered by private entities, which will provide coverage of outpatient prescription drugs. Part D prescription drug formularies are required to include drugs within each therapeutic category and class of covered Part D drugs, though not necessarily all the drugs in each category or class. Any negotiated prices for our products covered by a Part D prescription drug plan likely will be lower than the prices we might otherwise obtain, and payment of Medicare Coverage Gap discounts may further reduce realization on Part D drugs. Further, CMS is proposing to relax Part D coverage requirements to give plans more leverage in negotiating their formularies.

With respect to drugs eligible for reimbursement under Medicare Part B, on November 27, 2020, CMS issued an interim final rule implementing a Most Favored Nations payment model under which reimbursement for certain Medicare Part B drugs and biologicals will be based on a price that reflects the lowest per capita Gross Domestic Product-adjusted (GDP-adjusted) price of any non-U.S. member country of the Organisation for Economic Co-operation and Development (OECD) with a GDP per capita that is at least sixty percent of the U.S. GDP per capita. This rule now has been rescinded but similar programs are the subject of current legislative proposals. Such rules and any additional healthcare reform measures could further constrain our business or limit the amounts that federal and state governments will pay for healthcare products and services, which could result in additional pricing pressures.

In addition, U.S. private health insurers often rely upon Medicare coverage policies and payment limitations in setting their own coverage and reimbursement policies. Any such coverage or payment limitations may result in a similar reduction in payments from non-governmental payors. Payment by private payors is also subject to payor-determined coverage and reimbursement policies that vary considerably and are subject to change without notice. We expect that coverage and reimbursement of Emflaza in the United States will vary from commercial payor to commercial payor. Many commercial payors, such as managed care plans, manage access to prescription drugs partly to control costs to their plans, and may use drug formularies and medical policies to limit their exposure. Exclusion from policies can directly reduce product usage in the payor's patient population and may negatively impact utilization in other payor plans, as well.

There has been recent negative publicity and increasing legislative and public scrutiny around pharmaceutical drug pricing in the U.S., in particular with respect to orphan drugs and specifically with respect to Emflaza. Moreover, U.S. government authorities and third-party payors are increasingly attempting to limit or regulate drug prices and reimbursement, often with particular focus on orphan drugs. These dynamics may give rise to heightened attention and potential negative reactions to pricing decisions for Emflaza and products for which we may receive regulatory approval in the future, possibly limiting our ability to generate revenue and attain profitability.

Moreover, in 2017, the U.S. Congress modified and amended certain provisions of the 2010 U.S. healthcare reform legislation (the Patient Protection and Affordable Care Act of 2010, as amended by the Health Care and Education Reconciliation Act of 2010, known collectively as the Affordable Care Act), which could have an impact on coverage and reimbursement for healthcare items and services covered by the federal and state healthcare programs as well as plans in the private health insurance market. The so-called "individual mandate" was repealed as part of tax reform legislation adopted in December 2017. Legal challenges to the Affordable Care Act continue to arise and there may be future efforts to modify, repeal, or otherwise invalidate all, or certain provisions of the Affordable Care Act. The Biden administration is expected to continue to take measures to further facilitate the implementation of the Affordable Care Act. We cannot assure that the Affordable Care Act, as currently enacted or as amended in the future, will not adversely affect our business and financial results and we cannot predict how future federal or state legislative or administrative changes relating to healthcare reform will affect our business.

Additionally, the Budget Control Act of 2011, among other things, created measures for spending reductions by Congress. Failure of the Joint Select Committee on Deficit Reduction to reach required deficit reduction goals triggered the legislation's automatic reduction to several government programs. This includes aggregate reductions of Medicare payments to providers up to 2% per fiscal year. While President Biden previously signed legislation to eliminate this reduction through the end of 2021, recent legislation will restart the reductions, which will thereafter remain in effect through 2031 unless additional congressional action is taken.

In the EU, reference pricing systems and other measures may lead to cost containment and reduced prices with respect to Translarna for the treatment of nmDMD and other product candidates that might receive marketing authorization in the

future. Our inability to promptly obtain coverage and profitable payment rates from both government-funded and private payors for our product or any of our product candidates that may receive marketing authorization, or a reduction in coverage for payment rates for our product or any such product candidates, could have a material adverse effect on our business, results of operations and financial condition. In addition, in the EU, an authorized trader, such as a wholesaler, can purchase a medicine in one EU member state and obtain a license to import the product into another EU member state. This process is called "parallel distribution". As a result, a purchaser in one EU member state may seek to import Translarna from another EU member state where Translarna is sold at a lower price. This could have a negative impact on our business, financial condition, results of operations and growth.

Similarly, sales of Emflaza in the United States could also be reduced if deflazacort is imported into the United States from lower-priced markets, whether legally or illegally. For example, in the United States, prices for pharmaceuticals are generally higher than in the bordering nations of Mexico and Canada. There have been proposals to legalize the import of pharmaceuticals from outside the United States and the FDA has finalized a guidance to facilitate the import of U.S. approved pharmaceutical and biologic products that were originally intended for marketing in a foreign country. If such legislation were enacted, our revenues from Emflaza could be reduced, and our business, results of operations and financial condition could be materially adversely affected.

Risks Related to Our Financial Position and Need for Additional Capital

We have incurred significant losses since our inception and based on our current commercial, research and development plans, we expect to continue to incur significant operating expenses for the foreseeable future. We may never generate profits from operations or maintain profitability.

Since inception, we have incurred significant operating losses. As of December 31, 2021, we had an accumulated deficit of $2,098.0 million. We have historically financed our operations primarily through the issuance and sale of our common stock in public offerings, our "at the market offerings" of our common stock, our initial public offering, proceeds from the Royalty Purchase Agreement, the private placements of our preferred stock, collaborations, bank and institutional lender debt, grant funding and clinical trial support from governmental and philanthropic organizations and patient advocacy groups in the disease areas addressed by our product candidates. Since 2014, we have also relied on revenues generated from net sales of Translarna for the treatment of nmDMD in territories outside of the United States, and since May 2017, we have generated revenue from net sales of Emflaza for the treatment of DMD in the United States. We have also relied on revenue associated with milestone and royalty payments from Roche pursuant to the SMA License Agreement under our SMA program. We also began to recognize revenue generated from net sales of Tegsedi for the treatment of stage 1 or stage 2 polyneuropathy in adult patients with hATTR amyloidosis in 2019 and Waylivra for the treatment of FCS in 2020 in Latin America and the Caribbean. Based on our current commercial, research and development plans, we expect to continue to incur significant operating expenses for the foreseeable future, which we anticipate will be partially offset by revenues generated from the sale of our products and our collaboration and royalty revenues. We expect to continue to generate operating losses through 2022 and, while we anticipate that operating losses generated in future periods should decline versus prior periods, we may never generate profits from operations or maintain profitability. The net losses we incur may fluctuate significantly from period to period.

From time to time, we have engaged in strategic transactions to expand and diversify our product pipeline, including through the acquisition of assets or businesses. In connection with these acquisitions, we have entered into agreements through which we have ongoing obligations, including obligations to make contingent payments upon the achievement of certain development, regulatory and net sales milestones or upon a percentage of net sales of certain products. See "Item 1. Business-Our Ongoing Acquisition-Related Obligations" for further information regarding our acquisitions and our ongoing obligations. We may engage in additional strategic transactions to expand and diversify our product pipeline, including through the acquisition of assets, businesses, or rights to products, product candidates or technologies or through strategic alliances or collaborations and we may incur expenses, including with respect to transaction costs, subsequent development costs or any upfront, milestone or other payments or other financial obligations associated with any such transaction.

Our current ability to generate revenue from sales of Translarna is dependent upon our ability to maintain our marketing authorizations in the EEA and Brazil of Translarna for the treatment of nmDMD in ambulatory patients aged two years

and older and in Russia for the treatment of nmDMD in patients aged two years and older. The marketing authorization in the EEA is subject to annual review and renewal by the European Commission following reassessment by the EMA of the benefit-risk balance of the authorization and is further subject to a specific obligation to conduct and report the results of Study 041, a multi-center, randomized, double-blind, 18-month, placebo-controlled trial, followed by an 18-month open-label extension, according to an agreed protocol, in order to confirm the efficacy and safety of Translarna. Enrolling, conducting and reporting a clinical trial is a time-consuming, expensive and uncertain process that takes years to complete, and we expect that we will incur material costs related to the implementation and conduct of Study 041. We may experience unknown complications with Study 041 and may not achieve the pre-specified endpoint with statistical significance, which would have a material adverse effect on our ability to maintain our marketing authorization in the EEA.

If, in any annual renewal cycle, the EMA determines that the balance of benefits and risks of using Translarna for the treatment of nmDMD has changed materially or that we have not or are unable to comply with the specific obligation to complete Study 041 or any other requirement that has been or may be placed on the marketing authorization, the European Commission could, at the EMA's recommendation, vary, suspend, withdraw or refuse to renew the marketing authorization for Translarna or impose other specific obligations or restrictions, which would have a materially adverse effect on our business. We expect to incur significant costs in connection with our efforts to maintain our marketing authorization in the EEA. If our marketing authorization in the EEA is not renewed, or our product label is materially restricted, we would lose all, or a significant portion of, our ability to generate revenue from sales of Translarna, whether pursuant to a commercial or a reimbursed early access program, or EAP program, and throughout all territories. For additional information, see the risk factor under "Risks Related to Regulatory Approval of our Products and our Product Candidates" titled, "*Our marketing authorization in the EEA for Translarna for the treatment of nmDMD is a "conditional marketing authorization" that requires annual review and renewal by the European Commission following reassessment by the EMA of the benefit-risk balance of the authorization and is further conditioned upon our ability to satisfy the specific obligation to conduct and report results from Study 041 by the end of the third quarter of 2022, and, as such, there is ongoing risk that we may be unable to maintain such authorization. If we are unable to obtain renewal of such marketing authorization in any future renewal cycle, we could lose all, or a significant portion of, our ability to generate revenue from sales of Translarna, whether pursuant to a commercial or an EAP program, which would have a material adverse effect on our business, financial performance and results of operations."*

We also expect that our efforts to advance Translarna for the treatment of nmDMD in the United States will be time-consuming and may be expensive. For additional information, see the risk factor under "Risks Related to Development and Commercialization of our Products and our Product Candidates" titled, "D*elays or failures in obtaining regulatory approval in the United States, may prevent us from commercializing Translarna for nmDMD in that territory and our ability to generate revenue will be materially impaired. In the event that the FDA requires us to conduct additional clinical trials in nmDMD which, if successful, may enable FDA review of an NDA submission by us, we would expect to incur significant costs, which may have a material adverse effect on our business and results of operations."*

We anticipate that our expenses will continue to increase in connection with our commercialization efforts in the United States, the EEA, Latin America and other territories, including the expansion of our infrastructure and corresponding sales and marketing, legal and regulatory, distribution and manufacturing and administrative and employee-based expenses. In addition to the foregoing, we expect to continue to incur significant costs in connection with ongoing, planned and potential future clinical trials and studies in our splicing, gene therapy, Bio-e, metabolic and oncology programs and studies of emvododstat for COVID-19 as well as studies in our products for maintaining authorizations, including Study 041, label extensions and additional indications. We have begun seeking and intend to continue to seek marketing authorization for Translarna for the treatment of nmDMD in territories outside of the EEA, Brazil and Russia. We submitted an MAA to the EMA for the treatment of AADC deficiency with PTC-AADC in the EEA. We are also preparing a BLA for PTC-AADC for the treatment of AADC deficiency in the United States and we anticipate submitting a BLA to the FDA in the second quarter of 2022. We filed for marketing authorization with ANVISA for Waylivra for the treatment of FPL and we expect a regulatory decision on approval from ANVISA in the second half of 2022. These efforts may significantly impact the timing and extent of our commercialization expenses.

In addition, the clinical and regulatory developments noted in this risk factor may exacerbate the risks related to our commercialization efforts set forth under the heading "Risks Related to the Development and Commercialization of our Products and our Product Candidates," which could increase the costs associated with our commercial activities or have a

negative impact on our revenues. For additional information, see also "Risks Related to the Regulation of our Products and our Product Candidates" "*Commercialization of Translarna has been in, and is expected to continue to take place in, countries that tend to impose strict price controls, which may adversely affect our revenues. Failure to obtain and maintain acceptable pricing and reimbursement terms for Translarna for the treatment of nmDMD in the EEA and other countries where Translarna is available would delay or prevent us from marketing our product in such regions, which would adversely affect our anticipated revenue, growth and business.*"

We may seek to continue to expand and diversify our product pipeline through opportunistically in-licensing or acquiring the rights to products, product candidates or technologies and we may incur expenses, including with respect to transaction costs, subsequent development costs or any upfront, milestone or other payments or other financial obligations associated with any such transaction, which would increase our future capital requirements.

With respect to our outstanding 3.00% convertible senior notes due August 15, 2022, or the 2022 Convertible Notes, cash interest payments are payable on a semi-annual basis in arrears, which will require total funding of $4.5 million annually. The 2022 Convertible Notes will mature on August 15, 2022 and we will be required to pay any outstanding principal amount of the 2022 Convertible Notes at that time, unless earlier converted, redeemed or repurchased in accordance with their terms prior to such date. As of February 15, 2022, until the close of business on the business day immediately preceding the maturity date, holders may convert their 2022 Convertible Notes at any time. Upon conversion, we will pay or deliver, as the case may be, cash, shares of our common stock or any combination thereof at our election. With respect to our outstanding 1.50% convertible senior notes due September 15, 2026, or the 2026 Convertible Notes, cash interest payments are payable on a semi-annual basis in arrears, which will require total funding of $4.3 million annually. In addition, we expect to pay Marathon a single $50.0 million sales-based milestone in connection with Emflaza sales in 2022. We also expect to pay the former equityholders of Agilis an aggregate of $70.0 million upon the achievement of certain development and regulatory milestones in 2022 relating to PTC-AADC.

In addition, our expenses will increase if and as we:

- seek to satisfy contractual and regulatory obligations we assumed in connection with our acquisitions and collaborations;
- execute our commercial strategy for our products, including initial commercialization launches of our products, label extensions or entering new markets;
- are required to complete any additional clinical trials, non-clinical studies or CMC assessments or analyses in order to advance Translarna for the treatment of nmDMD in the United States or elsewhere;
- are required to take other steps, in addition to Study 041, to maintain our current marketing authorization in the EEA, Brazil and Russia for Translarna for the treatment of nmDMD or to obtain further marketing authorizations for Translarna for the treatment of nmDMD or other indications;
- utilize the Hopewell Facility to manufacture program materials for certain of our gene therapy product candidates;
- initiate or continue the research and development of our splicing, gene therapy, Bio-e, metabolic and oncology programs and our studies of emvododstat for COVID-19 as well as studies in our products for maintaining authorizations, including Study 041, label extensions and additional indications;
- seek to discover and develop additional product candidates;
- seek to expand and diversify our product pipeline through strategic transactions;
- maintain, expand and protect our intellectual property portfolio; and
- add operational, financial and management information systems and personnel, including personnel to support our product development and commercialization efforts.

Our ability to generate profits from operations and become and remain profitable depends on our ability to successfully develop and commercialize drugs that generate significant revenue. This will require us to be successful in a range of challenging activities, including:

- commercializing and marketing all of our products and products candidates;
- negotiating, securing, and maintaining adequate pricing, coverage and reimbursement terms, on a timely basis, with third-party payors for our products and product candidates;

- maintaining the marketing authorization of Translarna for the treatment of nmDMD in the EEA, including successfully obtaining annual renewals of the marketing authorization, fulfilling the specific obligation to conduct and report the results of Study 041 to the EMA, and meeting any ongoing requirements related to the marketing authorization;
- advancing Translarna for the treatment of nmDMD in the United States, including, whether we will be required to perform additional clinical trials, non-clinical studies or CMC assessments or analyses at significant cost which, if successful, may enable FDA review of an NDA re-submission by us and, ultimately, may support approval of Translarna for nmDMD in the United States;
- maintaining orphan exclusivity in the United States for Emflaza;
- successfully completing any post-marketing requirements imposed by regulatory agencies with respect to our products;
- expanding the territories in which we are approved to market our products;
- successfully advancing our other programs and collaborations, including our splicing, gene therapy, Bio-e, metabolic and oncology programs and studies of emvododstat for COVID-19 as well as studies in our products for additional indications;
- maintaining a global commercial infrastructure, including the sales, marketing and distribution capabilities to effectively market and sell our products and product candidates throughout the world;
- implementing marketing and distribution relationships with third parties in territories where we do not pursue direct commercialization;
- identifying patients eligible for treatment with our products and product candidates;
- successfully developing or commercializing any product candidate or product that we may in-license or acquire;
- protecting our rights to our intellectual property portfolio related to Translarna and other products and product candidates; and
- contracting for the manufacture and distribution of commercial quantities of our products and product candidates.

We may never succeed in these activities and, even if we do, may never generate revenues that are significant enough to generate profits from operations. Even if we do generate profits from operations, we may not be able to sustain or increase profitability on a quarterly or annual basis. Our failure to generate profits from operations and remain profitable would decrease the value of our company and could impair our ability to raise capital, expand our business, maintain our research and development efforts, diversify our product offerings or continue our operations. A decline in the value of our company could also cause our stockholders to lose all or part of their investment in our company.

We may need additional funding. If we are unable to raise capital when needed, we could be forced to delay, reduce or eliminate our product development programs or commercialization efforts.

As noted in the prior risk factor, we expect to incur significant expenses related to our clinical, regulatory, commercial, legal, research and development, and other business efforts. We believe that our cash flows from product sales, together with existing cash and cash equivalents, including our Convertible Notes offerings, public offerings of common stock, our "at the market offering" of our common stock pursuant to an At the Market Offering Sales Agreement with Cantor Fitzgerald and RBC Capital Markets, LLC, or the Sales Agreement, proceeds from the Royalty Purchase Agreement and marketable securities, will be sufficient to fund our operating expenses and capital expenditure requirements for at least the next twelve months. We have based this estimate on assumptions that may prove to be wrong, and we could use our capital resources sooner than we currently expect.

Our future capital requirements will depend on many factors, including:

- our ability to commercialize and market our products and product candidates;
- our ability to negotiate, secure and maintain adequate pricing, coverage and reimbursement terms, on a timely basis, with third-party payors for our products and product candidates;
- our ability to maintain the marketing authorization in the EEA for Translarna for the treatment of nmDMD, including whether the EMA determines on an annual basis that the benefit-risk balance of Translarna supports renewal of our marketing authorization in the EEA, on the current approved label;
- the timing and outcome of Study 041;

- the costs, timing and outcome of our efforts to advance Translarna for the treatment of nmDMD in the United States, including, whether we will be required to perform additional clinical trials, non-clinical studies or CMC assessments or analyses at significant cost which, if successful, may enable FDA review of an NDA re-submission by us and, ultimately, may support approval of Translarna for nmDMD in the United States;
- our ability to maintain orphan exclusivity in the United States for Emflaza;
- our ability to successfully complete any post-marketing requirements imposed by regulatory agencies with respect to our products;
- the progress, results and costs of our activities under our splicing, gene therapy, Bio-e, metabolic and oncology programs and studies of emvododstat for COVID-19 as well as studies in our products for maintaining authorizations, label extensions and additional indications;
- the scope, costs and timing of our commercialization activities, including product sales, marketing, legal, regulatory, distribution and manufacturing, for our products and for any of our other product candidates that may receive marketing authorization or any additional indications or territories in which we receive authorization to market our products;
- our ability to utilize the Hopewell Facility to manufacture program materials for certain of our gene therapy product candidates;
- the costs, timing and outcome of regulatory review of our other product candidates, including those in our splicing, gene therapy, Bio-e, metabolic and oncology programs and studies of emvododstat for COVID-19 as well as studies in our products for maintaining authorizations, label extensions and additional indications;
- our ability to satisfy our obligations under the indentures governing our Convertible Notes;
- the timing and scope of growth in our employee base;
- revenue received from commercial sales of or products or any of our other product candidates;
- our ability to obtain additional and maintain existing reimbursed named patient and cohort EAP programs for our products and product candidates on adequate terms, or at all;
- the ability and willingness of patients and healthcare professionals to access our products and product candidates through alternative means if pricing and reimbursement negotiations in the applicable territory do not have a positive outcome;
- the costs of preparing, filing and prosecuting patent applications, maintaining, and protecting our intellectual property rights and defending against intellectual property-related claims;
- the extent to which we acquire or invest in other businesses, products, product candidates, and technologies, including the success of any acquisition, in-licensing or other strategic transaction we may pursue, and the costs of subsequent development requirements and commercialization efforts, including with respect to our acquisitions of Emflaza, Agilis, Censa and of BioElectron's assets, and our licensing of Tegsedi and Waylivra; and
- our ability to establish and maintain collaborations, including our collaborations with Roche and the SMA Foundation, and our ability to obtain research funding and achieve milestones under these agreements.

Conducting preclinical testing and clinical trials is a time-consuming, expensive and uncertain process that takes years to complete, and we may never generate the necessary data or results required to obtain regulatory approval and achieve product sales for certain product candidates or indications. In addition, our products and product candidates, if approved, may not achieve sustained commercial success. Likewise, if we fail to maintain our marketing authorization or lose non-patent market exclusivity for our products and product candidates, we will be unable to commercialize and generate revenue from the sales of those products.

Accordingly, we may need to continue to rely on additional financing in connection with our continuing operations and to achieve our business objectives. In addition, we may seek additional capital due to favorable market conditions or based on strategic considerations, even if we believe that we have sufficient funds for our current or future operating plans. Additional financing may not be available to us on acceptable terms or at all. If we are unable to raise capital when needed or on attractive terms, we could be forced to delay, reduce or eliminate our research and development programs or our commercialization efforts.

We may engage in strategic transactions to acquire assets, businesses, or rights to products, product candidates or technologies or form collaborations or make investments in other companies or technologies that could harm our operating results, dilute our stockholders' ownership, increase our debt, or cause us to incur significant expense.

As part of our business strategy, we may engage in additional strategic transactions to expand and diversify our product pipeline, including through the acquisition of assets, businesses, or rights to products, product candidates or technologies or through strategic alliances or collaborations, similar to our acquisitions of Emflaza, Agilis, Censa and BioElectron's assets and the Tegsedi-Waylivra Agreement. We may not identify suitable strategic transactions, or complete such transactions in a timely manner, on a cost-effective basis, or at all. Moreover, we may devote resources to potential opportunities that are never completed or we may incorrectly judge the value or worth of such opportunities. Even if we successfully execute a strategic transaction, we may not be able to realize the anticipated benefits of such transaction, may incur additional debt or assume unknown or contingent liabilities in connection therewith, and may experience losses related to our investments in such transactions. Integration of an acquired company or assets into our existing business may not be successful and may disrupt ongoing operations, require the hiring of additional personnel and the implementation of additional internal systems and infrastructure, and require management resources that would otherwise focus on developing our existing business. Even if we are able to achieve the long-term benefits of a strategic transaction, our expenses and short-term costs may increase materially and adversely affect our liquidity. Any of the foregoing could have a detrimental effect on our business, results of operations and financial condition.

In addition, future strategic transactions may entail numerous operational, financial and legal risks, including:

- incurrence of substantial debt, dilutive issuances of securities or depletion of cash to pay for acquisitions;
- exposure to known and unknown liabilities, including possible intellectual property infringement claims, violations of laws, tax liabilities and commercial disputes;
- higher than expected acquisition and integration costs;
- difficulty in integrating operations and personnel of any acquired business;
- increased amortization expenses or, in the event that we write-down the value of acquired assets, impairment losses;
- impairment of relationships with key suppliers or customers of any acquired business due to changes in management and ownership;
- inability to retain personnel, customers, distributors, vendors and other business partners integral to an in-licensed or acquired product, product candidate or technology;
- potential failure of the due diligence processes to identify significant problems, liabilities or other shortcomings or challenges;
- entry into indications or markets in which we have no or limited direct prior development or commercial experience and where competitors in such markets have stronger market positions; and
- other challenges associated with managing an increasingly diversified business.

If we are unable to successfully manage any strategic transaction in which we may engage, our ability to develop new products and continue to expand and diversify our product pipeline may be limited.

Raising additional capital may cause dilution to our stockholders, restrict our operations or require us to relinquish rights to our technologies or product candidates.

Until such time, if ever, as we can generate enough product revenues to cover our expenses, we expect to supplement our cash needs through a combination of equity offerings, debt financings, collaborations, strategic alliances, grants and clinical trial support from governmental and philanthropic organizations and patient advocacy groups in the disease areas addressed by our product candidates; marketing, distribution, licensing or other arrangements.

To the extent that we raise additional capital through the sale of equity or convertible debt securities, our shareholders' ownership interest will be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect the rights of our common stockholders. Debt financing, if available, may involve agreements that include

covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, entering into agreements involving licenses to our intellectual property, making capital expenditures or declaring dividends.

If we raise additional funds through collaborations, strategic alliances or marketing, distribution or licensing arrangements with third parties, we may have to relinquish valuable rights to our technologies, future revenue streams, research programs or product candidates; or grant licenses on terms that may not be favorable to us. If we are unable to raise additional funds through equity or debt financings when needed, we may be required to delay, limit, reduce or terminate our product development or future commercialization efforts or grant rights to develop and market product candidates that we would otherwise prefer to develop and market ourselves.

Our ability to use our net operating losses and certain other tax attributes to offset potential taxable income and related income taxes that would otherwise be due is subject to limitation under the provisions of Sections 382 and 383 of the Internal Revenue Code as a result of ownership changes of the Company and could be subject to further annual limitations under such provisions. In addition, we may not generate sufficient future taxable income to use our net operating losses and certain other tax attributes.

If a corporation undergoes an "ownership change" within the meaning of Sections 382 and 383 of the Internal Revenue Code of 1986, as amended, or Sections 382 and 383, the corporation's ability to utilize any net operating losses, or NOLs, and certain tax credits and other tax attributes generated before such an ownership change, is limited. We believe that we have in the past experienced ownership changes within the meaning of Sections 382 and 383 that have resulted in limitations under Sections 382 and 383 (and similar state provisions) on the use of our NOLs and other tax attributes.

Sections 382 and 383 are extremely complex provisions with respect to which there are many uncertainties, and we have not requested a ruling from the United States Internal Revenue Service, or IRS, to confirm our analysis of the ownership change limitations related to the NOLs and other tax attributes generated by us. Therefore, we have not established whether the IRS would agree with our analysis regarding the application of Sections 382 and 383. We continue to fully evaluate the impact of a limitation on the use of our NOLs and other tax attributes under Sections 382 and 383.

Moreover, our ability to use these NOLs to offset potential future taxable income and related income taxes that would otherwise be due is dependent upon our generation of future taxable income. In 2021, we generated NOLs which will be carried forward.

Changes in our effective income tax rates and future changes to U.S. and non-U.S. tax laws could adversely affect our results of operations.

We are subject to income taxes in the Unites States and various ex-U.S. jurisdictions. Taxes will be incurred as income is earned in these different jurisdictions. Various factors may have favorable or unfavorable effects on our effective income tax rate. These factors include, but are not limited to, interpretations of existing tax laws, changes in tax laws and rates, the accounting for stock options and other share-based compensation, changes in accounting standards, future levels of research and development spending, changes in the mix and level of pre-tax earnings by taxing jurisdiction, the outcome of examinations by the IRS and other jurisdictions, the accuracy of our estimates for unrecognized tax benefits, the realization of deferred tax assets, or by changes to our ownership or capital structure. The impact on our income tax provision resulting from the above-mentioned factors and others may be significant and could adversely affect our results of operations.

Changes in tax laws or regulations, including further regulatory developments arising from U.S. tax reform legislation as well as multi-jurisdictional changes enacted in response to the action items provided by the Organization for Economic Cooperation and Development (OECD), may increase tax uncertainty and the amount of tax we pay.

As part of Congress's response to the COVID-19 pandemic, the Families First Coronavirus Response Act, or FFCR Act, was enacted on March 18, 2020, the CARES Act was enacted on March 27, 2020, COVID relief provisions were included in the Consolidated Appropriations Act, 2021, or CAA, which was enacted on December 27, 2020, and the American Rescue Plan Act of 2021, or ARPA, was enacted on March 11, 2021. All contain numerous tax provisions. In particular, the CARES Act retroactively and temporarily (for taxable years beginning before January 1, 2021) suspends application

of the 80%-of-income limitation on the use of NOLs, which was enacted as part of the 2017 Tax Act. It also provides that NOLs arising in any taxable year beginning after December 31, 2017, and before January 1, 2021 are generally eligible to be carried back up to five years. The CARES Act also temporarily (for taxable years beginning in 2019 or 2020) relaxes the limitation of the tax deductibility for net interest expense by increasing the limitation from 30% to 50% of adjusted taxable income.

Regulatory guidance under the 2017 Tax Act, which was enacted on December 22, 2017, the FFCR Act, the CARES Act, the CAA, and the ARPA is and continues to be forthcoming, and such guidance could ultimately increase or lessen the impact of these laws on our business and financial condition. It is also possible that Congress will enact additional legislation in connection with the COVID-19 pandemic, and as a result of the changes in the U.S. presidential administration and control of the U.S. Senate, additional tax legislation may also be enacted.

Although we monitor actual and potential changes to the tax laws in the United States and other jurisdictions, it is very difficult to assess to what extent these changes may impact the way in which we conduct our business or our effective tax rate due to the unpredictability and interdependency of these changes. Changes in tax laws and related regulations and practices could have a material adverse effect on our business operations, cash flows, effective tax rate, financial position and results of operations.

Risks Related to Regulatory Approval of our Products and our Product Candidates

Our marketing authorization in the EEA for Translarna for the treatment of nmDMD is a "conditional marketing authorization" that requires annual review and renewal by the European Commission following reassessment by the EMA of the benefit-risk balance of the authorization and is further conditioned upon our ability to satisfy the specific obligation to conduct and report results from Study 041 by the end of the third quarter of 2022, and, as such, there is ongoing risk that we may be unable to maintain such authorization. If we are unable to obtain renewal of such marketing authorization in any future renewal cycle, we could lose all, or a significant portion of, our ability to generate revenue from sales of Translarna, whether pursuant to a commercial or an EAP program, which would have a material adverse effect on our business, financial performance and results of operations.

Conditional marketing authorizations based on incomplete clinical data, including our marketing authorization for Translarna for the treatment of nmDMD, may be granted in the EEA for a limited number of listed medicinal products for human use, including products designated as orphan medicinal products under EU law, if (1) the EMA determines that the benefit-risk balance of the product is positive, (2) it is likely that the applicant will be in a position to provide the required comprehensive clinical trial data, (3) unmet medical needs will be fulfilled and (4) the benefit to public health of the immediate availability on the market of the medicinal product outweighs the risk inherent in the fact that additional data are still required. Specific obligations or conditions, including with respect to the completion of ongoing or new studies, and with respect to the collection of pharmacovigilance data, may be specified in the conditional marketing authorization. Conditional marketing authorizations are only valid for one year, and must be renewed annually by the European Commission after an assessment by the EMA of the ongoing positive benefit-risk balance in favor of continued authorization and the need for additional or modified conditions.

We received initial marketing authorization for Translarna for the treatment of nmDMD in ambulatory patients aged five years and older from the European Commission in August 2014 as a "conditional marketing authorization." In July 2018, the European Commission approved a label-extension request to our marketing authorization for Translarna in the EEA to include patients from two to up to five years of age. In July 2020, the European Commission approved the removal of the statement "efficacy has not been demonstrated in non-ambulatory patients" from the indication statement for Translarna. The marketing authorization is subject to annual review and renewal by the European Commission following reassessment by the EMA of the benefit-risk balance of the authorization and is further conditioned upon our satisfaction of the specific obligation to conduct and submit results from Study 041 by the end of the third quarter of 2022 to the EMA. We expect that as part of the annual EMA assessment, the EMA will consider the ongoing status of Study 041. We are also required to implement measures, including pharmacovigilance plans, which are detailed in the risk management plan.

Our marketing authorization was previously conditioned upon our submission to the EMA of the final efficacy and safety report from ACT DMD during 2015. Although we have fulfilled the condition to submit the ACT DMD report to the EMA, that trial did not meet the primary efficacy endpoint of change from baseline at week 48 in distance walked in the 6-minute walk test. The EMA and European Commission did not approve our request for full marketing authorization of Translarna for the treatment of nmDMD and, instead, approved the renewal of our conditional marketing authorization with the specific obligation to confirm the efficacy and safety of Translarna for the treatment of nmDMD in ambulatory patients aged 5 years or older via Study 041.

Enrolling, conducting and reporting a clinical trial is a time-consuming, expensive and uncertain process that takes years to complete, and we expect that we will incur material costs related to the implementation and conduct of Study 041. We expect that conducting a placebo-controlled trial in nmDMD of this size will be challenging and we have enrolled patients in countries with a different standard of care for nmDMD patients and at clinical trial sites that are inexperienced with nmDMD clinical trials, which may affect our ability to accurately evaluate the study and maintain compliance with applicable regulatory requirements and laws. In addition, we may experience unknown complications with Study 041 and may not achieve the pre-specified endpoint with statistical significance, which would have a materially adverse effect on our ability to maintain our marketing authorization in the EEA.

If we fail to satisfy our obligations under the marketing authorization, or if it is determined in any annual renewal cycle that the balance of benefits and risks of using Translarna has changed materially, the European Commission could, at the EMA's recommendation, vary, suspend, withdraw or refuse to renew the marketing authorization for Translarna. The EMA may also impose other new conditions to our marketing authorization (in addition to Study 041), and may make other recommendations, including new label restrictions. In the event that we do secure annual renewal of the marketing authorization for any given annual renewal cycle, the EMA could nevertheless later determine that we have not complied, or are unable to comply, with any conditions that have been or may be placed on the marketing authorization, including those related to Study 041, which could result in the withdrawal of our marketing authorization or other outcome that would have a materially adverse effect on our business, results of operations and financial condition.

If our marketing authorization in the EEA is not renewed, or our product label is materially restricted, we would lose all, or a significant portion of, our ability to generate revenue from sales of Translarna, whether pursuant to a commercial or an EAP program and throughout all territories, which would have a material adverse effect on our business, results of operations and financial condition.

If we are not able to comply with applicable laws and regulations for our products or product candidates, we will not be able to obtain or maintain product approvals and commercialize our product or product candidates, and our ability to generate revenue will be materially impaired.

Our products and product candidates, and the activities associated with their development and commercialization, including their design, testing, manufacture, safety, efficacy, recordkeeping, labeling, storage, approval, advertising, promotion, sale and distribution, are subject to comprehensive regulation by the FDA and EMA (and/or by EEA member state authorities) and by comparable authorities in other countries, including ANVISA where we have received marketing authorization for Translarna for the treatment of nmDMD in ambulatory patients aged two years and older in Brazil, Tegsedi for the treatment of stage 1 or stage 2 polyneuropathy in adult patients with hATTR amyloidosis in Brazil and Waylivra for the treatment of FCS in Brazil. Failure to obtain, maintain or renew marketing authorization for any of our products or product candidates, as applicable, will prevent us from commercializing such product or product candidate.

As noted in the foregoing risk factors, we may not maintain the approvals we have received or receive further necessary approvals from the FDA, the EMA, ANVISA or other regulators to further commercialize any of our products or to commercialize any product candidate in any market. The approval procedures vary among countries, can involve additional testing, and the time for approval may materially differ. Approval by the FDA does not ensure approval by regulatory authorities in other countries or jurisdictions, and approval by one regulatory authority outside the United States does not ensure approval by regulatory authorities in other countries or jurisdictions or by the FDA. However, the failure to obtain approval in one jurisdiction may compromise our ability to obtain approval elsewhere. In addition, there is substantial risk that regulators in the applicable territories will not agree with our interpretation of the results of ACT DMD and the totality

of clinical data from our trials, which would have a material adverse effect on our ability to generate revenue, or may prevent us from generating any revenue, from the sales of Translarna for the treatment of nmDMD in those territories.

Securing marketing authorization requires the timely preparation and submission of extensive preclinical and clinical data and supporting information to regulatory authorities for each therapeutic indication to establish the product candidate's safety and efficacy. In response to changes in the regulatory environment or requests from regulators, we may elect, or be obliged, to postpone a regulatory submission to include additional analyses, including those intended to strengthen our submission or facilitate regulator review, which could cause delays in getting our products to market and substantially increase our costs. Securing marketing authorization also requires the submission of information about the product manufacturing process to, and inspection of manufacturing facilities by, the regulatory authorities. Changes to manufacturers, product candidate formulation, manufacturing processes and other product candidate attributes, such as the method of delivery, during product candidate development may also require additional studies to demonstrate the comparability of the product candidate using prior processes, formulation, or manufacturers, or with the prior attributes, to the product candidate using new the processes, formulation, or manufacturers, or with the new attributes.

Regulatory authorities may determine that any of our products or product candidates are not effective or are only moderately effective, or have undesirable or unintended side effects, toxicities, safety profiles or other characteristics that preclude us from obtaining marketing authorization or that prevent or limit commercial use.

The process of obtaining marketing authorizations is expensive, may take many years, if approval is obtained at all, and can vary substantially based upon a variety of factors, including the type, complexity and novelty of the product candidates involved. Changes in marketing authorization policies during the development period, changes in or the enactment of additional statutes or regulations, or changes in regulatory review for each submitted product application, may cause delays in the approval or rejection of an application. Regulatory authorities have substantial discretion in the approval process and may refuse to accept any application or may decide that our data are insufficient for approval and require additional preclinical, clinical or other studies. In addition, varying interpretations of the data obtained from preclinical and clinical testing could delay, limit or prevent marketing authorization of a product candidate. Any marketing authorization we ultimately obtain may be limited or subject to restrictions or post-approval commitments that render the approved product not commercially viable. For example, the marketing authorization granted on a conditional basis by the EMA in the EEA for Translarna is limited to ambulatory nmDMD patients aged two years and older who have been identified through genetic testing and is subject to the specific obligation to conduct Study 041 and annual reassessment by the EMA of the benefit-risk analysis.

In addition, marketing authorizations in countries outside the United States do not ensure pricing approvals in those countries or in any other countries, and marketing authorizations and pricing approvals do not ensure that reimbursement will be obtained.

We may not be able to obtain orphan drug exclusivity for our products or product candidates in either the United States or the EU. If our competitors are able to obtain orphan drug designations for their products in the United States and those products are determined by the FDA to be the "same drug" as our products or product candidate(s) under applicable FDA standards, we may not be able to obtain approval for a significant period of time. Similarly, if our competitors are able to obtain orphan drug designations for their products in the EU and those products can be classified as a "similar medicinal product" within the meaning of EU law, we may not be able to obtain approval by the applicable regulatory authority for a significant period of time.

Regulatory authorities in some jurisdictions, including the EU and the United States, may designate drugs for relatively small patient populations as orphan drugs. We have obtained orphan drug designations from the EMA and from the FDA for Translarna for the treatment of nmDMD, Evrysdi for the treatment of SMA, PTC-AADC for the treatment of AADC, PTC-AS for the treatment of Angelman syndrome and PTC923 for the treatment of patients with hyperphenylalaninemia, including hyperphenylalaninemia caused by PKU. The FDA has also granted an orphan drug designation to PTC-FA for the treatment of Friedreich ataxia, emvododstat for the treatment of AML and unesbulin for the treatment of LMS and DIPG. We may also seek orphan drug exclusivity for other product candidates, if we believe that the product candidate may qualify. We, however, may not be able to obtain orphan drug designation in the future for any of our other product

candidates. Obtaining orphan drug exclusivity, both in the EU and in the United States, may be important to a product candidate's future success.

In the EU, if an orphan designated product subsequently receives the first marketing authorization for the indication for which it has received such a designation, the product is entitled to 10 years of market exclusivity, which, subject to certain exceptions, precludes the EMA from accepting another marketing application for a similar medicinal product, even if the new marketing application relies on independently generated data submitted as part of a full marketing authorization application dossier. The EU exclusivity period can be reduced to six years, at the end of the fifth year, if a drug no longer meets the criteria for orphan drug designation, including if the drug is sufficiently profitable so that market exclusivity is no longer justified. In addition, a competing similar medicinal product may in limited circumstances be authorized prior to the expiration of the market exclusivity period, including if it is shown to be safer, more effective or otherwise clinically superior to the orphan product. In this context, a "similar medicinal product" is a medicinal product containing a similar active substance or substances as contained in a currently authorized orphan medicinal product, and which is intended for the same therapeutic indication. Product candidates can also lose orphan designation, and the related benefits, prior to obtaining a marketing authorization if it is demonstrated that the orphan designation criteria are no longer met.

In the United States, if a product with an orphan drug designation subsequently receives the first marketing authorization for the indication for which it has such designation, the product is entitled to seven years of market exclusivity which precludes the FDA from approving another marketing application for the "same drug" for the same indication for that time period. When determining whether a drug is the "same drug" as an orphan designated product, the FDA looks to the products' molecular features and use. The specific sameness criteria, however, varies based on whether the product is composed of small or large molecules and if the product is a gene therapy. Moreover, for gene therapies, the sameness criteria is currently evolving. For example, the FDA recently issued a final guidance document specific to sameness determinations. Depending on product characteristics, sameness may be determined by the FDA on a case by case basis, making it difficult to predict when FDA may approve a product and whether periods of exclusivity will effectively block competitors seeking to market products that are the same or similar to ours for the same intended use. Accordingly, whether any of our products or product candidates will be deemed to be the same as another product or product candidate is uncertain.

Obtaining orphan drug designation, however, does not guarantee that we will be able to receive ultimate marketing approval. Orphan drug designation neither shortens the development time or regulatory review time of a product candidate nor gives the product candidate any advantage in the regulatory review or approval process. Moreover, the FDA may grant orphan drug designation to multiple products that are considered to be the "same drug" for the same indication. If a competitor obtains an orphan drug designation for and approval of a product with orphan drug exclusivity for the same indication as one of our product candidates before we do and if the competitor's product is the same drug, in the United States or a similar medicinal product, in the EU, as ours, we could be excluded from the market for a period of time.

We also may not be able to maintain any orphan drug designations or exclusivities. For instance, orphan drug designations may be revoked if the FDA finds that the request for designation contained an untrue statement of material fact or omitted material information, or if the FDA finds that the product candidate was not eligible for designation at the time of the submission of the request. Even if we are able to receive and maintain orphan drug designations, we may ultimately not receive any period of regulatory exclusivity if our product candidates are approved. For instance, we may not receive orphan product regulatory exclusivity if the indication for which we receive FDA approval is broader than the orphan drug designation. Orphan exclusivity may also be lost for the same reasons that designation may be lost. Orphan exclusivity may further be lost if we are unable to assure a sufficient quantity of the product to meet the needs of patients with the rare disease or condition.

Further, even if we do receive orphan drug exclusivity upon approval of a product candidate, this exclusivity is not absolute. For example, if a competitive product that is the same drug or a similar medicinal product as Translarna or another product candidate that has been granted orphan drug exclusivity is shown to be "clinically superior" to our product candidate as determined by the FDA or EMA, respectively, any orphan drug exclusivity we have obtained will not block the approval of such competitive product. Orphan exclusivity also would not block FDA from approving a drug that is the same as our product candidates for different indications or products that are different from ours for the same indication.

Moreover, marketing exclusivity would not prevent a provider from prescribing or using another drug off-label and third-party payors may reimburse for products off-label even if not indicated for the orphan condition.

The respective orphan designation and exclusivity frameworks in the United States and in the EU are subject to change, and any such changes may affect our ability to obtain, or the impact of obtaining, EU or United States orphan designations in the future.

We rely on non-patent market exclusivity periods under the Orphan Drug Act to commercialize Emflaza for the approved indication in the United States and we may rely on non-patent market exclusivity periods for other product candidates in the future. Failure to maintain exclusivity periods would have a material adverse effect on our ability to commercialize our products, which in turn would have a material adverse effect on our business, financial statements and results of operations.

As we presently have no patent rights to protect the approved use of Emflaza, we rely on non-patent market exclusivity periods under the Orphan Drug Act to commercialize Emflaza in the United States.

As noted in the foregoing risk factor, generally, if a product with an orphan drug designation subsequently receives the first marketing authorization for the indication for which it has such designation, the product is entitled to a period of market exclusivity, which, subject to certain exceptions, precludes the FDA from approving another marketing application for the same drug for the same indication for that time period. As previously discussed, however, the protection provided by orphan drug exclusivity is limited and orphan drug exclusivity may be withdrawn.

Emflaza's seven-year period of orphan drug exclusivity related to the treatment of DMD in patients five years and older expires in February 2024 while its orphan drug exclusivity related to the treatment of DMD in patients two years of age to less than five expires in June 2026.

Under the Orphan Drug Act, during the seven-year exclusivity period, the FDA may not approve any other applications to market any drug considered the "same drug" as the drug with the orphan drug exclusivity for the same rare disease or condition, except in limited circumstances, such as if the second applicant demonstrates the clinical superiority of its product to the product with orphan drug exclusivity through a demonstration of superior safety, superior efficacy, or a major contribution to patient care. In addition, if a company seeks orphan drug designation for a drug considered the "same drug" as a drug previously approved for the orphan indication at issue, the FDA will not designate the "same drug" as an orphan drug unless the company articulates a plausible hypothesis of the clinical superiority of its drug to the approved drug, and, following such designation, if the previously approved drug has unexpired orphan drug exclusivity, the FDA will not approve the subsequent drug unless the sponsor demonstrates clinical superiority over the previously approved drug prior to approval. As a result, in the event that a competitive product that is the "same drug" as Emflaza is shown to be "clinically superior" to Emflaza as determined by the FDA, our orphan drug exclusivity will not block the approval of such competitive product. In addition, orphan drug exclusivity does not prevent the FDA from approving a different drug for the same disease or condition, or the same drug for a different disease or condition.

In addition, we can lose any periods of granted orphan drug exclusivity under certain circumstances, such as if the FDA finds that the request for designation contained an untrue statement of material fact or omitted material information, or if the FDA finds that the product candidate was not eligible for designation at the time of the submission of the request. Orphan exclusivity may further be lost if we are unable to assure the availability of sufficient quantities of Emflaza to meet the needs of patients.

Further, the Orphan Drug Act is subject to change, and any such changes may affect our ability to maintain the respective market exclusivity period under those laws. Any reduction or limitation to the marketing exclusivity periods for Emflaza would materially limit our ability to commercialize the product, which in turn would have a material adverse effect on our business, financial statements and results of operations.

All pharmaceutical products for which marketing authorization has been granted, including our products, are subject to extensive and rigorous governmental regulation and could be subject to restrictions or withdrawal from the market. We may also be subject to penalties if we fail to comply with regulatory requirements or if we experience unanticipated problems with our products, when and if any of them are approved, as well as our product candidates during development.

We, our products and product candidates, our operations, our facilities, our suppliers and our contract manufacturers, distributors, contract research organizations, clinical trial sites and contract testing laboratories are subject to extensive regulation by governmental authorities in the EEA, the United States, and other territories, with regulations differing from country to country.

We are not permitted to market our product candidates in the EEA, the United States, or other territories until we have received requisite regulatory approvals. In order to receive and maintain such approvals, and to be compliant with regulatory authority requirements, we and our third-party service providers must comply on a continuous basis with a broad array of regulations and requirements. Depending on the stage of product development and whether a product is approved these requirements may relate to establishment registration and product listing, the payment of user fees, manufacturing processes, risk management measures, quality and pharmacovigilance systems (including reporting of manufacturing deviations and adverse events), pre- and post-approval clinical and pre-clinical data, labeling, packaging, advertising, marketing and promotional activities (including product sampling), record keeping, distribution, storage, and import and export of pharmaceutical products. Any regulatory approval of any of our products or product candidates, once obtained, may be withdrawn. For example, our marketing authorization for Translarna for the treatment of nmDMD in the EEA is subject to annual review and renewal by the European Commission following reassessment by the EMA of the benefit-risk balance of the authorization, as well as the specific obligation to conduct and report the results of Study 041. After approving a drug, the FDA may withdraw product approval if compliance with regulatory standards is not maintained or if safety problems occur after the product reaches the market. Requirements for additional clinical trials and studies to confirm safety and effectiveness may be imposed as a condition of marketing approval. In addition, the FDA requires surveillance programs to monitor approved products that have been commercialized, as well as REMS, and the agency has the power to require changes in labeling or to prevent further marketing and distribution of a product. For example, we were obligated to perform certain FDA post-marketing requirements in connection with our marketing authorization for Emflaza in the United States, including pre-clinical and clinical safety studies. Additionally, our marketing authorizations for Translarna, Tegsedi and Waylivra in Brazil and our marketing authorization for Translarna in Russia are subject to renewal every five years. There is no guarantee that we will be able to complete our post-marketing obligations in accordance with the established timetables. Failure to complete the required studies in accordance with the established timetables or failure to provide the requisite periodic reports on the status of post-marketing studies in the absence of good cause could result in an enforcement action. Accordingly, we and others with whom we work must continue to expend time, money, and effort in all areas of regulatory compliance, including manufacturing and distribution.

For additional information with respect to the risks related to renewal of our marketing authorization in the EEA, see the risk factor titled "*Our marketing authorization in the EEA for Translarna for the treatment of nmDMD is a "conditional marketing authorization" that requires annual review and renewal by the European Commission following reassessment by the EMA of the benefit-risk balance of the authorization and is further conditioned upon our ability to satisfy the specific obligation to conduct and report results from Study 041 by the end of the third quarter of 2022, and, as such, there is ongoing risk that we may be unable to maintain such authorization. If we are unable to obtain renewal of such marketing authorization in any future renewal cycle, we could lose all, or a significant portion of, our ability to generate revenue from sales of Translarna, whether pursuant to a commercial or an EAP program, which would have a material adverse effect on our business, financial performance and results of operations."*

We are required to submit safety and other post-market information and reports, implement pharmacovigilance plans, and comply with cGMP requirements related to manufacturing including, quality control, quality assurance and complaints and corresponding maintenance of records and documents, requirements regarding the distribution of samples to healthcare professionals and recordkeeping, among other things, in connection with the marketing authorizations described above and any future marketing authorizations we may receive. Application holders must further notify the FDA, and depending on the nature of the change, obtain FDA pre-approval for product and manufacturing changes.

Regulatory authorities, including the EMA and local regulatory authorities in EEA member states, subject a marketed product, its manufacturer and the manufacturing facilities to ongoing review and periodic inspections and the EMA is responsible for coordinating inspections, undertaken by the competent authorities of applicable member states, of our manufacturing facilities to assess whether our manufacturing, and other procedures, comply with cGMP. Similar regulatory and inspection requirements apply in other jurisdictions including those imposed by the FDA in the United States. The FDA will typically inspect a manufacturer, including contract manufacturer organizations and clinical research sites, following acceptance of an NDA or BLA, which can delay FDA approval, especially if unsatisfactory inspection results are observed. Following approval, product sponsors and their contractors are subject to periodic unannounced FDA inspections to monitor and ensure compliance with FDA's regulatory requirements, including cGMPs. If an FDA inspection were to occur and compliance issues at our facilities or at the facilities of our contract manufacturers or research organizations were identified, it could also result in disruption of production or distribution of a product or product candidate, disruption, cancellation, or suspension of a study, or require substantial resources to correct.

Even if marketing authorization of a product candidate is granted, the approval may be subject to limitations on the indicated uses for which the product may be marketed, the product may have labeling that includes significant restrictions, warnings, including black box warnings, and contraindications, the regulatory authorities may not approve label claims necessary for successful product marketing, or the approval may be subject to significant conditions of approval, including the requirement of a REMS. A regulatory authority also may impose requirements for costly post-marketing studies or clinical trials and surveillance to monitor the safety or efficacy of the product. In addition, the competent authorities of each EU member state and the FDA closely regulate the post-approval marketing and promotion of drugs to ensure drugs are marketed only for the approved indications and in accordance with the provisions of the approved labeling and regulatory requirements. Such regulatory authorities can impose stringent restrictions on our communications regarding off-label use and if we do not comply with the laws governing promotion of approved drugs, we may be subject to enforcement action for off-label promotion. For example, violations of the FDCA relating to the promotion of prescription drugs may lead to civil and criminal penalties, investigations alleging violations of federal and state healthcare fraud and abuse laws, as well as state consumer protection laws.

In addition, later discovery of previously unknown adverse events or other problems with our products, manufacturers or manufacturing processes, or failure to comply with regulatory requirements, both before and after product approval, may yield various results which could negatively affect our business, including:

- restrictions on such products, manufacturers or manufacturing processes;
- changes to or restrictions on the labeling or marketing of a product;
- modifications to promotional pieces;
- issuance of corrective information;
- clinical holds or termination of clinical trials;
- changes in the way a product is administered;
- liability for harm caused to patients or subjects;
- adverse publicity, reputational harm, or the product becoming less competitive;
- regulatory authority issuance of safety alerts, Dear Healthcare Provider letters, press releases, or other communications containing warnings or other safety information about the product;
- restrictions on product distribution or use;
- requirements to implement a REMS;
- requirements to conduct post-marketing studies or clinical trials;
- warning, cyber or untitled letters;
- withdrawal of the products from the market or marketing suspensions;
- refusal to approve pending applications or supplements to approved applications that we submit;
- recall of products;
- fines, restitution or disgorgement of profits or revenues;
- suspension or withdrawal of marketing authorizations;
- refusal to permit the import or export of our products;
- product seizure or detention;
- injunctions;

- the imposition of civil or criminal penalties; or
- FDA debarment, suspension and debarment from government contracts, and refusal of orders under existing government contracts, exclusion from federal healthcare programs, consent decrees, or corporate integrity agreements.

Non-compliance with regulatory requirements regarding safety monitoring or pharmacovigilance, and with requirements related to the development of products for the pediatric population, can also result in significant financial penalties. Similarly, failure to comply with regulatory requirements regarding the protection of personal information can also lead to significant penalties and sanctions.

Not only will we be responsible for our own conduct, but we will also be responsible for the conduct of our employees, independent contractors, consultants, commercial partners, manufacturers, investigators, and contract research organizations. To the extent that any of these third parties engage in intentional, reckless, negligent, or unintentional failures to comply applicable legal and regulatory requirements, we may be subject to regulatory enforcement action, legal actions and liability, and serious harm to our reputation. Moreover, it is possible for a whistleblower to pursue a False Claims Act case against us as a result of such third party conduct, even if the government considers the claim unmeritorious and declines to intervene, which could require us to incur costs defending against such a claim.

Any of the above events could prevent us from achieving or maintaining market acceptance of the particular product candidate, if approved, or could substantially increase the costs and expenses of developing and commercializing such product, which in turn could delay or prevent us from generating significant revenues from its sale. Any of these events could further have other material and adverse effects on our operations and business and could adversely impact our stock price and could significantly harm our business, financial condition, results of operations, and prospects.

We are also subject to laws and license and registration requirements covering the distribution of marketed products. If we fail to comply with any of these requirements, we may be subject to action by regulatory agencies, which could negatively affect our business. Regulatory agencies may also change existing requirements or adopt new requirements or policies. We may be slow to adapt or may not be able to adapt to these changes or new requirements. Any new requirements could further prevent, limit or delay regulatory approval of product candidates, could limit marketability of approved products, or could impose additional burdensome and costly regulatory obligations.

Commercialization of Translarna has been in, and is expected to continue to take place in, countries that tend to impose strict price controls, which may adversely affect our revenues. Failure to obtain and maintain acceptable pricing and reimbursement terms for Translarna for the treatment of nmDMD in the EEA and other countries where Translarna is available would delay or prevent us from marketing our product in such regions, which would adversely affect our business, results of operations, and financial condition.

In some countries, particularly the member states of the EEA, the pricing of prescription pharmaceuticals is subject to strict governmental control. Each country in the EEA has its own pricing and reimbursement regulations and may have other regulations related to the marketing and sale of pharmaceutical products in the country. We generally will not be able to commence commercial sales of Translarna for the treatment of nmDMD pursuant to the marketing authorization granted by the European Commission in any particular member state of the EEA until we conclude the applicable pricing and reimbursement negotiations and comply with any licensing, employment or related regulatory requirements in that country. In some countries we may be required to conduct additional clinical trials or other studies of our product, including trials that compare the cost-effectiveness of our product to other available therapies in order to obtain reimbursement or pricing approval. We may not be able to conclude pricing and reimbursement negotiations or comply with additional regulatory requirements in the countries in which we seek to commercialize Translarna on a timely basis, or at all.

The pricing and reimbursement process varies from country to country and can take a substantial amount of time from initiation to completion. Pricing negotiations may continue after reimbursement has been obtained. We cannot predict the timing of Translarna's commercial launch in countries where we are awaiting pricing and reimbursement guidelines. While we have submitted pricing and reimbursement dossiers with respect to Translarna for the treatment of nmDMD in many EEA countries, we have only received both pricing and reimbursement approval on terms that are acceptable to us in a limited number of countries.

The price that is approved by governmental authorities in any country pursuant to commercial pricing and reimbursement processes may be significantly lower than the price we are able to charge for sales under our reimbursed EAP programs and various forms of national "market access agreements" may need to be entered into to achieve reimbursement. In some instances, reimbursement may be subject to challenge, reduction or denial by the government and other payors.

For example, in France, EAP and commercial sales of a product can begin while pricing and reimbursement rates are under discussion with the applicable government health programs. In the event that the negotiated price of the product is lower than the amount reimbursed for sales made prior to the conclusion of price negotiations, we may become obligated to repay such excess amount to the applicable government health program. We will make such retroactive reimbursement, if any, following the conclusion of price negotiations with the applicable government health authority.

Further, based on unsustainable economics imposed by the arbitration board in Germany upon the conclusion of an arbitration process in 2016 with us and the German Federal Association of the Statutory Health Insurances, we delisted Translarna from the German pharmacy ordering system, effective April 1, 2016. While some patients and healthcare professionals in Germany have been able to access Translarna through a reimbursed importation pathway possible under German law, there can be no assurance that other patients or healthcare professionals in Germany will be successful doing so or, if initially successful, that any or all will continue to be successful. We were required to reimburse payors in Germany the difference between the commercial price of Translarna and the price established by the arbitration board in Germany for sales made in Germany after December 2015, other than sales made pursuant to the reimbursed importation pathway.

Political, economic and regulatory developments may further complicate pricing and reimbursement negotiations and there can be considerable pressure by governments and other stakeholders on prices and reimbursement levels, including as part of cost containment measures. For example, these factors influenced the length of our pricing and reimbursement negotiations in England, which took place between mid-2014 to mid-2016, and culminated in a temporary managed access agreement between us, National Health Services England, the National Institute for Health and Care Excellence, or NICE, NorthStar clinical network and the patient organizations Muscular Dystrophy UK and Action Duchenne. The managed access agreement establishes the clinical details surrounding the use of Translarna, including the terms and conditions of a confidential financial arrangement and the collection of further data on the efficacy of Translarna for the treatment of nmDMD with NICE guidance, before future funding decisions are taken.

In addition, adverse clinical and regulatory developments may exacerbate these risks, including the developments noted in the foregoing risk factor titled, "*ACT DMD did not meet its primary efficacy endpoint, and there is substantial risk that regulators will not agree with our interpretation of the results of ACT DMD and the totality of clinical data from our trials in Translarna for the treatment of nmDMD, which would have a material adverse effect on our business, financial performance and results of operations.*"

Reference pricing used by various EU member states and parallel distribution, or arbitrage between low-priced and high-priced member states, can further reduce prices and revenues. Publication of discounts by third-party payors or authorities may lead to further pressure on prices or reimbursement levels within the country of publication and other countries.

If we fail to successfully secure and maintain pricing and reimbursement coverage for Translarna or are significantly delayed in doing so or if burdensome conditions are imposed by private payers, government authorities or other third-party payors on such reimbursement, planned launches in the affected countries will be delayed and our business, results of operations and financial condition could be adversely affected.

Our relationships with customers, healthcare providers and professionals, patients, patient organizations, and third-party payors are or will be subject to applicable anti-kickback, fraud and abuse, transparency and other healthcare laws and regulations, which could expose us to criminal sanctions, civil penalties, contractual damages, reputational harm and diminished profits and future earnings.

Healthcare providers, physicians and third-party payors play a primary role in the recommendation and prescription of any products or product candidates, including Translarna and Emflaza, for which we have obtained or may obtain marketing approval. Our arrangements with customers, healthcare providers and professionals and third-party payors may expose us to broadly applicable fraud and abuse, transparency and other healthcare laws and regulations that may constrain the

business or financial arrangements and relationships through which we market, sell and distribute our products for which we obtain marketing authorization.

Failure to maintain a comprehensive and effective compliance program, and to integrate the operations of any acquired businesses into a combined comprehensive and effective compliance program on a timely basis, could subject us to a range of regulatory actions that could adversely affect our ability to commercialize our products and could harm or prevent sales of the affected products, or could substantially increase the costs and expenses of commercializing and marketing our products.

Restrictions and reporting requirements under applicable U.S. federal and state healthcare laws and regulations, and equivalent laws and regulations in the EU and other countries in which we operate, include, and are not limited to, the following:

- Anti-corruption and anti-bribery laws and regulations, such as the U.S. Foreign Corrupt Practices Act, or FCPA, the UK Bribery Act of 2010, or Bribery Act, and similar statutes which have been adopted, or may be adopted in the future, by other countries in which we operate and with which we are or may be required to comply.
- Anti-kickback laws and regulations, including those applicable in the United States, the United Kingdom and other countries where we operate, which generally prohibit, among other things, persons from knowingly and willfully soliciting, offering, receiving or providing remuneration, directly or indirectly, in cash or in kind, to induce or reward either the referral of an individual for, or the purchase, order or recommendation of, any good or service, for which payment may be made in whole or in part under government funded healthcare programs. The U.S. federal statute imposes criminal penalties and has been broadly interpreted to apply to manufacturer arrangements with prescribers, purchasers and formulary managers, among others and many states have enacted equivalent state laws that apply not only to government payors but to commercial payors as well.
- False claim laws and regulations, including the U.S. False Claims Act and similar state laws, which may permit civil whistleblower or qui tam actions and may impose civil liability and criminal penalties on individuals and entities who submit, or cause to be submitted, false or fraudulent claims for payment to the government. Federal enforcement agencies have shown increased interest under the federal Anti-Kickback Stature and the federal civil False Claims Act in pharmaceutical companies' product and patient assistance programs, including reimbursement and co-pay support services and donations to independent charitable patient assistance programs. A number of investigations into these programs have resulted in significant civil and criminal settlements.
- Federal price reporting laws, including the Medicaid drug rebate statute, which requires manufacturers of covered outpatient drugs to calculate and submit complex pricing information that is used as the basis for reimbursement of certain drugs by, and payment of rebates to, the Medicaid program; the Medicare Prescription Drug, Improvement and Modernization Act of 2003, or Medicare Modernization Act, which requires manufacturers to calculate and report a drug's Average Sales Price used to reimburse providers for physician-administered drugs under Medicare Part B; and the Veterans Health Care Act of 1992, which requires, manufacturers of covered drugs (including all drugs approved under an NDA) to calculate and report a Federal Ceiling Price and offer their covered drugs for sale at no more than that price to the Department of Veterans Affairs, the Department of Defense, and other agencies. The Veterans Health Care Act also requires manufacturers to enter into pricing agreements with the Department of Health and Human Services to charge no more than a different ceiling price (derived from the Medicaid rebate percentage) to covered entities participating in the 340B drug discount program. Failure to accurately report drug pricing or provide the mandatory discounts may subject the manufacturer to specific civil monetary penalties. Failure to comply with the Veterans Health Care Act also jeopardizes payment by Medicaid for the manufacturer's drugs. Certain states have also enacted drug price transparency laws that require reporting of pricing information, including certain increases in a drug's wholesale acquisition cost and the reasons causing the price increase.
- Laws and regulations related to the privacy, security and transmission of individually identifiable health information, including HIPAA, as amended by the HITECH Act, and similar state laws, such as the California Consumer Privacy Act. For example, HIPAA, as amended by the HITECH Act, and their implementing regulations, impose obligations, including mandatory contractual terms, with respect to safeguarding the privacy, security and transmission of protected health information, and may impose criminal and civil liability for violations of those obligations. In addition, international data protection laws including the European General Data Protection Regulation, and supplementary member state, United Kingdom, European Economic Area, and

Swiss legislation may apply to some or all of the clinical or other protected data obtained, transmitted, or stored from those territories. These laws require specific, freely given and fully informed consent to be obtained from patients or clinical study participants. There are also other requirements for lawful processing, including transparency obligations, data minimization requirements, data transfer and compliance obligations with individuals' stringent rights to access their personal data and to otherwise control the processing of their personal data. There are data breach notification obligations, to supervisory authorities and to individuals, where there are potential risks to them arising from the data breach. These laws impose high regulatory fines in the event of breach of processing requirements of up to 4% of global annual turnover or EUR 20 million (whichever is the higher amount). Further certain privacy laws and genetic testing laws may apply directly to our operations and/or those of our collaborators and may impose restrictions on our use and dissemination of individuals' health information.

- HIPAA also imposes liability, including criminal liability, for, among other actions, knowingly and willfully executing, or attempting to execute, a scheme to defraud or to obtain, by means of false or fraudulent pretenses, representations or promises, any of the money or property owned by, or under the custody or control of, a healthcare benefit program, regardless of whether the payor is public or private, in connection with the delivery or payment for healthcare benefits, knowingly and willfully embezzling or stealing from a healthcare benefit program, willfully obstructing a criminal investigation of a healthcare offense and knowingly and willfully falsifying, concealing, or covering up by any trick or device a material fact or making any materially false statements in connection with the delivery of, or payment for, healthcare benefits, items, or services relating to healthcare matters. Notably, the Affordable Care Act amended the intent requirement of certain of these criminal statutes under HIPAA so that a person or entity no longer needs to have actual knowledge of the statute, or the specific intent to violate it, to have committed a violation.
- Laws and regulations governing the advertising and promotion of medicinal products, interactions with physicians and patients, misleading and comparative advertising and unfair commercial practices. For example, legislation adopted by individual EU member states that may apply to the advertising and promotion of medicinal products require that promotional materials and advertising in relation to medicinal products comply with the product's Summary of Product Characteristics, or SmPC, as approved by the competent authorities. The SmPC provides information to physicians concerning the safe and effective use of the medicinal product. Promotion of indications not covered by the SmPC is specifically prohibited.
- Laws and regulations regulating off-label promotion of medicinal products, which is prohibited in the EU. The applicable laws at EU level and in the individual EU member states also prohibit the direct-to-consumer advertising of prescription-only medicinal products. Violations of the rules governing the promotion of medicinal products in the EU could be penalized by administrative measures, fines and imprisonment. These laws may further limit or restrict the advertising and promotion of our products to the general public and may also impose limitations on our promotional activities with healthcare professionals.
- Laws and regulations in the United States, including the FDCA and other laws and regulations, that prohibit us from promoting any of our FDA approved products for off-label uses and that require compliance with FDA's advertising and promotional requirements. For example, the FDA requires that all product advertising and promotion be consistent with the FDA approved label, be truthful and non-misleading, be adequately substantiated, and have fair balance between product benefit claims and risks, among other requirements. This means, for example, that we cannot make claims about the use of our marketed products or their relative benefits compared to other treatments outside of their FDA approved indications and label and without adequate comparative studies, and we would not be able to discuss or provide information on off-label uses or safety benefits of such products in a promotional context. While physicians may choose to prescribe products for uses that are not described in the product's labeling and for uses that differ from those tested in clinical studies and approved by the regulatory authorities, we are prohibited from marketing and promoting the products for indications and uses that are not specifically approved by the FDA. Should the FDA or other regulatory authorities determine that our activities constituted the promotion of off-label use or a violation of its other promotional and marketing standards, we could face significant enforcement action and substantial penalties, including, but not limited to action to prevent us from distributing those products for the off-label use and could impose fines and penalties on us and our executives, and such a determination could also trigger civil or criminal liability under other applicable laws in the United States.
- Laws and regulations requiring that we disclose publicly payments made to certain healthcare professionals and healthcare organizations, including in certain EU member states and the United States. For example, in the United

States, under the federal Physician Payments Sunshine Act requirements, manufacturers of drugs, devices, biologics and medical supplies must report information related to certain payments and other transfers of value made to or at the request of covered recipients, such as physicians, certain other healthcare professionals, and teaching hospitals, as well as physician and immediate family ownership and investment interests in such manufacturers. A number of U.S. states and other countries have enacted their own transparency requirements that obligate manufacturers to report different types of spending related to physicians, certain hospitals and other healthcare organizations, and other covered recipients.

In addition, interactions between pharmaceutical companies and physicians are also governed by industry self-regulation codes of conduct and physicians' codes of professional conduct. In the United States, some state laws require pharmaceutical companies to comply with these industry and physician codes and the relevant compliance guidance for pharmaceutical manufacturers promulgated by the federal government. The provision of benefits or advantages to physicians to induce or encourage the prescription, recommendation, endorsement, purchase, supply, order or use of medicinal products is prohibited in the EU. The provision of benefits or advantages to physicians is also governed by the national laws of the EU member states, as well as codes of conduct issued by self-regulatory industry bodies. Moreover, agreements with physicians must often be the subject of prior notification and approval by the physician's employer, their competent professional organization, and the competent authorities of the individual EU member states. These requirements are provided in the national laws, industry codes, or professional codes of conduct, applicable in the EU member states.

Efforts to ensure that our business arrangements with third parties will comply with applicable healthcare laws, regulations, transparency requirements and self-regulatory codes have and will continue to involve substantial costs. We cannot guarantee that we, our employees, our consultants, our third-party contractors, or the physicians or other providers or entities with whom we expect to do business, are or will be in compliance with all federal, state and ex-U.S. regulations and codes. It is possible that governmental authorities could conclude that our business practices may not comply with current or future statutes, regulations or case law involving applicable fraud and abuse or other healthcare laws and regulations. If our operations are found to be in violation of any of these laws or any other governmental regulations that may apply to us, we may be subject to significant civil, criminal and administrative penalties, damages, fines, exclusion from government funded healthcare programs, such as Medicare and Medicaid, reputational harm, and the curtailment or restructuring of our operations. Exclusion, suspension and debarment from government funded healthcare, procurement and non-procurement programs would adversely affect, perhaps materially, our ability to commercialize, sell or distribute any drug. Even if we were not determined to have violated these laws, government investigations into these issues typically require the expenditure of significant time and resources and generate negative publicity, which could also have an adverse effect on our business, financial condition and results of operations.

Legislative and regulatory changes affecting the pharmaceutical industry or the healthcare system more broadly may increase the difficulty and cost for us to obtain or maintain marketing authorization of and commercialize our products and product candidates and affect the coverage and reimbursement we may obtain.

Our industry is highly regulated and changes in law may adversely impact our business, operations, or financial results. In the United States and some ex-U.S. jurisdictions, there have been a number of legislative and regulatory changes and proposed changes regarding the healthcare system that could prevent or delay marketing authorization of Translarna or any of our other product candidates, restrict or regulate post-approval activities and affect our ability to profitably sell any products or product candidates, including Translarna and Emflaza, for which we have obtained, or may obtain, marketing authorization.

Certain provisions of enacted or proposed legislative changes may negatively impact coverage and reimbursement of healthcare items and services. For example, in the United States, the Medicare Modernization Act changed the way Medicare covers and pays for pharmaceutical products. Cost reduction initiatives and other provisions of this legislation could decrease the coverage and reimbursement that we receive for any approved products. While the Medicare Modernization Act applies only to drug benefits for Medicare beneficiaries, private payors often follow Medicare coverage policy and payment limitations in setting their own policies. Therefore, any restrictions to coverage or reductions in reimbursement that result from the Medicare Modernization Act may result in a similar coverage restriction or

reimbursement reduction from private payors. In addition, private payors may implement coverage restrictions or payment reductions independently from federal programs such as Medicare.

Similarly, in the United States, the Affordable Care Act contains provisions that may reduce the profitability of drug products. However, legal challenges to the Affordable Care Act may contribute to the uncertainty of the ongoing implementation and impact of the Affordable Care Act and also underscore the potential for additional reform going forward. The Biden administration is expected to continue to take measures to further facilitate the implementation of the Affordable Care Act. We cannot assure that the Affordable Care Act, as currently enacted or as amended in the future, will not adversely affect our business and financial results.

Promulgated and proposed regulatory changes could also affect coverage or reimbursement of our products and in 2016, CMS issued a final rule regarding the Medicaid drug rebate program, which among other things, revises the manner in which the "average manufacturer price" is to be calculated by manufacturers participating in the program and implements certain amendments to the Medicaid rebate statute created under the ACA. More recently, Congress amended the Medicaid statute, effective October 1, 2019, to exclude prices paid by secondary manufacturers for an authorized generic drug (but not a product approved under the BLA process) from the NDA holder's AMP for the brand, thereby increasing the rebate amount and the 340B price for the brand. This was implemented by CMS in a final rule issued December 31, 2020. The rule also expanded the definition of products identified as "line extensions" and, in certain circumstances, required inclusion of patient copay assistance in Medicaid best price (effective January 1, 2023), thereby potentially increasing Medicaid rebates paid by manufacturers for such drugs. 340B program guidance regulations on civil monetary penalties for statutory violations, which had been finalized in early 2017 but deferred, recently also went into effect. On November 27, 2020, CMS issued an interim final rule implementing a Most Favored Nation payment model under which reimbursement for certain Medicare Part B drugs and biologicals will be based on a price that reflects the lowest per capita Gross Domestic Product-adjusted (GDP-adjusted) price of any non-U.S. member country of the Organisation for Economic Co-operation and Development (OECD) with a GDP per capita that is at least sixty percent of the U.S. GDP per capita. This rule now has been rescinded, but similar programs have been included in current proposed legislation.

We anticipate that the U.S. Congress, administrative agencies, state legislatures and the private sector will continue to consider and may adopt healthcare policies intended to curb rising healthcare costs. These cost containment measures may include:

- controls on government funded reimbursement for drugs;
- caps or mandatory discounts under certain government sponsored programs;
- controls on healthcare providers;
- challenges to the pricing of drugs or limits on reimbursement of specific products through other means;
- reform of drug importation laws and policies;
- expansion of use of managed care systems in which the healthcare providers contract to provide comprehensive healthcare for a fixed cost per person; and
- requirements or restrictions related to direct-to-consumer advertising or drug marketing practices.

We are unable to predict what additional legislation, regulations or policies, if any, relating to the healthcare industry or third-party coverage and reimbursement may be enacted in the future or what effect such legislation, regulations or policies would have on our business. In particular, we are unable to predict what changes the Biden administration will implement through the U.S. Congress or future executive orders and how these would impact us. Any cost containment measures, including those listed above, or other healthcare system reforms that are adopted, could significantly decrease the available coverage and the price we might establish for our products, which would have an adverse effect on our net revenues and operating results. Changes in FDA laws, regulations, and policies may also make it more difficult to obtain and maintain marketing authorizations.

In the EU, similar political, economic and regulatory developments may affect our ability to profitably commercialize Translarna and our product candidates. In addition to continuing pressure on prices and cost containment measures, legislative developments at the EU or member state level may result in significant additional requirements or obstacles that may increase our operating costs. We cannot predict how future changes relating to healthcare reform in the EU, the United States, or other territories, will affect our business.

Legislative and regulatory proposals have also been made to expand post-approval requirements, limit regulatory exclusivity periods or the applicability of such exclusivity periods, restrict sales and promotional activities for pharmaceutical products and to otherwise encourage competition in the market and bring down drug prices, including proposals related to drug importation. We cannot be sure whether additional legislative or regulatory changes will be enacted in any territory in which we are authorized, or become authorized, to market Translarna, Emflaza, or any of our other product candidates, or whether applicable regulations, guidance or interpretations will be changed, or what the impact of such changes on the marketing authorizations of our products or product candidates, if any, may be. In addition, increased scrutiny by the U.S. Congress of the FDA's approval process or by comparable ex-U.S. bodies overseeing regulatory authorities in other territories may significantly delay or prevent marketing authorization, as well as subject us to more stringent product labeling and post-marketing testing and other requirements. We cannot predict how future changes relating to pre- and post-marketing approval and requirements will affect our business.

Risks Related to Our Business

We may expend our resources to pursue a particular product, product candidate or indication and fail to capitalize on product candidates or indications that may be more profitable or for which there is a greater likelihood of success.

We focus on products, research programs and product candidates for specific indications. As a result, we may forgo or delay pursuit of opportunities with other product candidates or for other indications that later prove to have greater commercial potential.

For example, in connection with our acquisition of Agilis, we paid upfront consideration comprised of $49.2 million in cash and 3,500,907 shares of our common stock. Agilis equityholders may become entitled to receive contingent payments from us based on the achievement of certain development, regulatory and net sales milestones as well as based upon a percentage of net sales of certain products. Additionally, we entered into a Rights Exchange Agreement, pursuant to which we issued 2,821,176 shares of our common stock and paid $36.9 million, in the aggregate, to the Participating Rightholders in exchange for the cancellation and forfeiture by the Participating Rightholders of their rights to receive certain milestone-based contingent payments under the Agilis Merger Agreement. We may never realize the anticipated benefits of the acquisition of Agilis and by investing our resources in this product, we may be required to forgo or delay other opportunities.

In addition, we have previously commenced clinical trials that were not successful for a number of reasons, including inconsistent or negative data and difficulties identifying qualified patients. Our resource allocation decisions may cause us to fail to capitalize on viable commercial products or profitable market opportunities. Our spending on current and future research and development programs and product candidates for specific indications may not yield any commercially viable products.

Notwithstanding our large investments to date and anticipated future expenditures in proprietary technologies for both small-molecule and gene therapy drug discovery, to date we have been granted marketing authorization for a limited number of commercial products and have not achieved profitability. We may never realize a return on investment. We may not be able to successfully renew or satisfy the ongoing requirements of our current marketing authorizations for our current products and we may never successfully develop any other marketable drugs or indications using our scientific approach. As a result of pursuing the development of product candidates using our proprietary technologies, we may fail to develop product candidates or address indications based on other scientific approaches that may offer greater commercial potential or for which there is a greater likelihood of success. Research programs to identify new product candidates require substantial technical, financial and human resources. These research programs may initially show promise in identifying potential product candidates, yet fail to yield product candidates for clinical development.

If we do not accurately evaluate the commercial potential or target market for a particular product candidate, we may relinquish valuable rights to that product candidate through collaboration, licensing or other royalty arrangements in cases in which it would have been more advantageous for us to retain sole development and commercialization rights to such product candidate.

We contract with third parties for the manufacture and distribution of our products and certain of our product candidates, which may increase the risk that we will not have sufficient quantities of our products or product candidates, such quantities may not meet the applicable regulatory quality standards, or such quantities at an acceptable cost, which could delay, prevent or impair our commercialization or development efforts. For certain of our product candidates, we may also directly engage in manufacturing, which will require significant expenditures and compliance with FDA's manufacturing requirements.

We have limited personnel with experience in drug manufacturing and currently rely on third parties to manufacture our products and certain product candidates on a clinical or commercial scale. We currently rely on third parties for supply of the active pharmaceutical ingredients used in all of our products and product candidates. We outsource most of the manufacturing, packaging, labeling and distribution of our products and certain of our product candidates to third parties, including our commercial supply of Translarna and Emflaza. In 2021, we began cGMP manufacturing of clinical material at the Hopewell Facility for certain of our gene therapy product candidates other than PTC-AADC. We still rely on third-party manufacturers to complete product testing for all of our gene therapy product candidates that we manufacture at the Hopewell Facility as well as to provide sufficient quantities of certain program materials that we have not yet transitioned to Hopewell. With respect to the Hopewell Facility, we are required to directly comply with the applicable regulatory authorities' manufacturing requirements and are subject to inspection in the same way that our contract manufacturers are. Utilizing our own manufacturing will require a significant continued investment and we may not be successful in maintaining our own manufacturing capacity, especially given the complexities of gene therapy manufacturing. For additional information, see the risk factor under "Risks Related to Our Gene Therapy Platform" titled, *"We have limited experience manufacturing gene therapy products or product candidates on our own and could encounter problems and delays in operating our biologics manufacturing facility that could adversely affect our business."*

We do not directly control manufacturing for most of our products and product candidates and we are dependent on and will continue to be dependent on, our contract manufacturers for compliance with cGMP or good distribution practice, or GDP, or similar regulatory requirements outside the EU and the United States for manufacture of both active drug substances and finished drug products. Should we or our contract manufacturers fail to comply with these requirements, we and they could face significant regulatory and commercial consequences. For example, the FDA regularly inspects manufacturing and other drug/biologic facilities. Our manufacturers and manufacturing facilities must also be approved by the FDA pursuant to inspections that will be conducted after we submit our marketing applications to the agency and will be subject to continuing FDA and other regulatory authority inspections should we receive marketing approval. If we or our contract manufacturers cannot successfully manufacture material that conforms to our specifications and the strict regulatory requirements of the EU member state regulatory authorities, FDA, or other ex-U.S. regulatory agencies, we or they will not be able to secure and/or maintain regulatory approval for the manufacturing facilities, and we would not be able to secure and/or maintain, or may be delayed in securing regulatory approval of marketing applications or supplements for the applicable products or product candidates. In addition, we or third-party manufacturers or distributors may not be able to comply with cGMP or good distribution practice, or GDP, or similar regulatory requirements outside the EU and the United States. Our failure, or the failure of our third-party manufacturers or distributors, over whom we have no direct control, to comply with applicable regulations could result in sanctions being imposed on us, including fines, injunctions, civil penalties, delays, suspension or withdrawal of approvals, clinical holds or termination of clinical studies, warning or untitled letters, regulatory communications warning the public about safety issues with a product, import or export refusals, license revocation, seizures, detentions, or recalls of product candidates or product, operating restrictions, criminal prosecutions or debarment, suits under the civil False Claims act, corporate integrity agreements, or consent decrees any of which could significantly and adversely affect supplies of our products or product candidates and our business, results of operations and financial condition could be materially adversely affected.

In addition, we have no direct control over the ability of our contract manufacturers to maintain adequate quality control, quality assurance and qualified personnel. Furthermore, all of our contract manufacturers are engaged with other companies to supply and/or manufacture materials or products for such companies, which exposes our manufacturers to regulatory risks for the production of such other materials and products. As a result, failure to meet the regulatory requirements for the production of those materials and products may generally affect the regulatory status of our contract manufacturers' facilities. If the FDA, EU member state regulatory authorities or a comparable ex-U.S. regulatory agency do not approve these or our facilities for the manufacture of our product candidates or if it withdraws its approval in the future, we may need to find alternative manufacturing facilities, which would negatively impact our ability to develop,

obtain regulatory approval for or market our products or product candidates, if approved. There is also no guarantee that we would be able to find alternative manufacturing facilities or enter into agreements with alternative manufacturers on favorable terms. There may be limited manufacturers who would have the ability to manufacture our products and product candidates, especially our gene therapy product candidates. To the extent that we decide to manufacture our own clinical and commercial supply for our PTC-AADC program as an alternative source of supply, there is no guarantee that we will be able to cost-effectively produce sufficient quantities of our program materials. Moreover, any alternative manufacturers would need to be approved by FDA, which approval is not guaranteed. We, accordingly, may not be able to make alternative manufacturing arrangements, which could adversely affect our products, product candidates, and our business, results of operations and financial condition.

We currently rely on a single source for the production of some of our raw materials and we obtain our supply of the drug substance for Translarna from two third-party manufacturers. We engage two separate manufacturers to provide bulk drug product for Translarna. We have a relationship with three manufacturers that are capable of providing fill and finish services for our finished commercial and clinical Translarna product.

We do not currently have any agreements with third-party manufacturers for the long-term commercial supply of Translarna or any of our product candidates, although we may seek to establish such arrangements in the future. In the event that we are unable to procure supply from a validated manufacturer, we would seek to identify and qualify replacement suppliers, however this process would likely delay our ability to supply Translarna to patients or advance our clinical trials. We may be unable to conclude agreements for commercial or clinical supply of Translarna with third-party manufacturers, or we may be unable to do so on acceptable terms.

We currently have contracts with multiple pharmacy and hospital distributors in the EU that distribute Translarna for limited commercial and EAP programs. We have engaged with third-party logistic providers, or 3PLs, which distribute Translarna for the majority of our commercial and EAP programs on our behalf.

We obtain our supply of the drug substance for Emflaza through a third-party manufacturer that is currently the only third-party manufacturer qualified to provide Emflaza drug substance for use in the United States. All of our drug product manufacturing, processing and packaging needs for Emflaza tablet and suspension product are fulfilled through two different exclusive supply agreements that we assumed in connection with our acquisition of Emflaza. We expect to fulfill all of our requirements for Emflaza tablets as well as secondary packaging of pre-filled Emflaza oral suspension bottles pursuant to one of these agreements, which has an automatic renewal provision subject to the termination rights of each party. We expect to fulfill all of our requirements for Emflaza suspension product pursuant to the other agreement. Through the seventh year anniversary of FDA approval of Emflaza, we are obligated to pay to the manufacturer of the Emflaza suspension product royalty payments, on a quarterly basis, based on a percentage (ranging from low to middle-low double digits) of, or a fixed payment with respect to, our annual net sales of suspension product in the United States, subject to reduction in accordance with the terms of the agreement. The royalty payments for the suspension product are subject to a minimum aggregate annual payment ranging from €0.5 million to €1.5 million per year.

If our drug substance provider or either of our drug product manufacturers becomes unable to provide drug substance or manufacture Emflaza product in sufficient quantities to meet projected demand, future sales could be adversely affected, which in turn could have a detrimental impact on our ability to maintain our marketing authorization in the United States and on our ability to commercialize Emflaza, which in turn would have a material adverse effect on our business, financial results and results of operations. Further, as we presently have no patent rights to protect the approved use of Emflaza, we rely upon market exclusivity periods available to us under the Orphan Drug Act to commercialize Emflaza for DMD in the United States. As the holder of orphan exclusivity, we are required to assure the availability of sufficient quantities of Emflaza to meet the needs of patients. Failure to do so could result in loss of the drug's orphan exclusivity in the United States, which would have a material adverse effect on our ability to generate revenue from sales of Emflaza.

We utilize third parties for the commercial distribution of Emflaza, including a 3PL to warehouse Emflaza as well as specialty pharmacies to sell and distribute Emflaza to patients. The specialty pharmacies provide us with third-party call center services to provide patient support and financial services, prescription intake and distribution, reimbursement adjudication, and ongoing compliance support. If we are unable to effectively manage this distribution process, the continuance of our commercial launch and sales of Emflaza may be delayed or compromised.

Pursuant to the Tegsedi-Waylivra Agreement, we have entered into a master supply agreement with Akcea whereby Akcea or its affiliates will manufacture and supply, or cause to be manufactured and supplied, Tegsedi and Waylivra in quantities sufficient to support the commercialization of Tegsedi and Waylivra in the PTC Territory. This is currently the only manufacturing and supply agreement that we have entered into for the drug substance of Tegsedi and Waylivra. If the master supply agreement is terminated and we are unable to find an alternative third party contractor, we may encounter delays in manufacturing Tegsedi and Waylivra.

We have a commercial manufacturing services agreement with MassBio to provide sufficient quantities of our PTC-AADC program materials to meet anticipated clinical trial and commercial scale demands. This is currently the only manufacturing services agreement that we have entered into for PTC-AADC. If the commercial manufacturing services agreement is terminated and we are unable to find an alternative third party contractor, we may encounter delays in manufacturing PTC-AADC.

Even if we are able to establish and maintain arrangements with third-party manufacturers and distributors, reliance on such service providers as well as the use of specialty pharmacies and a call center entails additional risks, including:

- reliance on the third party for regulatory compliance and quality assurance;
- the possible breach of the manufacturing agreement by the third party;
- the possible misappropriation of our proprietary information, including our trade secrets and know-how;
- the possibility of commercial supplies of our products not being distributed to commercial vendors or end users in a timely manner, resulting in lost sales;
- the possibility of clinical supplies not being delivered to clinical sites on time, leading to clinical trial interruptions;
- the possibility of third-party resources not being devoted in the manner necessary to satisfy our requirements within the expected time frame;
- the possibility of third parties not providing us with accurate or timely information regarding their inventories, the number of patients who are using our products, or serious adverse events and/or product complaints regarding our products;
- the possibility of third parties being unable to satisfy their financial obligations to us or to others; and
- the possible termination or nonrenewal of a critical agreement by the third party at a time that is costly or inconvenient to us.

Many additional factors could cause production or distribution interruptions with the manufacture and distribution of any of our products and product candidates, including human error, natural disasters, labor disputes, acts of terrorism or war, equipment malfunctions, contamination, supply chain disruption, including disruptions caused by the COVID-19 pandemic, or raw material shortages. We have experienced delays in receiving certain raw materials in connection with supply chain disruptions caused by the COVID-19 pandemic, however, these delays did not affect or delay our manufacturing given our existing inventories for such materials. If the supply chain disruptions caused by the COVID-19 pandemic creates more prolonged delays, the supplies of our products or products candidates may be significantly and adversely affected and our business, results of operations and financial condition could be materially adversely affected.

Our products and product candidates and any other products that we may develop may compete with other product candidates and products for access to manufacturing facilities. There are a limited number of manufacturers that operate under cGMP regulations and that might be capable of manufacturing for us. In addition, changes in cGMP regulations could negatively impact our ability or the ability of our contract manufacturers to complete the manufacturing process of our products and our product candidates in a compliant manner on the schedule we require for commercial and clinical trial use, respectively.

If we or the third parties that we engage to manufacture product for our commercial sales, preclinical tests and clinical trials should, prior to the time that we have validated alternative providers, cease to continue to do so for any reason, we likely would experience delays in our ability to supply Translarna, Emflaza, Tegsedi or Waylivra to patients or in our ability to advance our clinical trials while we identify and qualify replacement suppliers and we may be unable to obtain replacement supplies on terms that are favorable to us. In addition, if we are not able to obtain adequate supplies of our

products or product candidates or the drug substances used to manufacture them, we will lose commercial sales revenue and it will be more difficult for us to develop our product candidates and compete effectively.

We or our contract manufacturers may also encounter other impediments or difficulties that could adversely affect our products, product candidates, and our business, results of operations and financial condition. For example, we or our manufacturers may experience shortages in raw materials and components, not be able to scale up manufacturing capacities to support more advanced clinical trials or product commercialization, may not be able to qualify or validate facilities, equipment, and processes, or may not be able to obtain or develop the necessary technological capabilities, either through knowledge transfer or independent development. To the extent that any contract manufacturers develop proprietary manufacturing processes or procedures, should we need to change manufacturers, we may not be able to transfer such know-how to a new manufacturer. In such a case, the new manufacturer would need to invest substantial time, money, and effort to develop its own processes and procedures, which would require FDA approval.

Third parties might illegally distribute and sell counterfeit or unfit versions of our products that do not meet our rigorous manufacturing and testing standards. A patient who receives a counterfeit or unfit drug may be at risk for a number of dangerous health consequences. Our reputation and business could suffer harm as a result of counterfeit or unfit drugs sold under our brand name. In addition, thefts of inventory at warehouses, plants or while in-transit, which are not properly stored and which are sold through unauthorized channels, could adversely impact patient safety, our reputation and our business.

Our current and anticipated future dependence upon others for the manufacture and distribution of Translarna, Emflaza, Tegsedi, Waylivra and certain of our product candidates may adversely affect our business, financial condition, results of operations and limit our ability to grow including our ability to develop product candidates and commercialize our products that receive regulatory approval on a timely and competitive basis.

We rely on third parties to conduct our preclinical and clinical trials, and those third parties may not perform satisfactorily, including failing to meet deadlines for the completion of such trials.

We do not independently conduct preclinical or clinical trials for our products or product candidates. We rely on third parties, such as contract research organizations, clinical data management organizations, medical institutions and clinical investigators, to perform this function. While we have agreements governing the activities of such third parties, we have limited influence and control over their actual performance and activities. For instance, our third-party service providers are not our employees, and except for remedies available to us under our agreements with such third parties we cannot control whether or not they devote sufficient time and resources to our ongoing clinical, non-clinical, and preclinical programs. If these third parties do not successfully carry out their contractual duties, meet expected deadlines or conduct our preclinical studies or clinical trials in accordance with regulatory requirements or our stated protocols, if they need to be replaced or if the quality or accuracy of the data they obtain is compromised due to the failure to adhere to our protocols, regulatory requirements or for other reasons, our trials may be repeated, extended, delayed, or terminated, we may not be able to obtain, or may be delayed in obtaining, marketing approvals for our product candidates, we may not be able to, or may be delayed in our efforts to, successfully commercialize our product candidates, or we or they may be subject to regulatory enforcement actions. As a result, our results of operations and the commercial prospects for our product candidates would be harmed, our costs could increase and our ability to generate revenues could be delayed. To the extent we are unable to successfully identify and manage the performance of third-party service providers in the future, our business may be materially and adversely affected. Further, any of these third parties may terminate their engagements with us at any time. If we need to enter into alternative arrangements, it would delay our product development activities.

Our reliance on these third parties for clinical development activities reduces our control over these activities but does not relieve us of our responsibilities. For example, we remain responsible for ensuring that each of our clinical trials is conducted in accordance with the general investigational plan and protocols for the trial. Moreover, the FDA requires us to comply with standards, commonly referred to as GCP for conducting, recording and reporting the results of clinical trials to assure that data and reported results are credible and accurate and that the rights, integrity and confidentiality of trial participants are protected. We also are required to register ongoing clinical trials and post the results of completed clinical trials on a government-sponsored database, ClinicalTrials.gov, within certain timeframes. Failure to do so can result in fines, adverse publicity and civil and criminal sanctions. In addition, we will be required to report certain financial

interests of our third-party investigators if these relationships exceed certain financial thresholds or meet other criteria. The FDA or comparable ex-U.S. regulatory authorities may question the integrity of the data from those clinical trials conducted by investigators who may have conflicts of interest. We must further ensure that our preclinical trials are conducted in accordance with good laboratory practices, or GLPs, as appropriate. Regulatory authorities enforce these requirements through periodic inspections of trial sponsors, clinical and preclinical investigators, and trial sites. Similar GCP and transparency requirements apply in the EU. Failure to comply with the applicable regulatory requirements, including with respect to clinical trials conducted outside the EU and United States, can also lead regulatory authorities to refuse to accept into account clinical trial data submitted as part of a marketing application, as well as other regulatory consequences, as further described above.

For example, in the first half of 2013 inspectors acting at the request of the EMA conducted GCP inspections of selected clinical sites from our completed Phase 2b clinical trial of Translarna for the treatment of nmDMD and our clinical trial site relating to our then pending marketing authorization application for approval of Translarna for the treatment of nmDMD. Following these inspections, we received inspection reports containing a combination of critical and major findings. These findings related to waivers we granted to admit patients to our Phase 2b clinical trial of Translarna for the treatment of nmDMD in advance of formal approval of protocol amendments that would have established their eligibility for the trial, as well as our oversight of our trial sites and the completeness or sufficiency of clinical trial documentation. In response to these findings, we described to the EMA the enhanced internal procedures and controls we have implemented, and the internal quality assurance department we have established, since the conclusion of our Phase 2b clinical trial of Translarna for the treatment of nmDMD. In addition, we proposed corrective action plans to address the inspectors' specific findings. If we do not meet our commitment to the corrective actions we proposed to the EMA, we may face additional consequences, including rejection of data or other direct action by national regulatory authorities, which could require us to conduct additional clinical trials or other supportive studies to maintain our marketing authorization in the EEA for Translarna for the treatment of nmDMD or to obtain full approval from the EMA.

Furthermore, third parties that we rely on for our clinical development activities may also have relationships with other entities, some of which may be our competitors. If these third parties do not successfully carry out their contractual duties, meet expected deadlines or conduct our clinical trials in accordance with regulatory requirements or our stated protocols, we will not be able to obtain, or may be delayed in obtaining, marketing authorizations for our product candidates and will not be able to, or may be delayed in our efforts to, successfully commercialize our product candidates. Our product development costs will increase if we experience delays in testing or obtaining marketing authorizations.

We also rely on other third parties to store and distribute drug supplies for our clinical trials. Any performance failure on the part of our distributors could delay clinical development or marketing authorizations of our products or product candidates or commercialization of our products, producing additional losses and depriving us of potential product revenue.

We currently depend, and expect to continue to depend, on collaborations with third parties for the development and commercialization of some of our products and product candidates. If those collaborations are not successful, we may not be able to capitalize on the market potential of these products and product candidates.

For each of our product candidates, we plan to evaluate the merits of retaining commercialization rights for ourselves or entering into selective collaboration arrangements with leading pharmaceutical or biotechnology companies, such as our collaborations with Roche and the SMA Foundation, for our spinal muscular atrophy program, including Evrysdi. We have entered into arrangements with certain third parties to market or distribute Translarna for the treatment of nmDMD in certain countries and, as we continue to implement our commercialization plans for Translarna, we anticipate that we will engage additional third parties to perform these functions for us in other countries. We generally plan to seek collaborators for the development and commercialization of product candidates that have high anticipated development costs, are directed at indications for which a potential collaborator has a particular expertise, or involve markets that require a large sales and marketing organization to serve effectively. Our likely collaborators for any marketing, distribution, development, licensing or broader collaboration arrangements may include: large and mid-size pharmaceutical companies, regional and national pharmaceutical companies and/or biotechnology companies.

We will have limited control over the amount and timing of resources that our collaborators dedicate to the development or commercialization of our product candidates and our collaborators will be subject to the same product development and commercialization risks that we are subject to. Our ability to generate revenues from these arrangements will depend on our collaborators' desire and ability to successfully perform the functions assigned to them in these arrangements. In particular, the commercial success of Evrysdi will depend on the success of Roche's commercialization program. Furthermore, the successful development of another product candidate from our spinal muscular atrophy program will depend on the success of our collaborations with the SMA Foundation and Roche, including whether Roche pursues clinical development of any other compounds identified under the collaborations.

Collaborations involving our products and product candidates, including our collaborations with the SMA Foundation and Roche, pose the following risks to us:

- collaborators have significant discretion in determining the efforts and resources that they will apply to these collaborations;
- collaborators may not pursue development and commercialization of our products and product candidates or may elect not to continue or renew development or commercialization programs, based on clinical trial results, changes in the collaborators' strategic focus or available funding, or external factors such as an acquisition that diverts resources or creates competing priorities;
- collaborators may delay clinical trials, provide insufficient funding for a clinical trial program, stop a clinical trial or abandon a product candidate, repeat or conduct new clinical trials or require a new formulation of a product candidate for clinical testing;
- collaborators could independently develop, or develop with third parties, products that replace or compete directly or indirectly with our products or product candidates if the collaborators believe that competitive products are more likely to be successfully developed or can be commercialized under terms that are more economically attractive than ours;
- collaborators may fail to comply with the applicable regulatory requirements, subjecting them or us to potential regulatory enforcement action;
- a collaborator with marketing and distribution rights to one or more products may not commit sufficient resources to the marketing and distribution of such product or products;
- collaborators may not properly maintain or defend our intellectual property rights or may use our proprietary information in such a way as to invite litigation that could jeopardize or invalidate our intellectual property or proprietary information or expose us to potential litigation;
- collaborators may infringe the intellectual property rights of third parties, which may expose us to litigation and potential liability;
- disputes may arise between the collaborator and us as to the ownership of intellectual property arising during the collaboration;
- we may grant exclusive rights for our products or product candidates to our collaborators, which would prevent us from collaborating with others, or from using our products or product candidates ourselves;
- disputes may arise between the collaborators and us that result in the delay or termination of the collaboration, which may include ending research, development or commercialization activities for our products or product candidates or that result in costly litigation or arbitration that diverts management attention and resources; and
- collaborations may be terminated and, if terminated, may result in a need for additional capital to pursue further development or commercialization of the applicable product candidates.

Collaboration agreements may not lead to development or commercialization of product candidates in the most efficient manner or at all. If a collaborator of ours were to be involved in a business combination, the continued pursuit and emphasis on our product development or commercialization program could be delayed, diminished or terminated.

We may rely on third parties to perform many essential services for any products that we commercialize, including services related to warehousing and inventory control, distribution, government price reporting, customer service, accounts receivable management, cash collection, and pharmacovigilance and adverse event reporting. If these third parties fail to perform as expected or to comply with legal and regulatory requirements, our ability to commercialize our product candidates will be significantly impacted and we may be subject to regulatory sanctions.

We may retain third-party service providers to perform a variety of functions related to the sale and distribution of our product candidates, key aspects of which will be out of our direct control. These service providers may provide key services related to warehousing and inventory control, distribution, customer service, accounts receivable management, and cash collection. If we retain a service provider, we would substantially rely on it as well as other third-party providers that perform services for us, including entrusting our inventories of products to their care and handling. If these third-party service providers fail to comply with applicable laws and regulations, fail to meet expected deadlines, or otherwise do not carry out their contractual duties to us, or encounter physical or natural damage at their facilities, our ability to deliver product to meet commercial demand would be significantly impaired and we may be subject to regulatory enforcement action.

In addition, we may engage third parties to perform various other services for us relating to pharmacovigilance and adverse event reporting, safety database management, fulfillment of requests for medical information regarding our product candidates and related services. If the quality or accuracy of the data maintained by these service providers is insufficient, or these third parties otherwise fail to comply with regulatory requirements, we could be subject to regulatory sanctions.

Additionally, we may contract with a third party to calculate and report pricing information mandated by various government programs. If a third party fails to timely report or adjust prices as required, or errors in calculating government pricing information from transactional data in our financial records, it could impact our discount and rebate liability, and potentially subject us to regulatory sanctions or False Claims Act lawsuits.

Our business and operations would suffer in the event of computer system failures, cyber-attacks or a deficiency in our, or our collaborators' or third-party vendors', cyber-security.

We collect, store and transmit large amounts of confidential information, including personal information, operational and financial transactions and records, clinical trial data and information relating to intellectual property, on internal information systems and through the information systems of collaborators and third-party vendors with whom we contract. Despite our implementation of security measures, including implementing the National Institute of Standards and Technology cybersecurity framework, instituting a training and compliance program on cybersecurity for all employees and doing a yearly external audit and penetration test, these information systems are vulnerable to damage from computer viruses, malware, natural disasters, terrorism, war, telecommunication and electrical failures, cyber-attacks or cyber-intrusions over the Internet or other mechanisms, attachments to emails, persons inside our organization, or persons with access to systems inside our organization. No such security measures can eliminate the possibility of the information systems' improper functioning or the improper access or disclosure of confidential or personally identifiable information such as in the event of cyber-attacks. The risk of a security breach or disruption, particularly through cyber-attacks or cyber-intrusion, including by computer hackers, criminals, ex-U.S. governments, and cyber terrorists, has generally increased as the number, intensity and sophistication of attempted attacks and intrusions from around the world have increased. Additionally, outside parties may attempt to fraudulently induce employees, collaborators, or other third-party vendors to disclose sensitive information or take other actions, including making fraudulent payments or downloading malware, by using "spoofing" and "phishing" emails or other types of attacks. If such an event were to occur and cause interruptions in our operations, it could result in a material disruption of our clinical and commercialization activities and business operations, in addition to possibly requiring substantial expenditures of resources to remedy, despite our having a security risk insurance policy and disaster recovery and incident response plans. For example, the loss of clinical trial data from completed or ongoing or planned clinical trials could result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce the data. To the extent that any disruption or security breach was to result in a loss of or damage to our data or applications, or inappropriate disclosure of confidential or proprietary information, we could incur material legal claims and liability, damage to our reputation, suffer loss or harm to our intellectual property rights, face significant financial exposure, including incurring significant costs to remediate possible injury to the affected parties and the further research, development and commercial efforts of our products and product candidates could be delayed.

Product liability and other civil lawsuits against us could cause us to incur substantial liabilities and to limit clinical trials or commercialization of any current or future products.

We face an inherent risk of product liability exposure related to the commercialization of our products and any product candidate that we may market or commercialize, any gene therapy product materials that we manufacture for third parties at the Hopewell Facility and in connection with the human clinical trials testing of our products and product candidates. If we cannot successfully defend ourselves against claims that our product candidates, products or gene therapy product materials caused injuries, we will incur substantial liabilities. Regardless of merit or eventual outcome, liability claims may result in:

- reduced resources of our management to pursue our business strategy;
- decreased demand for our products or any product candidates that we may develop;
- decreased demand for the gene therapy product materials that we manufacture for third parties at the Hopewell Facility;
- injury to our reputation and significant negative media attention;
- the inability to continue current clinical trials or begin planned clinical trials;
- withdrawal or reduced enrollment of clinical trial participants;
- significant costs to defend the related claims/litigation;
- increased insurance costs, or an inability to maintain appropriate insurance coverage;
- substantial monetary awards to trial participants, patients and/or their families;
- loss of revenue;
- the inability to commercialize or to continue commercializing any products or product candidates;
- initiation of investigations and enforcement actions by regulators; and
- the withdrawal of products from the market, product recalls, or the cessation of development or regulatory disapproval of product candidates or withdrawal of approvals, as well as labeling, marketing, or promotional restrictions.

Because emvododstat for COVID-19 is being developed under an emergency Declaration, we may be eligible for limited liability protection under the Public Readiness and Emergency Preparedness Act, or PREP Act. The PREP Act provides limited immunity for manufacturers from claims for losses arising out of the administration or use of a "covered countermeasure." However, the PREP Act does not provide complete immunity as injured persons may still bring a suit for "willful misconduct" under some circumstances. The PREP Act also does not provide immunity against federal enforcement actions or claims under federal law for equitable relief. "Covered countermeasures" include "qualified pandemic or epidemic products", such as those for COVID-19. For these immunities to apply, the Secretary of the U.S. Department of Health and Human Services, or HHS, must issue a declaration of a public health emergency, as was done for COVID-19. To be covered by PREP Act immunity, activities and products must further meet the criteria set forth in the HHS declaration of immunity from liability, and the therapeutic must be authorized by the FDA, or authorized for investigational or emergency use for the applicable emergency. The federal government has continuously revised its PREP Act declaration and has provided multiple advisory opinions regarding its interpretation of the PREP Act declarations throughout the COVID-19 pandemic. Accordingly, interpretation of the scope of the PREP Act may change. Additionally, the PREP Act may not provide adequate coverage or immunity for all potential claims related to our COVID-19 product candidate.

We have product liability insurance that covers our commercial sales, sales pursuant to reimbursed EAP programs and clinical trials up to a $25.0 million annual aggregate limit, and subject to a per claim deductible. Our insurance limits may not be adequate to cover all liabilities and defense costs that we may incur. We may need to further increase our insurance coverage as we commercialize our products, or as and when we begin commercializing any other product candidate that receives marketing authorization. The cost of insurance coverage is highly variable, based on a wide range of factors. We may not be able to maintain insurance coverage at a reasonable cost or in an amount adequate to satisfy any liability or defense costs that may arise.

In addition, we could be subject to other costly civil litigation, including contractual claims with respect to our expected manufacturing of gene therapy product materials for potential external customers. If our customers believe that we have

violated our contractual terms, they may seek reimbursement for the cost of our gene therapy product materials or other related losses, the cost of which could be significant.

If we fail to comply with environmental, health and safety laws and regulations, we could become subject to fines or penalties or incur costs that could have a material adverse effect on the success of our business.

We are subject to numerous environmental, health and safety laws and regulations, including those governing laboratory procedures, manufacturing and the handling, use, storage, treatment and disposal of hazardous materials and wastes. Our operations currently, and may in the future, involve the use of hazardous and flammable materials, including chemicals and medical and biological materials, and produce hazardous waste products. Even if we contract with third parties for the disposal of these materials and wastes, we cannot eliminate the risk of contamination or injury from these materials. In the event of contamination or injury resulting from our use of hazardous materials or disposal of hazardous wastes, we could be held liable for any resulting damages, and any liability could exceed our resources.

Although we maintain workers' compensation insurance to cover us for costs and expenses, we may incur due to injuries to our employees resulting from the use of hazardous materials, this insurance may not provide adequate coverage against potential liabilities. We also maintain liability insurance for some of these risks, but our liability policy excludes pollution and has an aggregate coverage limit of $11.0 million.

In addition, we may incur substantial costs in order to comply with current or future environmental, health and safety laws and regulations. These current or future laws and regulations may impair our research, development or manufacturing and distribution efforts. Failure to comply with these laws and regulations also may result in substantial fines, penalties or other sanctions.

Our future success depends on our ability to retain our chief executive officer and other key executives and to attract, retain and motivate qualified personnel.

We are highly dependent on Dr. Stuart W. Peltz, our co-founder and Chief Executive Officer, and the other principal members of our executive, commercial and scientific teams. Although we have formal employment agreements with each of our executive officers, these agreements do not prevent our executives from terminating their employment with us at any time. We do not maintain "key person" insurance on any of our executive officers. The loss of the services of any of these persons might impede the achievement of our research, development and commercialization objectives.

Recruiting and retaining qualified scientific, clinical, manufacturing and sales and marketing personnel will also be critical to our success. Additionally, because the field of gene therapies and gene therapy manufacturing is new and complex, we might face a shortage of skilled individuals with substantial gene therapy and gene therapy manufacturing experience. As a result, competition for skilled personnel, including in gene therapy research and gene therapy manufacturing, is intense and the turnover rate can be high. We may not be able to attract and retain these personnel on acceptable terms given the competition among numerous pharmaceutical and biotechnology companies for similar personnel. We also experience competition for the hiring of scientific and clinical personnel from universities and research institutions. In addition, we rely on consultants and advisors, including scientific and clinical advisors, to assist us in formulating our research and development and commercialization strategy. Our consultants and advisors may be employed by employers other than us and may have commitments under consulting or advisory contracts with other entities that may limit their availability to us.

We are in the process of expanding our development, regulatory, and sales and marketing capabilities, and as a result, we may encounter difficulties in managing our growth, which could disrupt our operations.

In connection with our commercialization plans and business strategy, including our continued commercialization of Translarna and Emflaza, our ongoing commercial launches of Tegsedi and Waylivra and, if approved, PTC-AADC and other product candidates, we have experienced and may to continue to experience significant growth in our employee base for sales, marketing, operational, managerial, financial, human resources, drug development, quality, regulatory and medical affairs and other areas. This growth has imposed and will continue to impose significant added responsibilities on members of management, including the need to recruit, hire, retain, motivate and integrate additional employees, including

employees who joined us in connection with any of our acquisitions or other strategic transactions. Also, our management may have to divert a disproportionate amount of its attention away from our day-to-day activities and devote a substantial amount of time to managing these growth activities, including any applicable integration. To manage our recent and anticipated future growth, we must continue to implement and improve our managerial, operational and financial systems, expand our facilities and continue to recruit and train additional qualified personnel. Due to our limited financial resources and the limited experience of our management team in managing a company with such growth, we may not be able to effectively manage the expansion of our operations or recruit and train additional qualified personnel. In addition, we may need to adjust the size of our workforce as a result of changes to our expectations for our business, which can result in diversion of management attention, disruptions to our business, and related expenses. For example, following our receipt of the Refuse to File letter from the FDA in 2016, we implemented a reorganization of our operations in March 2016 that resulted in a one-time charge for the related work-force reduction. The physical expansion of our operations may lead to significant costs and may divert our management and business development resources. Any inability to manage growth could delay the execution of our business plans or disrupt our operations.

Risks Related to our Intellectual Property

If we are unable to obtain and maintain patent protection for our technology and products, or if the scope of the patent protection is not sufficiently broad, our competitors could develop and commercialize technology and products similar or identical to ours, and our ability to successfully commercialize our technology and products may be adversely affected.

Our success depends in large part on our ability to obtain and maintain patent protection or other intellectual property rights in the United States and other countries with respect to our proprietary technology and products. One primary way that we seek to protect our proprietary position is by filing patent applications in the United States and in certain ex-U.S. jurisdictions related to our novel technologies, product and product candidates that are important to our business. This process is expensive and time-consuming, and we may not be able to file and prosecute all necessary or desirable patent applications at a reasonable cost or in a timely manner. It is also possible that we will fail to identify patentable aspects of our research and development output or miss an opportunity to file a patent application. Moreover, if we license technology or product candidates from third parties in the future, these license agreements may not permit us to control the preparation, filing and prosecution of patent applications, or to maintain or enforce the patents, covering this intellectual property. These agreements could also give our licensors the right to enforce the licensed patents without our involvement, or to decide not to enforce the patents at all. Therefore, in these circumstances, these patents and applications may not be prosecuted and enforced in a manner consistent with the best interests of our business.

The patent position of biotechnology and pharmaceutical companies generally is highly uncertain, involves complex legal and factual questions and has in recent years been the subject of much litigation. As a result, the issuance, scope, validity, enforceability and commercial value of our patent rights are highly uncertain. Our pending and future patent applications may not result in patents being issued which protect our technology or products, in whole or in part, or which effectively prevent others from commercializing competitive technologies and products. Changes in either the patent laws or interpretation of the patent laws in the United States and other countries may diminish the value of our patents or narrow the scope of our patent protection.

The laws of ex-U.S. countries may not protect our rights to the same extent as the laws of the United States. For example, patent law in many countries restricts the patentability of methods of treatment of the human body more than U.S. law does. In addition, we may not pursue or obtain or be able to pursue or obtain patent protection in all major markets. Assuming the other requirements for patentability are met, currently, the first to file a patent application is generally entitled to the patent. However, prior to March 16, 2013, in the United States, the first to invent was entitled to the patent. Publications of discoveries in the scientific literature often lag behind the actual discoveries, and patent applications in the United States and other jurisdictions are typically not published until 18 months after filing, or in some cases not at all. Therefore, we cannot know with certainty whether we were the first to make the inventions claimed in our patents or pending patent applications, or that we were the first to file for patent protection of such inventions. In addition, the Leahy-Smith America Invents Act of 2011, or the Act, which reformed certain patent laws in the U.S., may create additional uncertainty. The significant changes engendered by the Act include switching from a “first-to-invent” system to a “first-

to-file" system, and the implementation of new procedures that permit competitors to challenge our patents in the USPTO after grant, including *inter partes* review and post grant review.

Moreover, we may be subject to a third party anonymously submitting prior art to a patent office or may become involved in addressing patentability objections based on third-party submission of references, or may become involved in oppositions, derivation proceedings, reexamination, *inter partes* review, post grant review, interference proceedings or other patent office proceedings or litigation, in the United States or elsewhere, challenging our patent rights or the patent rights of others. An adverse determination in any such submission, proceeding or litigation could reduce the scope of, or invalidate, our patent rights, allow third parties to commercialize our technology or products and compete directly with us, without payment to us, or result in our inability to manufacture or commercialize products without infringing third-party patent rights. In addition, if the breadth or strength of protection provided by our patents and patent applications is threatened, it could dissuade companies from collaborating with us to license, develop or commercialize our product or current or future product candidates.

Even if our patent applications issue as patents, they may not issue in a form that will provide us with any meaningful protection, prevent competitors from competing with us or otherwise provide us with any competitive advantage. Our competitors may be able to circumvent our owned or licensed patents by developing similar or alternative technologies or products in a non-infringing manner. In addition, other companies may attempt to circumvent any regulatory data protection or market exclusivity that we obtain under applicable legislation, which may require us to allocate significant resources to prevent such circumvention. Legal and regulatory developments in the EU and elsewhere may also result in clinical trial data and other information, that would ordinarily be treated as trade secret, submitted as part of a marketing authorization application becoming publicly available. The EMA Policy on publication of clinical data and other such information, as well as the current application of EU freedom of information regulations, could impact our proprietary information (comprising both clinical and non-clinical data and other information) that would normally be maintained by a regulatory body as commercially confidential. Such developments could enable other companies to circumvent our intellectual property rights and use our clinical trial data or other information to obtain marketing authorizations in the EU and in other jurisdictions where we have not been able to obtain any intellectual property or regulatory protection, resulting in loss of market share. Such developments may also require us to allocate significant resources or engage in litigation to prevent other companies from circumventing or violating our intellectual property rights. Our attempts to prevent third parties from circumventing our intellectual property and other rights may ultimately be unsuccessful. We may also fail to take the required actions or pay the necessary fees to maintain our patents.

For example, during 2015, we were notified by the EMA that it had received from another pharmaceutical company a request under Regulation (EC) No 1049/2001 seeking access to aspects of our marketing authorization for Translarna for the treatment of nmDMD. Following the decision of the EMA to release such documentation with only minimal redactions we initiated litigation before the General Court of the EU to prevent disclosure of this information. In the first quarter of 2018, the Court ruled in favor of the EMA, allowing the EMA to release the documentation. We appealed the General Court's decision to the CJEU but the CJEU dismissed our appeal in January 2020 and released the information to the requester.

An issued patent may be challenged as to its inventorship, scope, validity or enforceability, and our owned and licensed patents may be challenged on such a basis in the courts or patent offices in the United States and abroad. Such challenges may result in loss of exclusivity or freedom to operate or in patent claims being narrowed, invalidated or held unenforceable, in whole or in part, which could limit our ability to stop others from using or commercializing similar or identical technology and products, or limit the duration of the patent protection of our technology and products. Given the amount of time required for the development, testing and regulatory review of new product candidates, patents protecting such candidates might expire before or shortly after such candidates are commercialized. As a result, our patent portfolio may not provide us with sufficient rights to exclude others from commercializing products similar or identical to ours.

We may become involved in lawsuits to protect or enforce our patents or other intellectual property, which could be expensive, time consuming and unsuccessful.

Competitors may infringe our patents, trademarks, copyrights, trade secrets or other intellectual property. To counter infringement or unauthorized use, we may be required to file a lawsuit and claims for damages, which can be expensive

and time consuming. Any claims we assert against perceived infringers could provoke these parties to assert counterclaims against us alleging that we infringe their intellectual property or defenses, such that they do not infringe our intellectual property or that our intellectual property is invalid or unenforceable. In addition, in a patent infringement proceeding, a court may decide that a patent of ours is invalid or unenforceable, in whole or in part, construe the patent's claims narrowly or may refuse to stop the other party from using the technology at issue on the grounds that our patents do not cover the technology in question.

Third parties may initiate legal proceedings alleging that our patents are invalid and unenforceable or that we are infringing their intellectual property rights, the outcome of which would be uncertain and could have a material adverse effect on the success of our business.

Our commercial success depends upon our ability and the ability of our collaborators to develop, manufacture, market and sell our products and our product candidates and use our proprietary technologies without infringing the intellectual property and other proprietary rights of third parties. There is considerable intellectual property litigation in the biotechnology and pharmaceutical industries, and we may become party to, or threatened with, future adversarial proceedings or litigation regarding intellectual property rights with respect to our products and technology, including interference or derivation proceeding, *inter partes* review or post-grant review proceedings before the U.S. Patent and Trademark Office. The risks of being involved in such litigation and proceedings may also increase as our product candidates are disclosed while approaching commercialization, and as we gain greater visibility as a public company. Third parties may assert infringement claims against us based on existing or future intellectual property rights. We may not be aware of all such intellectual property rights potentially relating to our product and our product candidates. Since patent applications in the United States and other jurisdictions are typically not published until 18 months after filing, or in some cases not at all, with new publications occurring continuously, there may be patents or patent applications relating to our product or our product candidates that we are unaware of. There may also be pending or future patent applications that, if issued, would block us from commercializing our commercial products. Thus, we do not know with certainty whether any of our products or product candidates, or our commercialization thereof, would or would not infringe any third party's intellectual property.

If we are found to infringe a third party's intellectual property rights, or in order to avoid or settle litigation, we could be required to obtain a license to continue developing and marketing our products and technology. However, we may not be able to obtain any required license on commercially reasonable terms or at all. Even if we were able to obtain a license, it could be non-exclusive, thereby giving our competitors access to the same technologies licensed to us, and could require us to make substantial payments. We could be forced, including by court order, to cease commercializing an alleged infringing technology or product. In addition, we could be found liable for monetary damages, including treble damages and attorney's fees if we are found to have willfully infringed a patent or other intellectual property right. A finding of infringement could prevent us from commercializing our products or our product candidates or force us to cease some of our business operations, which could materially harm our business. Claims that we have misappropriated the confidential information or trade secrets of third parties could have a similar negative impact on our business.

For example, it is possible that one or more third parties might bring a patent infringement or other legal proceeding against us regarding Translarna or Emflaza. In order to successfully challenge the validity of any issued U.S. patent that may allegedly include ataluren or deflazacort within the scope of a granted claim, we would need to overcome that patent's presumption of validity in district court or prove unpatentability by a preponderance of the evidence before the USPTO. There is no assurance that a court or the USPTO would find these claims to be invalid or unpatentable, respectively. In addition, we believe that the public notice given by our testing of ataluren in clinical trials for the purpose of seeking FDA approval would be a valid defense against any infringement claims in the United States prior to commercialization based on the availability of any statutory research exemptions. However, there can be no assurance that our interpretation of the exemption would be upheld.

We may be subject to claims by third parties asserting that we or our employees have misappropriated their intellectual property, or claiming ownership of what we regard as our own intellectual property.

Many of our employees were previously employed at universities or other biotechnology or pharmaceutical companies, including our competitors or potential competitors. Although we try to ensure that our employees do not use the proprietary

information or know-how of others in their work for us, we may be subject to claims that we or these employees have used or disclosed intellectual property, including trade secrets or other proprietary information, of any such employee's former employer. Litigation may be necessary to defend against these claims.

In addition, while we typically require our employees and contractors who may be involved in the development of intellectual property to execute agreements assigning such intellectual property to us, we may be unsuccessful in executing such an agreement with each party who in fact develops intellectual property that we regard as our own. Our and their assignment agreements may not be self-executing or may be breached, and we may be forced to bring claims against third parties, or defend claims they may bring against us, to determine the ownership of what we regard as our intellectual property.

If we fail in prosecuting or defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights or personnel. Even if we are successful in prosecuting or defending against such claims, litigation could result in substantial costs and be a distraction to management.

Intellectual property litigation could cause us to spend substantial resources and could distract our personnel from their normal responsibilities.

Even if resolved in our favor, litigation or other legal proceedings relating to intellectual property claims may cause us to incur significant expenses and could distract our technical and management personnel from their normal responsibilities. In addition, there could be public announcements of the results of hearings, motions or other interim proceedings or developments. If securities analysts or investors perceive these results to be negative, it could have a substantial adverse effect on the price of our common stock. Such litigation or proceedings could substantially increase our operating losses and reduce the resources available for development, sales, marketing or distribution activities. We may not have sufficient financial or other resources to adequately conduct such litigation or proceedings. Some of our competitors may be able to sustain the costs of such litigation or proceedings more effectively than we can because of their greater financial resources. Uncertainties resulting from the initiation and continuation of patent litigation or other proceedings could have a material adverse effect on our ability to compete in the marketplace.

Without patent protection, our marketed products may face generic competition.

Certain of the products we market have no or limited patent protection and, as a result, potential competitors face fewer regulatory barriers in introducing competing products. Without patent protection or other regulatory exclusivity, we may not be able to exclude others from, among other things, selling or importing similar products in any jurisdiction. In some instances, we may rely on trade secrets and other unpatented proprietary information to protect our commercial position with respect to such products, although we may be unable to provide adequate protection for our commercial position via these means. In other instances, we may need to rely on regulatory exclusivity to protect our commercial position.

Furthermore, generic competition against a branded product often results in decreases in the prices at which the branded product can be sold, particularly when there is more than one generic product available in the marketplace. Third-party companies could also develop products that are similar, but not identical, to our marketed products, such as an alternative formulation of our product or an alternative formulation combined with a different delivery technology, and seek approval in the United States by referencing our products and relying, to some degree, on the FDA's finding that our products are safe and effective in their approved indications. In addition, legislation enacted in the United States allows for, and in a few instances, in the absence of specific instructions from the prescribing physician, mandates the dispensing of generic products rather than branded products where a generic version is available.

On February 9, 2017, the FDA approved the corticosteroid Emflaza for the treatment of patients 5 years and older with DMD. Although approved for other indications outside of the United States, this was the first approval for deflazacort in the United States and the first approval in the United States for the use of a corticosteroid to treat DMD. Emflaza's seven-year period of orphan drug exclusivity related to the treatment of DMD in patients five years and older expires in February 2024. Emflaza's orphan drug exclusivity related to the treatment of DMD in patients two years of age to less than five expires in June 2026.

We rely on regulatory exclusivity for Emflaza and currently have no issued patents that could prevent a third-party company from seeking to introduce a generic Emflaza formulation in the United States for the treatment of DMD or another indication, and we may never be able to obtain such patent protection. Such third-party companies may also obtain patents covering a new deflazacort formulation or method of use.

If we are unable to protect the confidentiality of our trade secrets, our business and competitive position would be harmed.

In addition to seeking patents and regulatory exclusivity for some of our technology and products, we also rely on trade secrets, including unpatented know-how, technology and other proprietary information, to maintain our competitive position. More particularly, we may rely on trade secrets and other unpatented proprietary information to protect our competitive position related to our products and product candidates, especially when patent protection is not obtainable. We seek to protect these trade secrets, in part, by entering into non-disclosure and confidentiality agreements with parties who have access to them, such as our employees, corporate collaborators, outside scientific collaborators, contract manufacturers, consultants, advisors, partners and other third parties. We also enter into confidentiality and invention or patent assignment agreements with our employees and consultants. However, we cannot guarantee that we have executed these agreements with each party that may have or have had access to our trade secrets or that the agreements we have executed will provide adequate protection. Any party with whom we have executed such an agreement may breach that agreement and disclose our proprietary information, including our trade secrets, and we may not be able to obtain adequate remedies for such breaches. Enforcing a claim that a party illegally disclosed or misappropriated a trade secret is difficult, expensive and time-consuming, and the outcome is unpredictable. In addition, some courts inside and outside the United States are less willing or unwilling to protect trade secrets. If any of our trade secrets were to be lawfully obtained or independently developed by a competitor, we would have no right to prevent them, or those to whom they communicate it, from using that technology or information to compete with us. If any of our trade secrets were to be obtained or independently developed by a competitor, our competitive position would be harmed. If our employees, corporate collaborators, outside scientific collaborators, contract manufacturers, employees, consultants, advisors, partners and other third parties develop new inventions or processes related to our products independently, or jointly with us, that may be applicable to our products under development, disputes may arise about ownership or proprietary rights to those inventions and processes. Enforcing a claim that a third party illegally obtained and is using any of our inventions or trade secrets is expensive and time-consuming, and the outcome is unpredictable. In addition, courts outside of the United States are sometimes less willing to protect trade secrets. Moreover, our competitors may independently develop equivalent knowledge, methods and know-how.

We have not yet registered our trademarks in all of our potential markets, and failure to secure those registrations could adversely affect our business.

Our trademark applications may be refused registration, and our registered trademarks may not be maintained or may be found to be unenforceable. During trademark examination proceedings, our trademark applications may be rejected. Although we are given an opportunity to respond to those rejections, we may not be able to overcome them. In addition, in the U.S. Patent and Trademark Office and Trademark Offices in many other jurisdictions, third parties are given an opportunity to oppose pending trademark applications or to seek cancellation of registered trademarks. Opposition or cancellation proceedings may be filed against our trademarks, and our trademarks may not survive such proceedings. In addition, if we do not secure registrations for our trademarks, we may encounter difficulty enforcing our trademark rights against third parties in the jurisdictions where we do not have registered rights.

If we are not able to obtain adequate trademark protection or regulatory approval for our brand names, we may be required to re-brand affected products, which could cause delays in getting such products to market and substantially increase our costs.

To protect our rights in any trademark we intend to use for our products or product candidates, we may seek to register such trademarks. Trademark registration is territory-specific and we must apply for trademark registration in the United States as well as any other country where we intend to commercialize our product or product candidates. Failure to obtain trademark registrations may place our use of the trademarks at risk or make them subject to legal challenges, which could force us to choose alternative names for our product or product candidates. In addition, the FDA, and other regulatory

authorities outside the United States, conduct an independent review of proposed product names for pharmaceuticals, including an evaluation of the potential for confusion with other pharmaceutical product names for medications, which could result in medication errors in prescribing, dispensing and consumption. These regulatory authorities may also object to a proposed product name if they believe the name inappropriately makes or implies a therapeutic claim. If the FDA or other regulatory authorities outside the United States object to any of our proposed product names, we may be required to adopt alternative names for our product or product candidates. If we adopt alternative names, either because of our inability to obtain a trademark registration or because of objections from regulatory authorities, we would lose the benefit of our existing trademark applications and the rights attached thereto. Consequently, we may be required to expend significant additional resources in an effort to adopt a new product name that would be registrable under applicable trademark laws, not infringe the existing rights of third parties and be acceptable to the FDA and other regulatory authorities, which could cause delays in getting our products to market and substantially increase our costs. Furthermore, in the United States and many other jurisdictions, a trademark registration may be cancelled through cancellation or forfeiture proceedings brought by a third party or from non-use of the trademark in that jurisdiction. We may not be able to build a successful brand identity for a new trademark in a timely manner or at all, which would limit our ability to commercialize our product or our product candidates.

Our rights to develop and commercialize PTC-AADC and our other gene therapy product candidates are subject, in part, to the terms and conditions of licenses granted to us by others.

We depend upon the intellectual property rights granted to us under licenses from third parties that are important or necessary to the development of PTC-AADC for the treatment of AADC deficiency and our other gene therapy product candidates. In particular, we have in-licensed certain intellectual property rights and know-how from the NTU relevant to PTC-AADC for the treatment of AADC deficiency. Any termination of these licenses could result in the loss of significant or all rights licensed to us and could harm or prevent our ability to commercialize PTC-AADC for the treatment of AADC deficiency and our other gene therapy product candidates. Each of our existing gene therapy licensing agreements are exclusive but are limited to particular fields, such as AADC deficiency and are subject to certain retained rights.

Our current gene therapy license agreements, including our agreement with NTU pursuant to which we have in-licensed certain intellectual property rights and know-how relevant to PTC-AADC for the treatment of AADC deficiency, or the License Agreement, impose various obligations, including certain payment obligations, including contingent payments to be made upon reaching certain development and regulatory milestones. If we fail to satisfy our obligations, the licensor may have the right to terminate the agreement. Disputes may arise between us and any of our licensors regarding intellectual property subject to such agreements and other issues. Such disputes over intellectual property that we have licensed or the terms of our license agreements, including with respect to PTC-AADC for the treatment of AADC deficiency, may prevent or impair our ability to maintain our current arrangements on acceptable terms, or at all, or may impair the value of the arrangement to us. Any such dispute could have a material adverse effect on our business and our ability to realize the anticipated benefits of our acquisition of Agilis. If we cannot maintain a necessary license agreement, including with respect to PTC-AADC for the treatment of AADC deficiency, or if the agreement is terminated, we may be unable to successfully develop and commercialize the affected product candidates.

If we fail to comply with our obligations in our intellectual property licenses and funding arrangements with third parties, we could lose rights that are important to our business.

We are a party to a number of license agreements and expect to enter into additional licenses in the future. Our existing licenses impose, and we expect that future licenses will impose, various diligence, milestone payment, royalty, insurance and other obligations on us. If we fail to comply with these obligations, the licensor may have the right to terminate the license, in which event we might not be able to market any product that is covered by these agreements, which could materially adversely affect the value of the product candidate being developed under such license agreement. Termination of these license agreements or reduction or elimination of our licensed rights may result in our having to negotiate new or reinstated licenses with less favorable terms or cause us to lose rights in important intellectual property or technology.

We have also received grant funding for some of our development programs from philanthropic organizations and patient advocacy groups pursuant to agreements that impose development and commercialization diligence obligations on us. If we fail to comply with these obligations, the applicable organization could require us to grant to the organization exclusive

rights under certain of our intellectual property, which could materially adversely affect the value to us of product candidates covered by that intellectual property even if we are entitled to a share of any consideration received by such organization in connection with any subsequent development or commercialization of the product candidates.

Some of our patented technology was developed with U.S. federal government funding. When new technologies are developed with U.S. government funding, the government obtains certain rights in any resulting patents, including a nonexclusive license authorizing the government to use the invention for non-commercial purposes. These rights may permit the government to disclose our confidential information to third parties and to exercise "march-in" rights to use or allow third parties to use our patented technology. The government can exercise its march-in rights if it determines that action is necessary because we fail to achieve practical application of the U.S. government-funded technology, because action is necessary to alleviate health or safety needs, to meet requirements of federal regulations or to give preference to U.S. industry. In addition, U.S. government-funded inventions must be reported to the government and U.S. government funding must be disclosed in any resulting patent applications. Furthermore, our rights in such inventions are subject to government license rights and certain restrictions on manufacturing products outside the United States.

Risks Related to our Common Stock

Servicing the Convertible Notes requires a significant amount of cash. We may not have sufficient cash flow from our business to make payments on our debt, and we may not have the ability to raise the funds necessary to settle conversions of, or to repurchase, the Convertible Notes upon a fundamental change, which could adversely affect our business, financial condition and results of operations.

In August 2015, we incurred indebtedness in the amount of $150.0 million in aggregate principal with additional accrued interest under the 2022 Convertible Notes, for which interest is payable semi-annually in arrears on February 15 and August 15 of each year, beginning on February 15, 2016. The 2022 Convertible Notes will mature on August 15, 2022 and we will be required to pay any outstanding principal amount of the 2022 Convertible Notes at that time, unless earlier converted, redeemed or repurchased in accordance with their terms prior to such date. As of February 15, 2022, until the close of business on the business day immediately preceding the maturity date, holders may convert their 2022 Convertible Notes at any time. Upon conversion, we will pay or deliver, as the case may be, cash, shares of our common stock or any combination thereof at our election. In September 2019, we incurred indebtedness in the amount of $287.5 million in aggregate principal with additional accrued interest under the 2026 Convertible Notes, for which interest is payable semi-annually in arrears on March 15 and September 15 of each year, beginning on March 15, 2020. Our ability to make scheduled payments of the principal of, to pay interest on or to refinance the Convertible Notes depends on our future performance, which is subject to economic, financial, competitive and other factors beyond our control. Our business may not generate cash flow from operations in the future sufficient to service our debt, including the Convertible Notes. If we are unable to generate cash flow, we may be required to adopt one or more alternatives, such as selling assets, restructuring debt or obtaining additional equity capital on terms that may be unfavorable to us or highly dilutive. Our ability to refinance our indebtedness will depend on the capital markets and our financial condition at the time we seek to refinance such indebtedness. We may not be able to engage in any of these activities or engage in these activities on desirable terms, which could result in a default on our debt obligations.

Upon conversion of the Convertible Notes, unless we elect to deliver solely shares of our common stock to settle such conversion (other than paying cash in lieu of delivering any fractional shares), we will be required to make cash payments in respect of the Convertible Notes being converted. However, we may not have enough available cash or be able to obtain financing at the time we are required to repurchase Convertible Notes, to pay the Convertible Notes at maturity or to pay cash upon conversions of Convertible Notes. In addition, our ability to repurchase Convertible Notes or to pay cash upon conversions of Convertible Notes may be limited by law, by regulatory authority or by agreements governing our future indebtedness. Our failure to repurchase Convertible Notes at a time when the repurchase is required by the applicable indenture, to make interest payments on the Convertible Notes when due under the applicable indenture or to pay any cash payable on future conversions of the Convertible Notes as required by the applicable indenture would constitute a default under each indenture governing the Convertible Notes. An event of default under the applicable indenture governing the Convertible Notes or the fundamental change itself could also lead to a default under agreements governing our future indebtedness. If the repayment of any such related indebtedness were to be accelerated after any applicable notice or grace

periods, we may not have sufficient funds to repay the indebtedness, repurchase the Convertible Notes, make interest payments on the Convertible Notes or make cash payments upon conversions of the Convertible Notes.

In addition, we have reclassified all of the outstanding principal of the 2022 Convertible Notes as a current rather than long-term liability in accordance with applicable accounting rules, resulting in a material reduction of our net working capital. Similarly, even if holders of the 2026 Convertible Notes do not elect to convert their 2026 Convertible Notes, we could be required to make the same reclassification under applicable accounting rules of the 2026 Convertible Notes, which would result in a material reduction of our net working capital. Any of these factors could materially and adversely affect our business, financial condition and results of operations.

Provisions in our corporate charter documents and under Delaware law could make an acquisition of us, which may be beneficial to our stockholders, more difficult and may prevent attempts by our stockholders to replace or remove our current management.

Provisions in our corporate charter and our bylaws may discourage, delay or prevent a merger, acquisition or other change in control of us that stockholders may consider favorable, including transactions in which our stockholders might otherwise receive a premium for their shares. These provisions could also limit the price that investors might be willing to pay in the future for shares of our common stock, thereby depressing the market price of our common stock. In addition, because our board of directors is responsible for appointing our management team, these provisions may frustrate or prevent any attempts by our stockholders to replace or remove our current management by making it more difficult for stockholders to replace members of our board of directors. Among other things, these provisions:

- provide for a classified board of directors such that not all members of the board are elected at one time;
- allow the authorized number of our directors to be changed only by resolution of our board of directors;
- limit the manner in which stockholders can remove directors from the board;
- establish advance notice requirements for stockholder proposals that can be acted on at stockholder meetings and nominations to our board of directors;
- require that stockholder actions must be effected at a duly called stockholder meeting and prohibit actions by our stockholders by written consent;
- limit who may call stockholder meetings;
- authorize our board of directors to issue preferred stock without stockholder approval, which could be used to institute a "poison pill" that would work to dilute the stock ownership of a potential hostile acquirer, effectively preventing acquisitions that have not been approved by our board of directors; and
- require the approval of the holders of at least 75% of the votes that all our stockholders would be entitled to cast to amend or repeal certain provisions of our charter or bylaws.

Moreover, because we are incorporated in Delaware, we are governed by the provisions of Section 203 of the Delaware General Corporation Law, which prohibits a person who owns in excess of 15% of our outstanding voting stock from merging or combining with us for a period of three years after the date of the transaction in which the person acquired in excess of 15% of our outstanding voting stock, unless the merger or combination is approved in a prescribed manner.

The price of our common stock may be volatile and fluctuate substantially, which could result in substantial losses for purchasers of our common stock and lawsuits against us and our officers and directors.

Our stock price has been and will likely continue to be volatile. The stock market in general and the market for smaller pharmaceutical and biotechnology companies in particular have experienced extreme volatility that has often been unrelated to the operating performance of particular companies. As a result of this volatility, our stockholders may not be able to sell their common stock at or above the price at which they purchased it. The market price for our common stock may be influenced by many factors, including:

- expectations with respect to our gene therapy platform, including any potential regulatory submissions and potential approvals, including those related to PTC-AADC;

- the commercialization of Evrysdi and the development of the SMA program with Roche and the SMA Foundation;
- any developments related to our ability or inability to execute our commercialization strategy for any of our products;
- our ability to resolve the matters set forth in the FDA's denial of our appeal to the Complete Response Letter we received from the FDA in connection with our NDA for Translarna for the treatment of nmDMD, and our ability to perform additional clinical trials, non-clinical studies or CMC assessments or analyses at significant cost;
- our ability to maintain our marketing authorization for Translarna for the treatment of nmDMD in Brazil, Russia and in the EEA, which is subject to the specific obligation to conduct Study 041 and is also subject to annual review and renewal by the European Commission following reassessment of the benefit-risk balance of the authorization by the EMA;
- any developments related to Study 041, including with respect to design, timing, conduct, and enrollment, and developments with respect to any clinical or non-clinical trial required by other regulatory agencies, including the FDA for Translarna for the treatment of nmDMD;
- results of clinical trials of any other product candidate that we develop;
- announcements by us or our competitors of significant acquisitions, licenses, strategic collaborations, joint ventures, collaborations or capital commitments;
- negative publicity around our products or product candidates;
- other developments concerning our regulatory submissions;
- whether regulators in other territories agree with our interpretation of the results of ACT DMD;
- the success of competitive products or technologies;
- results of clinical trials of product candidates of our competitors, including negative results that investors may associate with our product candidates;
- regulatory or legal developments in the United States and other countries;
- developments or disputes concerning patent applications, issued patents or other proprietary rights;
- our ability to realize the benefits of our acquisitions or other business combinations;
- the recruitment or departure of key personnel;
- the loss of distributors, suppliers or manufacturers;
- the level of expenses related to any of our products, product candidates or clinical development programs;
- actual or anticipated changes in estimates as to financial results, development timelines or recommendations by securities analysts;
- variations in our financial results or those of companies that are perceived to be similar to us;
- announcements with respect to litigation;
- changes in the structure of healthcare payment systems;
- market conditions in the pharmaceutical and biotechnology sectors;
- general economic, industry and market conditions; and
- the other factors described in this "Risk Factors" section.

Companies that have experienced volatility in the market price of their stock have frequently been the subject of securities class action and shareholder derivative litigation. For example, in 2018 we settled a securities class action lawsuit initiated against us and certain of our current and former executive officers during 2016, as well as derivative lawsuits brought against us, as a nominal defendant, certain of our current and former executive officers and certain of our current and former directors during 2017. We could be the target of other such litigation in the future. Class action and derivative lawsuits, whether successful or not, could result in substantial costs, damage or settlement awards and a diversion of our management's resources and attention from running our business, which could materially harm our reputation, financial condition and results of operations.

We are currently incurring and expect to continue to incur increased costs as a result of operating as a public company, including compliance with Section 404 of the Sarbanes-Oxley Act of 2002, and our management is and will continue to be required to devote substantial time to compliance initiatives. In addition, the failure to establish and maintain adequate finance infrastructure and accounting systems and controls could impair our ability to comply with the financial reporting and internal controls requirements for publicly traded companies.

As a public company, we incur significant legal, accounting and other expenses that we did not incur as a private company. In addition, the Sarbanes-Oxley Act of 2002, or Sarbanes-Oxley, the Dodd-Frank Act, the listing requirements of Nasdaq and other applicable securities rules and regulations impose various requirements on public companies, including establishment and maintenance of effective disclosure and financial controls and corporate governance practices. Our management and other personnel have and will need to continue to devote a substantial amount of time to these compliance initiatives. Moreover, these rules and regulations have and will continue to increase our legal and financial compliance costs and will continue to make some activities more time-consuming and costly. For example, these rules and regulations have made it more difficult and more expensive for us to obtain director and officer liability insurance.

Pursuant to Section 404 Sarbanes-Oxley, or Section 404, we are required to furnish a report by our management on the effectiveness of our internal control over financial reporting and an attestation report on internal control over financial reporting issued by our independent registered public accounting firm. Compliance with Section 404, including documentation and evaluation of our internal control over financial reporting, is both costly and challenging. If we are not able to comply with the requirements of Section 404 in a timely manner each year, we could be subject to sanctions or investigations by the SEC, Nasdaq or other regulatory authorities which would require additional financial and management resources and could adversely affect the market price of our common stock. Furthermore, if we cannot provide reliable financial reports or prevent fraud, our business and results of operations could be harmed and investors could lose confidence in our reported financial information.

Because we do not anticipate paying any cash dividends on our capital in the foreseeable future, capital appreciation, if any, will be our stockholders sole source of gain.

We have never declared or paid cash dividends on our capital stock. We currently intend to retain all of our future earnings, if any, to finance the development and growth of our business. The terms of any future debt agreements may preclude us from paying dividends. As a result, capital appreciation, if any, of our common stock will be our stockholders sole source of gain for the foreseeable future.

The issuance of additional shares of our common stock or the sale of shares of our common stock by our stockholders could dilute our stockholders' ownership interest in the Company and could significantly reduce the market price of our common stock.

Sales of a substantial number of shares of our common stock in the public market could occur at any time. These sales, or the perception in the market that the holders of a large number of shares intend to sell shares, could reduce the market price of our common stock.

We have issued a significant number of equity awards under our equity compensation plans or as inducement grants to new hire employees pursuant to Nasdaq rules. The shares underlying these awards are registered on a Form S-8 registration statement. As a result, upon vesting these shares can be freely exercised and sold in the public market upon issuance, subject to volume limitations applicable to affiliates. The exercise of options and the subsequent sale of the underlying common stock or the sale of restricted stock upon vesting could cause a decline in our stock price. These sales also might make it difficult for us to sell equity securities in the future at a time and at a price that we deem appropriate.

Certain of our employees, executive officers and directors have entered or may enter into Rule 10b5-1 plans providing for sales of shares of our common stock from time to time. Under a Rule 10b5-1 plan, a broker executes trades pursuant to parameters established by the employee, director or officer when entering into the plan, without further direction from the employee, officer or director. A Rule 10b5-1 plan may be amended or terminated in some circumstances. Our employees, executive officers and directors may also buy or sell additional shares outside of a Rule 10b5-1 plan when they are not in possession of material, nonpublic information.

Additionally, certain shares that we issued in connection with our acquisitions or other strategic transactions have not yet been sold and are currently restricted as a result of securities laws. These shares may be freely sold in the public market subject to any requirements and restrictions, including any applicable volume limitations, imposed by Rule 144 under the Securities Act. The sale or resale of these shares in the public market, or the market's expectation of such sales, may result in an immediate and substantial decline in our stock price. Such a decline will adversely affect our investors and also might make it difficult for us to sell equity securities in the future at a time and at a price that we deem appropriate. Sales of substantial amounts of shares of our common stock or other securities by our stockholders or by us, including sales made under the Sales Agreement, pursuant to which we may offer and sell shares of our common stock having an aggregate offering price of up to $125 million from time to time, through the Sales Agent by any method that is deemed to be an "at the market" offering as defined in Rule 415(a)(4) promulgated under the Securities Act, or the issuance of shares of our common stock upon conversion of our outstanding Convertible Notes or any future securities convertible or exchangeable into our common stock or in connection with a strategic transaction or otherwise, could dilute our stockholders, lower the market price of our common stock and impair our ability to raise capital through the sale of equity securities.

Item 1B. Unresolved Staff Comments

None.

Item 2. Properties

Our principal facilities consist of approximately 126,000 square feet of research and office space located at 100, 200, 250 and 400 Corporate Court, Middlesex Business Center, South Plainfield, New Jersey, that we occupy under leases that expire in 2024, with two consecutive five-year renewal options to renew the leases after 2024 and at 4041 Hadley Road, South Plainfield New Jersey that we occupy under a lease that will expire in May 2022. Additionally, we entered into a lease agreement for approximately 103,000 square feet of laboratory and office space in Bridgewater, New Jersey. The rental term for such facility commenced on May 1, 2020 with an initial term of seven years and two consecutive five year renewal periods at our option. We also have entered into a lease agreement for approximately 220,500 square feet of office, manufacturing and laboratory space at a facility located in Hopewell Township, New Jersey. The rental term for such facility commenced on July 1, 2020, with an initial term of fifteen years and two consecutive 10-year renewal periods at our option. We lease approximately 6,500 square feet of office space in Dublin, Ireland, that we occupy under a lease that expires in 2024. Additionally, we lease approximately 5,000 square feet of office space in Sao Paulo, Brazil, that we occupy under a lease that expires in 2025. We also lease additional office space in the U.S. and other countries to support our operations as a global organization, but these leases are not material to us.

Item 3. Legal Proceedings

From time to time in the ordinary course of our business, we are subject to claims, legal proceedings and disputes. We are not currently aware of any material legal proceedings which we are a party to or of which any of our property is the subject.

Item 4. Mine Safety Disclosures

None.

PART II

Item 5. Market for Registrant's Common Equity, Related Stockholder Matters and Issuers Purchases of Equity Securities

Market Information

Our common stock has been publicly traded on the Nasdaq Global Select Market under the symbol "PTCT" since June 20, 2013. Prior to that time, there was no public market for our common stock.

Holders

As of February 18, 2022, there were 97 holders of record of our common stock. This number does not include beneficial owners whose shares are held in street name.

Recent Sales of Unregistered Securities

We did not sell any of our equity securities or any options, warrants, or rights to purchase our equity securities during the period covered by this Annual Report on Form 10-K that were not registered under the Securities Act of 1933, as amended, or the Securities Act, and that have not otherwise been described in a Current Report on Form 8-K or a Quarterly Report on Form 10-Q.

Purchase of Equity Securities

We did not purchase any of our registered equity securities during the period covered by this Annual Report on Form 10-K.

Item 6. [Reserved]

Item 7. Management's Discussion and Analysis of Financial Condition and Results of Operations.

The following discussion and analysis is meant to provide material information relevant to an assessment of the financial condition and results of operations of our company, including an evaluation of the amounts and certainty of cash flows from operations and from outside resources, so as to allow investors to better view our company from management's perspective. The following discussion of our financial condition and results of operations should be read in conjunction with our financial statements and the notes to those financial statements appearing elsewhere in this Annual Report on Form 10-K. This discussion contains forward-looking statements that involve significant risks and uncertainties. As a result of many factors, such as those set forth in Part I, Item 1A. Risk Factors, of this Annual Report on Form 10-K, our actual results may differ materially from those anticipated in these forward-looking statements.

We are a science-driven global biopharmaceutical company focused on the discovery, development and commercialization of clinically differentiated medicines that provide benefits to patients with rare disorders. Our ability to innovate to identify new therapies and to globally commercialize products is the foundation that drives investment in a robust and diversified pipeline of transformative medicines. Our mission is to provide access to best-in-class treatments for patients who have few or no treatment options. Our strategy is to leverage our strong scientific and clinical expertise and global commercial infrastructure to bring therapies to patients. We believe that this allows us to maximize value for all of our stakeholders. We have a portfolio pipeline that includes several commercial products and product candidates in various stages of development, including clinical, pre-clinical and research and discovery stages, focused on the development of new treatments for multiple therapeutic areas for rare diseases.

We have two products, Translarna™ (ataluren) and Emflaza® (deflazacort), for the treatment of Duchenne muscular dystrophy, or DMD, a rare, life threatening disorder. Translarna has marketing authorization in the European Economic Area, or EEA, and Brazil for the treatment of nonsense mutation Duchenne muscular dystrophy, or nmDMD, in ambulatory patients aged two years and older and in Russia for the treatment of nmDMD in patients aged two years and older. In

July 2020, the European Commission approved the removal of the statement "efficacy has not been demonstrated in non-ambulatory patients" from the indication statement for Translarna. During the year ended December 31, 2021, we recognized $236.0 million in sales of Translarna. We hold worldwide commercialization rights to Translarna for all indications in all territories. Emflaza is approved in the United States for the treatment of DMD in patients two years and older. During the year ended December 31, 2021, Emflaza achieved net sales of $187.3 million.

Our marketing authorization for Translarna in the EEA is subject to annual review and renewal by the European Commission following reassessment by the European Medicines Agency, or EMA, of the benefit-risk balance of the authorization, which we refer to as the annual EMA reassessment. In June 2021, the European Commission renewed our marketing authorization, making it effective, unless extended, through August 5, 2022. In February 2022, we submitted a marketing authorization renewal request to the EMA. This marketing authorization is further subject to a specific obligation to conduct and submit the results of an 18-month, placebo-controlled trial, followed by an 18-month open-label extension, which we refer to together as Study 041. We expect results from the placebo-controlled trial to be available in mid-2022. We then expect to submit a report on the placebo-controlled trial and the open-label extension data that has been collected to date to the EMA by the end of the third quarter of 2022, as required.

Each country, including each member state of the EEA, has its own pricing and reimbursement regulations. In order to commence commercial sale of product pursuant to our Translarna marketing authorization in any particular country in the EEA, we must finalize pricing and reimbursement negotiations with the applicable government body in such country. As a result, our commercial launch will continue to be on a country-by-country basis. We also have made, and expect to continue to make, product available under early access programs, or EAP programs, both in countries in the EEA and other territories. Our ability to negotiate, secure and maintain reimbursement for product under commercial and EAP programs can be subject to challenge in any particular country and can also be affected by political, economic and regulatory developments in such country.

There is substantial risk that if we are unable to renew our EEA marketing authorization during any annual renewal cycle, or if our product label is materially restricted, or if Study 041 does not provide the data necessary to maintain our marketing authorization, we would lose all, or a significant portion of, our ability to generate revenue from sales of Translarna in the EEA and other territories.

Translarna is an investigational new drug in the United States. During the first quarter of 2017, we filed a New Drug Application, or NDA, for Translarna for the treatment of nmDMD over protest with the United States Food and Drug Administration, or FDA. In October 2017, the Office of Drug Evaluation I of the FDA issued a Complete Response Letter for the NDA, stating that it was unable to approve the application in its current form. In response, we filed a formal dispute resolution request with the Office of New Drugs of the FDA. In February 2018, the Office of New Drugs of the FDA denied our appeal of the Complete Response Letter. In its response, the Office of New Drugs recommended a possible path forward for the ataluren NDA submission based on the accelerated approval pathway. This would involve a re-submission of an NDA containing the current data on effectiveness of ataluren with new data to be generated on dystrophin production in nmDMD patients' muscles. We followed the FDA's recommendation and collected, using newer technologies via procedures and methods that we designed, such dystrophin data in a new study, Study 045, and announced the results of Study 045 in February 2021. Study 045 did not meet its pre-specified primary endpoint. We expect results from the placebo-controlled trial of Study 041 to be available in mid-2022, and subject to a positive outcome in that study, we expect to re-submit the NDA.

We hold the rights for the commercialization of Tegsedi® (inotersen) and Waylivra® (volanesorsen) for the treatment of rare diseases in countries in Latin America and the Caribbean pursuant to a Collaboration and License Agreement, or the Tegsedi-Waylivra Agreement, dated August 1, 2018, by and between us and Akcea Therapeutics, Inc., or Akcea, a subsidiary of Ionis Pharmaceuticals, Inc. Tegsedi has received marketing authorization in the United States, European Union, or EU, and Brazil for the treatment of stage 1 or stage 2 polyneuropathy in adult patients with hereditary transthyretin amyloidosis, or hATTR amyloidosis. We have initiated our commercial launch for Tegsedi for the treatment of hATTR amyloidosis in Brazil and we continue to make Tegsedi available in certain other countries within Latin America and the Caribbean through early access programs. In August 2021, ANVISA, the Brazilian health regulatory authority, approved Waylivra as the first treatment for familial chylomicronemia syndrome, or FCS, in Brazil and we have initiated our commercial launch in Brazil while continuing to make Waylivra available in certain other countries within Latin

America and the Caribbean through EAP programs. Waylivra has also received marketing authorization in the EU for the treatment of FCS. Additionally, we submitted an application to ANVISA in December 2021 for the approval of Waylivra for the treatment of familial partial lipodystrophy, or FPL, and we expect a regulatory decision on approval in the second half of 2022.

We also have a spinal muscular atrophy, or SMA, collaboration with F. Hoffman-La Roche Ltd. and Hoffman-La Roche Inc., which we refer to collectively as Roche, and the Spinal Muscular Atrophy Foundation, or SMA Foundation. The SMA program has one approved product, Evrysdi® (risdiplam), which was approved by the FDA in August 2020 for the treatment of SMA in adults and children two months and older and by the European Commission in March 2021 for the treatment of 5q SMA in patients two months and older with a clinical diagnosis of SMA Type 1, Type 2 or Type 3 or with one to four SMN2 copies. Evrysdi also received marketing authorization for the treatment of SMA in Brazil in October 2020 and Japan in June 2021. In January 2022, the FDA granted priority review of a supplemental new drug application for Evrysdi to expand the indication to include pre-symptomatic infants under two months old with SMA. In addition to our SMA program, our splicing platform also includes PTC518, which is being developed for the treatment of Huntington's disease, or HD. We announced the results from our Phase 1 study of PTC518 in healthy volunteers in September 2021 demonstrating dose-dependent lowering of huntingtin messenger ribonucleic acid and protein levels, that PTC518 efficiently crosses blood brain barrier at significant levels and that PTC518 was well tolerated. We expect to initiate a Phase 2 study of PTC518 in the first quarter of 2022.

We have a pipeline of gene therapy product candidates for rare monogenic diseases that affect the central nervous system, or CNS, including PTC-AADC for the treatment of Aromatic L-Amino Acid Decarboxylase, or AADC, deficiency, a rare CNS disorder arising from reductions in the enzyme AADC that result from mutations in the dopa decarboxylase gene. In January 2020, we submitted a marketing authorization application, or MAA, for PTC-AADC for the treatment of AADC deficiency in the EEA to the EMA and we expect an opinion from the CHMP in April 2022. We are also preparing a biologics license application, or BLA, for PTC-AADC for the treatment of AADC deficiency in the United States. In response to discussions with the FDA, we intend to provide additional information concerning the use of the commercial cannula for PTC-AADC in young patients. We expect to submit a BLA to the FDA in the second quarter of 2022.

Our Bio-e platform consists of small molecule compounds that target oxidoreductase enzymes that regulate oxidative stress and inflammatory pathways central to the pathology of a number of CNS diseases. The two most advanced molecules in our Bio-e platform are vatiquinone and PTC857. We initiated a registration-directed Phase 2/3 placebo-controlled trial of vatiquinone in children with mitochondrial disease associated seizures in the third quarter of 2020. We have experienced delays in enrolling this trial due to the COVID-19 pandemic and now anticipate results from this trial to be available in the fourth quarter of 2022. We also initiated a registration-directed Phase 3 trial of vatiquinone in children and young adults with Friedreich ataxia in the fourth quarter of 2020 and anticipate results from this trial to be available in the second quarter of 2023. In the third quarter of 2021, we completed a Phase 1 trial in healthy volunteers to evaluate the safety and pharmacology of PTC857. PTC857 was found to be well-tolerated with no reported serious adverse events while demonstrating predictable pharmacology. We expect to initiate a Phase 2 trial of PTC857 for amyotrophic lateral sclerosis in the second quarter of 2022.

The most advanced molecule in our metabolic platform is PTC923, an oral formulation of synthetic sepiapterin, a precursor to intracellular tetrahydrobiopterin, which is a critical enzymatic cofactor involved in metabolism and synthesis of numerous metabolic products, for orphan diseases. We initiated a registration-directed Phase 3 trial for PTC923 for phenylketonuria, or PKU, in the third quarter of 2021 and expect results from this trial to be available by the end of 2022.

We also have two oncology agents in that are in clinical development, unesbulin and emvododstat. We completed our Phase 1 trials evaluating unesbulin in leiomyosarcoma, or LMS, and diffuse intrinsic pontine glioma, or DIPG, in the fourth quarter of 2021. We expect to initiate a registration-directed Phase 2/3 trial of unesbulin for the treatment of LMS in the second quarter of 2022 and we expect to initiate a registration-directed Phase 2 trial of unesbulin for the treatment of DIPG in the third quarter of 2022. We completed our Phase 1 trial evaluating emvododstat, a small molecule dihydrooratate dehydrogenase inhibitor that inhibits de novo pyrimidine nucleotide synthesis, in acute myelogenous leukemia, or AML, in the fourth quarter of 2021. We expect to provide further updates regarding our emvododstat program at a later date.

In June 2020, we initiated a Phase 2/3 clinical trial evaluating the efficacy and safety of emvododstat in patients hospitalized with COVID-19. In February 2021, we announced the completion of the first stage of the Phase 2/3 trial. We expect results from this trial to be available in the first half of 2022.

In addition, we have a pipeline of product candidates and discovery programs that are in early clinical, pre-clinical and research and development stages focused on the development of new treatments for multiple therapeutic areas for rare diseases.

COVID-19 Impact

The global pandemic caused by a strain of novel coronavirus, COVID-19, has impacted and is continuing to impact the timing of certain of our clinical trials and regulatory submissions as well as other aspects of our business operations. In particular, the following expectations have been revised as a result of the impact or expected impact of the COVID-19 pandemic:

- We have experienced delays in enrolling patients for our registration-directed Phase 2/3 placebo-controlled trial of vatiquinone in children with mitochondrial disease associated seizures as some patients have been unable or hesitant to travel to clinical sites due to the COVID-19 pandemic. We anticipate results from this trial to be available in the fourth quarter of 2022.

- As a result of the COVID-19 pandemic, the Brazilian Ministry of Health is continuing to experience significant delays processing centralized group purchase orders. Almost all of our product revenue for Translarna in Brazil is attributable to such purchase orders. These centralized group purchase order delays have caused, and may continue to cause, fluctuations in our ability to generate revenue in Brazil.

- As of the date of this Report on Form 10-K, except as otherwise disclosed with respect to Translarna product revenue in Brazil, our ability to generate revenue has not been significantly affected by the COVID-19 pandemic. However, due to travel restrictions, social distancing and the continued global uncertainty resulting from the COVID-19 pandemic, we may have difficulty identifying and accessing new patients, supporting existing patients and meeting with regulatory authorities or other governmental entities, which may negatively affect our future revenue. We continue to support our existing patient base and remotely connect with them, as necessary. We have not encountered any material issues in supplying those patients.

- As previously disclosed, in response to the global uncertainty caused by the COVID-19 pandemic, we are continuing to prioritize our expenses where we deem appropriate and strategically positioning our capital allocation.

The COVID-19 pandemic and responsive measures thereto may result in further negative impacts, including additional delays in our clinical and regulatory activities and further fluctuations in our revenue. We cannot be certain what the overall impact of the COVID-19 pandemic will be on our business and it has the potential to materially adversely affect our business, financial condition, results of operations, and prospects. For additional information, see "Item 1A. Risk Factors - *We face risks related to health epidemics and other widespread outbreaks of contagious disease, which are, and may continue to, delay our ability to complete our ongoing clinical trials and initiate future clinical trials, disrupt regulatory activities and have other adverse effects on our business and operations, including the novel coronavirus (COVID-19) pandemic, which has disrupted, and may continue to disrupt, our operations and may significantly impact our operating results. In addition, the COVID-19 pandemic has caused substantial disruption in the financial markets and economies, which could result in adverse effects on our business and operations.*"

Overview—Funding

The success of our products and any other product candidates we may develop, depends largely on obtaining and maintaining reimbursement from governments and third-party insurers. During 2021, our revenues were primarily generated from sales of Translarna for the treatment of nmDMD in countries where we were able to obtain acceptable commercial pricing and reimbursement terms and in select countries where we are permitted to distribute Translarna under

our EAP programs, and from sales of Emflaza for the treatment of DMD in the United States. We have also recognized revenue associated with milestone and royalty payments from Roche pursuant to a License and Collaboration Agreement, or the SMA License Agreement, by and among us, Roche and, for the limited purposes set forth therein, the SMA Foundation, under our SMA program.

See "Item 1. Business—Commercial Matters—Market Access Considerations" for additional information and "Item 1A. Risk Factors—*Commercialization of Translarna has been in, and is expected to continue to take place in, countries that tend to impose strict price controls, which may adversely affect our revenues. Failure to obtain and maintain acceptable pricing and reimbursement terms for Translarna for the treatment of nmDMD in the EEA and other countries where Translarna is available would delay or prevent us from marketing our product in such regions, which would adversely affect our business, results of operations, and financial condition*."

In January 2019, we closed an underwritten public offering of our common stock. We issued and sold an aggregate of 7,563,725 shares of common stock at a public offering price of $30.20 per share, including 843,725 shares issued upon exercise by the underwriter of its option to purchase additional shares in February 2019. We received net proceeds of approximately $224.2 million after deducting underwriting discounts and commissions and other offering expenses payable by us.

In August 2019, we entered into an At the Market Offering Sales Agreement, or the Sales Agreement, with Cantor Fitzgerald and RBC Capital Markets, LLC, or together, the Sales Agents, pursuant to which, we may offer and sell shares of our common stock, having an aggregate offering price of up to $125.0 million from time to time through the Sales Agents by any method that is deemed to be an "at the market offering" as defined in Rule 415(a)(4) promulgated under the Securities Act of 1933, as amended, or the Securities Act. During the year ended December 31, 2019, we issued and sold an aggregate of 63,926 shares of common stock pursuant to the Sales Agreement at a weighted average public offering price of $46.60 per share. We received net proceeds of $2.6 million after deducting agent discounts and commissions and other offering expenses payable by us. During the year ended December 31, 2020, we issued and sold an aggregate of 542,470 shares of common stock pursuant to the Sales Agreement at a weighted average public offering price of $53.37 per share. We received net proceeds of $28.1 million after deducting agent discounts and commissions and other offering expenses payable by us. We did not issue or sell any shares of common stock pursuant to the Sales Agreement during the year ending December 31, 2021. The remaining shares of our common stock available to be issued and sold, under the Sales Agreement, have an aggregate offering price of up to $93.0 million as of December 31, 2021.

In September 2019, we closed an underwritten public offering of our common stock. We issued and sold an aggregate of 2,475,248 shares of common stock at a public offering price of $40.40 per share. The offering included an option to purchase up to an additional 371,287 shares for a period of 30 days following the offering. This option was not exercised by the underwriter. We received net proceeds of $97.0 million after deducting underwriting discounts and commissions and other offering expenses payable by us.

In September 2019, we issued $287.5 million aggregate principal amount of 1.50% convertible senior notes due September 15, 2026, or the 2026 Convertible Notes, which included an option to purchase up to an additional $37.5 million in aggregate principal amount of the 2026 Convertible Notes, which was exercised in full by the initial purchasers. We received net proceeds of $279.3 million after deducting the initial purchasers' discounts and commissions and the offering expenses payable by us. See "Item 7. Management's Discussion and Analysis of Financial Condition and Results of Operations—Liquidity and capital resources—Sources of Liquidity" for additional information.

On October 25, 2019, we completed our acquisition of substantially all of the assets of BioElectron Technology Corporation, or BioElectron, for total upfront consideration of $10.0 million in cash less (i) transaction expenses incurred by BioElectron, (ii) the amount of outstanding indebtedness of BioElectron including a $4.0 million loan advance to BioElectron plus accrued and unpaid interest thereon and (iii) $1.5 million held in an escrow account to secure potential indemnification obligations owed to us.

On April 29, 2020, we entered into a Rights Exchange Agreement, or the Rights Exchange Agreement, pursuant to which we issued 2,821,176 shares of our common stock and paid $36.9 million, in the aggregate, to certain former equityholders, or the Participating Rightholders, of Agilis Biotherapeutics, Inc., or Agilis, in exchange for the cancellation

and forfeiture by the Participating Rightholders of their rights to receive certain milestone-based contingent payments under the Agreement and Plan of Merger, dated as of July 19, 2018 by and among us, Agility Merger Sub, Inc. and, solely in its capacity as the representative, agent and attorney-in-fact of the equityholders of Agilis, Shareholder Representative Services LLC, or the Agilis Merger Agreement.

On May 29, 2020, we acquired Censa for total upfront consideration composed of (i) cash consideration of $15.0 million, which consisted of an upfront payment of $10.4 million and an additional $4.6 million for the net assets on Censa's opening balance sheet as of the date of the acquisition, and (ii) 845,364 shares of our common stock, which were valued at $42.9 million based on the closing stock price on the acquisition date. The number of shares issued was determined using a 30-day VWAP pursuant to the Censa Merger Agreement.

In July 2020, we entered into a Royalty Purchase Agreement, or the Royalty Purchase Agreement, with RPI 2019 Intermediate Finance Trust, or RPI, pursuant to which we sold to RPI 42.933%, or the Assigned Royalty Payment, of our right to receive sales-based royalty payments, or the Royalty, on worldwide net sales of Evrysdi and any other product developed pursuant to the SMA License Agreement. In consideration for the sale of the Assigned Royalty Payments, RPI paid us $650.0 million in cash consideration. The Royalty Purchase Agreement will terminate 60 days following the earlier of the date on which Roche is no longer obligated to make any payments of the Royalty pursuant to the SMA License Agreement and the date on which RPI has received $1.3 billion in respect of the Assigned Royalty Payments.

In June 2021, we filed a Certificate of Amendment to our Restated Certificate of Incorporation, which increased the number of authorized shares of our common stock from 125,000,000 to 250,000,000 shares.

To date, we have financed our operations primarily through our offering of 3.00% convertible senior notes due August 15, 2022, or the 2022 Convertible Notes offering, our offering of the 2026 Convertible Notes, and, together with the 2022 Convertible Notes, the Convertible Notes, our public offerings of common stock in February 2014, in October 2014, in April 2018, in January 2019, and in September 2019, the common stock issued in our "at the marketing offering", our initial public offering of common stock in June 2013, proceeds from the Royalty Purchase Agreement, private placements of our convertible preferred stock, collaborations, bank and institutional lender debt, grant funding and clinical trial support from governmental and philanthropic organizations and patient advocacy groups in the disease areas addressed by our product candidates. Since 2014, we have also relied on revenue generated from net sales of Translarna for the treatment of nmDMD in territories outside of the United States, and since May 2017, we have generated revenue from net sales of Emflaza for the treatment of DMD in the United States. We have also relied on revenue associated with milestone and royalty payments from Roche pursuant to the SMA License Agreement, under our SMA program.

As of December 31, 2021, we had an accumulated deficit of $2,098.0 million. We had a net loss of $523.9 million, $438.2 million, and $251.6 million for the fiscal years ended December 31, 2021, 2020, and 2019, respectively.

We anticipate that our expenses will continue to increase in connection with our commercialization efforts in the United States, the EEA, Latin America and other territories, including the expansion of our infrastructure and corresponding sales and marketing, legal and regulatory, distribution and manufacturing, including expanding our direct manufacturing capabilities at our leased biologics manufacturing facility and administrative and employee-based expenses. In addition to the foregoing, we expect to continue to incur ongoing research and development expenses for our products and product candidates, including our splicing, gene therapy, Bio-e, metabolic and oncology programs and our studies of emvododstat for COVID-19 as well as studies in our products for maintaining authorizations, including Study 041, label extensions and additional indications. In addition, we may incur substantial costs in connection with our efforts to advance our regulatory submissions. We continue to seek marketing authorization for Translarna for the treatment of nmDMD in territories that we do not currently have marketing authorization in and we may also seek marketing authorization for Translarna for other indications. We submitted an MAA to the EMA for the treatment of AADC deficiency with PTC-AADC in the EEA. We are also preparing a BLA for PTC-AADC for the treatment of AADC deficiency in the United States and we anticipate submitting a BLA to the FDA in the second quarter of 2022. We filed for marketing authorization for Waylivra with ANVISA for the treatment of FPL and we expect a regulatory decision on approval from ANVISA in the second half of 2022. These efforts may significantly impact the timing and extent of our commercialization expenses.

We may seek to expand and diversify our product pipeline through opportunistically in-licensing or acquiring the rights to products, product candidates or technologies and we may incur expenses, including with respect to transaction costs, subsequent development costs or any upfront, milestone or other payments or other financial obligations associated with any such transaction, which would increase our future capital requirements.

With respect to our outstanding 2022 Convertible Notes, cash interest payments are payable on a semi-annual basis in arrears, which require total funding of $4.5 million annually. The 2022 Convertible Notes will mature on August 15, 2022 and we will be required to pay any outstanding principal amount of the 2022 Convertible Notes at that time, unless earlier converted, redeemed or repurchased in accordance with their terms prior to such date. As of February 15, 2022, until the close of business on the business day immediately preceding the maturity date, holders may convert their 2022 Convertible Notes at any time. Upon conversion, we will pay or deliver, as the case may be, cash, shares of our common stock or any combination thereof at our election. With respect to our outstanding 2026 Convertible Notes, cash interest payments are payable on a semi-annual basis in arrears, which will require total funding of $4.3 million annually. In 2021, we paid Akcea an additional milestone payment of $4.0 million upon receipt of regulatory approval for Waylivra from ANVISA for the treatment of FCS. In addition, we expect to pay Marathon Pharmaceuticals, LLC (now known as Complete Pharma Holdings, LLC), or Marathon, a single $50.0 million sales-based milestone in connection with Emflaza sales in 2022. We also expect to pay the former equityholders of Agilis an aggregate of $70.0 million upon the achievement of certain development and regulatory milestones in 2022 relating to PTC-AADC. Furthermore, since we are a public company, we have incurred and expect to continue to incur additional costs associated with operating as such including significant legal, accounting, investor relations and other expenses.

We have never been profitable and we will need to generate significant revenues to achieve and sustain profitability, and we may never do so. Accordingly, we may need to obtain substantial additional funding in connection with our continuing operations. Adequate additional financing may not be available to us on acceptable terms, or at all. If we are unable to raise capital when needed or on attractive terms, we could be forced to delay, reduce or eliminate our research and development programs or our commercialization efforts.

Financial operations overview

To date, our net product revenues have consisted primarily of sales of Translarna for the treatment of nmDMD in territories outside of the United States and sales of Emflaza for the treatment of DMD in the United States. Our process for recognizing revenue is described below under “Critical accounting policies and significant judgments and estimates—Revenue recognition”.

Roche and the SMA Foundation Collaboration. In November 2011, we entered into the SMA License Agreement pursuant to which we are collaborating with Roche and the SMA Foundation to further develop and commercialize compounds identified under our SMA program with the SMA Foundation. The research component of this agreement terminated effective December 31, 2014. We are eligible to receive additional payments from Roche if specified events are achieved with respect to each licensed product, including up to $135.0 million in research and development event milestones, up to $325.0 million in sales milestones upon achievement of specified sales events, and up to double digit royalties on worldwide annual net sales of a commercial product. As of December 31, 2021, we had recognized a total of $160.0 million in milestone payments and $59.4 million royalties on net sales pursuant to the SMA License Agreement. As of December 31, 2021, there are no remaining research and development event milestones that we can receive. The remaining potential sales milestones as of December 31, 2021 are $300.0 million upon achievement of certain sales events.

Pursuant to the Royalty Purchase Agreement, we sold to RPI the Assigned Royalty Payment, in consideration for $650.0 million. We have retained a 57.067% interest in the Royalty and all economic rights to receive the remaining potential regulatory and sales milestone payments under the License Agreement. The Royalty Purchase Agreement will terminate 60 days following the earlier of the date on which Roche is no longer obligated to make any payments of the Royalty pursuant to the SMA License Agreement and the date on which RPI has received $1.3 billion in respect of the Assigned Royalty Payments.

Research and development expense

Research and development expenses consist of the costs associated with our research activities, as well as the costs associated with our drug discovery efforts, conducting preclinical studies and clinical trials, manufacturing development efforts and activities related to regulatory filings. Our research and development expenses consist of:

- external research and development expenses incurred under agreements with third-party contract research organizations and investigative sites, third-party manufacturing organizations and consultants;
- employee-related expenses, which include salaries and benefits, including share-based compensation, for the personnel involved in our drug discovery and development activities; and
- facilities, depreciation and other allocated expenses, which include direct and allocated expenses for rent and maintenance of facilities, IT, human resources, and other support functions, depreciation of leasehold improvements and equipment, and laboratory and other supplies.

We use our employee and infrastructure resources across multiple research projects, including our drug development programs. We track expenses related to our clinical programs and certain preclinical programs on a per project basis.

We expect our research and development expenses to fluctuate in connection with our ongoing activities, particularly in connection with Study 041 and other studies for Translarna for the treatment of nmDMD, our activities under our splicing, gene therapy, Bio-e, metabolic and oncology programs, and our studies of emvododstat for COVID-19 and performance of any post-marketing requirements imposed by regulatory agencies with respect to our products. The timing and amount of these expenses will depend upon the outcome of our ongoing clinical trials and the costs associated with our planned clinical trials. The timing and amount of these expenses will also depend on the costs associated with potential future clinical trials of our products or product candidates and the related expansion of our research and development organization, regulatory requirements, advancement of our preclinical programs, and product and product candidate manufacturing costs.

The following table provides research and development expense for our most advanced principal product development programs, for the years ended December 31, 2021, 2020, and 2019.

	December 31,		
	2021	2020	2019
		(in thousands)	
Global DMD Franchise	$ 83,791	$ 80,742	$ 113,312
PTC923	49,458	59,135	—
Gene Therapy	150,566	213,206	62,839
Bio-e	60,964	29,322	10,060
Oncology	18,618	16,467	21,199
Splicing	53,429	18,567	10,317
Emvododstat for COVID-19	38,348	13,590	—
Discovery	85,510	46,614	39,725
Total research and development	$ 540,684	$ 477,643	$ 257,452

The successful development of our product and product candidates is highly uncertain. This is due to the numerous risks and uncertainties associated with developing drugs, including the uncertainty of:

- the scope, rate of progress and expense of our clinical trials and other research and development activities;
- the potential benefits of our product and product candidates over other therapies;
- our ability to market, commercialize and achieve market acceptance for our products or any of our product candidates that we are developing or may develop in the future, including our ability to negotiate pricing and reimbursement terms acceptable to us;
- clinical trial results;
- the terms and timing of regulatory approvals; and
- the expense of filing, prosecuting, defending and enforcing patent claims and other intellectual property rights.

A change in the outcome of any of these variables with respect to the development of any of our products or product candidates could mean a significant change in the costs and timing associated with the development of that product candidates. For example, if the EMA or FDA or other regulatory authority were to require us to conduct clinical trials beyond those which we currently anticipate will be required for the completion of clinical development of any of our products or product candidate or if we experience significant delays in enrollment in any of our clinical trials, we could be required to expend significant additional financial resources and time on the completion of clinical development. In addition, the uncertainty with respect to the duration, nature and extent of negative impacts of the COVID-19 pandemic and responsive measures relating thereto on our ability to successfully enroll our current and future clinical trials, has caused us to experience delays, and may cause us to experience further delays, in our clinical trials and regulatory submissions.

Selling, general and administrative expense

Selling, general and administrative expenses consist primarily of salaries and other related costs for personnel, including share-based compensation expenses, in our executive, legal, business development, commercial, finance, accounting, information technology and human resource functions. Other selling, general and administrative expenses include facility-related costs not otherwise included in research and development expense; advertising and promotional expenses; costs associated with industry and trade shows; and professional fees for legal services, including patent-related expenses, accounting services and miscellaneous selling costs.

We expect that selling, general and administrative expenses will increase in future periods in connection with our continued efforts to commercialize our products, including increased payroll, expanded infrastructure, commercial operations, increased consulting, legal, accounting and investor relations expenses.

Interest expense, net

Interest expense, net consists of interest expense from the liability for the sale of future royalties related to the Royalty Purchase Agreement, the Convertible Notes outstanding, and from our credit and security agreement, or the Credit Agreement, with MidCap Financial Trust that was terminated in July 2020 offset by interest income earned on investments.

Critical accounting policies and significant judgments and estimates

Our management's discussion and analysis of our financial condition and results of operations is based on our financial statements, which we have prepared in accordance with generally accepted accounting principles in the United States. The preparation of these financial statements requires us to make estimates and assumptions that affect the reported amounts of assets and liabilities and the disclosure of contingent assets and liabilities at the date of the financial statements, as well as the reported revenues and expenses during the reporting periods. Actual results may differ from these estimates under different assumptions or conditions.

Effective January 1, 2021, we early adopted the Financial Accounting Standards Board, or the FASB, Accounting Standards Update, or ASU, 2020-06, "Debt—Debt with Conversion and Other Options (Subtopic 470-20) and Derivatives and Hedging—Contracts in Entity's Own Equity (Subtopic 815-40): Accounting for Convertible Instruments and Contracts in an Entity's Own Equity" using the modified retrospective method of adoption. ASU 2020-06 simplifies the accounting for convertible instruments by removing certain separation models in Subtopic 470- 20, Debt—Debt with Conversion and Other Options, for convertible instruments. Under ASU 2020-06, the embedded conversion features no longer are separated from the host contract for convertible instruments with conversion features that are not required to be accounted for as derivatives under Topic 815, Derivatives and Hedging, or that do not result in substantial premiums accounted for as paid-in capital. Consequently, a convertible debt instrument will be accounted for as a single liability measured at its amortized cost as long as no other features require bifurcation and recognition as derivatives. By removing those separation models, the interest rate of convertible debt instruments typically will be closer to the coupon interest rate when applying the guidance in Topic 835, Interest. We now account for our Convertible Notes as single liabilities measured at amortized cost. As a result, the adoption of the guidance had a material impact on the consolidated financial statements and accompanying notes, resulting in adjustments of $175.2 million, $54.8 million, and $120.4 million to the opening balances of additional paid-in capital, retained earnings, and long term debt, respectively, as of January 1, 2021.

Additionally, due to the adoption, we reversed the remaining balance of the deferred tax liability of $29.6 million, which was initially recorded in connection with the Convertible Notes. Additionally, we increased the existing valuation allowance by $29.6 million as part of the adoption adjustment. We concluded that the adoption of the ASU did not change our prior valuation allowance conclusions. We have updated our debt note (Note 8) with additional and modified disclosures as required by the standard upon adoption.

Of our policies, the following are considered critical to an understanding of our consolidated financial statements as they require the application of the most subjective and complex judgment, involving critical accounting estimates and assumptions impacting our consolidated financial statements:

- Revenue recognition related to net product revenue
- Liability for sale of future royalties
- Contingent consideration from business combinations
- Indefinite-lived intangible assets annual impairment assessment

Revenue recognition related to net product revenue

Our net product revenue primarily consists of sales of Translarna in territories outside of the U.S. and sales of Emflaza in the U.S., both for the treatment of DMD. We recognize revenue when performance obligations with customers have been satisfied. Our performance obligations are to provide products based on customer orders from distributors, hospitals, specialty pharmacies or retail pharmacies. The performance obligations are satisfied at a point in time when our customer obtains control of the product, which is typically upon delivery. We invoice customers after the products have been delivered and invoice payments are generally due within 30 to 90 days of invoice date. We determine the transaction price based on fixed consideration in its contractual agreements. Contract liabilities arise in certain circumstances when consideration is due for goods not yet provided. As we have identified only one distinct performance obligation, the transaction price is allocated entirely to the product sale. In determining the transaction price, a significant financing component does not exist since the timing from when we deliver product to when the customers pay for the product is typically less than one year. Customers in certain countries pay in advance of product delivery. In those instances, payment and delivery typically occur in the same month.

We record product sales net of any variable consideration, which includes discounts, allowances, rebates related to Medicaid and other government pricing programs, and distribution fees. We use the expected value or most likely amount method when estimating variable consideration, unless discount or rebate terms are specified within contracts. The identified variable consideration is recorded as a reduction of revenue at the time revenues from product sales are recognized. These estimates for variable consideration are adjusted to reflect known changes in factors and may impact such estimates in the quarter those changes are known. Revenue recognized does not include amounts of variable consideration that are constrained. During the years ended December 31, 2021, 2020, and 2019, net product sales in the United States were $187.3 million, $139.0 million, and $101.0 million, respectively, consisting solely of sales of Emflaza, and net product sales outside of the United States were $241.6 million, $194.4 million, and $190.3 million respectively, consisting of sales of Translarna, Tegsedi, and Waylivra. Translarna net product revenues made up $236.0 million, $191.9 million, and $190.0 million of the net product sales outside the United States for the years ended December 31, 2021, 2020, and 2019, respectively.

In relation to customer contracts, we incur costs to fulfill a contract but do not incur costs to obtain a contract. These costs to fulfill a contract do not meet the criteria for capitalization and are expensed as incurred. The Company considers any shipping and handling costs that are incurred after the customer has obtained control of the product as a cost to fulfill a promise. Shipping and handling costs associated with finished goods delivered to customers are recorded as a selling expense.

Liability for sale of future royalties

In July 2020, we entered into the Royalty Purchase Agreement with RPI, pursuant to which we sold to RPI the Assigned Royalty Payment. In consideration for the sale of the Assigned Royalty Payments, RPI paid us $650.0 million in cash consideration. The Royalty Purchase Agreement will terminate 60 days following the earlier of the date on which Roche is no longer obligated to make any payments of the Royalty pursuant to the SMA License Agreement and the date on which RPI has received $1.3 billion in respect of the Assigned Royalty Payments.

The cash consideration obtained pursuant to the Royalty Purchase Agreement is classified as debt and is recorded as "liability for sale of future royalties-current" and "liability for sale of future royalties-noncurrent" on our consolidated balance sheet based on the timing of the expected payments to be made to RPI. The fair value for the liability for sale of future royalties at the time of the transaction was based on our estimates of future royalties expected to be paid to RPI over the life of the arrangement, which was determined using forecasts from market data sources, which are considered Level 3 inputs. The liability will be amortized using the effective interest method over the life of the arrangement, in accordance with the respective guidance. We will utilize the prospective method to account for subsequent changes in the estimated future payments to be made to RPI.

Contingent consideration from business combinations

The consideration for our business acquisitions may include future payments that are contingent upon the occurrence of a particular event or events. The obligations for such contingent consideration payments are recorded at fair value on the acquisition date. The contingent consideration obligations are then evaluated each reporting period. Changes in the fair value of contingent consideration, other than changes due to payments, are recognized as a gain or loss and recorded within the change in the fair value of deferred and contingent consideration in the consolidated statements of operations. The fair value of development and regulatory milestones are estimated utilizing a probability adjusted, discounted cash flow approach. The discount rates are estimated utilizing Corporate B rated bonds maturing in the years of expected payments based on our estimated development timelines for the acquired product candidate. The fair value of the net sales milestones and royalties is based on probability adjusted sales estimates and estimated discount rates and utilizes an option pricing model with Monte Carlo simulation to simulate a range of possible payment scenarios, and the average of the payments in these scenarios is then discounted to calculate present fair value.

Indefinite-lived intangible assets annual impairment assessment

Indefinite-lived intangible assets consist of IPR&D acquired in business combinations. Intangible assets with indefinite lives, including IPR&D, are tested for impairment if impairment indicators arise and, at a minimum, annually. The indefinite-lived intangible asset impairment test consists of a one-step analysis that compares the fair value of the intangible asset with its carrying amount. If the carrying amount of an intangible asset exceeds its fair value, an impairment loss is recognized in an amount equal to that excess. Several methods may be used to determine the estimated fair value of the IPR&D. We utilize the "income method", and use estimated future net cash flows that are derived from projected sales revenues and estimated costs. These projections are based on factors such as relevant market size, patent protection, and expected pricing and industry trends. The estimated future net cash flows are then discounted to the present value using an appropriate discount rate. The estimated fair value is then compared to the carrying value of IPR&D. We performed a quantitative annual impairment test for our indefinite-lived intangible assets as of October 1, 2021 and concluded that no impairment exists as of December 31, 2021.

For a description of our significant accounting policies, see note 2 to our consolidated financial statements.

Year ended December 31, 2021 compared to year ended December 31, 2020

The following table summarizes revenues and selected expense and other income data for the year ended December 31, 2021 and 2020:

(in thousands)	Year ended December 31, 2021	2020	Change 2021 vs. 2020
Net product revenue	$ 428,904	$ 333,401	$ 95,503
Collaboration revenue	55,046	42,579	$ 12,467
Royalty revenue	54,643	4,786	$ 49,857
Cost of product sales, excluding amortization of acquired intangible assets	32,328	18,942	$ 13,386
Amortization of acquired intangible assets	54,751	36,892	$ 17,859
Research and development expense	540,684	477,643	$ 63,041
Selling, general and administrative expense	285,773	245,164	$ 40,609
Change in the fair value of deferred and contingent consideration	(500)	23,280	$ (23,780)
Settlement of deferred and contingent consideration	—	10,613	(10,613)
Interest expense, net	(86,022)	(56,352)	$ (29,670)
Other (expense) income, net	(57,875)	85,188	$ (143,063)
Income tax expense	(5,561)	(35,228)	$ 29,667

Net product revenue. Net product revenue was $428.9 million for the year ended December 31, 2021, an increase of $95.5 million, or 29%, from net product revenue of $333.4 million for the year ended December 31, 2020. Translarna net product revenues were $236.0 million for the year ended December 31, 2021, an increase of $44.1 million, or 23%, compared to $191.9 million for the year ended December 31, 2020. These results were driven by treatment of new patients, continued high compliance, and geographic expansion. Emflaza net product revenues were $187.3 million for the year ended December 31, 2021, an increase of $48.3 million, or 35%, compared to $139.0 million for the year ended December 31, 2021. These results were driven by continued new prescriptions, continued high compliance, and more favorable access. The remaining increase of $3.1 million was due to an increase in net product sales of Tegsedi and Waylivra.

Collaboration revenue. Collaboration revenue was $55.0 million for the year ended December 31, 2021, an increase of $12.5 million, or 29%, from collaboration revenue of $42.6 million for the year ended December 31, 2020. The increase is primarily related to three milestones that were triggered from Roche in the years ended December 31, 2021. In March 2021, the first commercial sale of Evrysdi in the EU was made. This event triggered a $20.0 million milestone payment to us from Roche. Additionally, in June 2021, the Japanese Ministry of Health, Labor and Welfare approved Evrysdi for the treatment of SMA in Japan. In August 2021, the first commercial sale of Evrysdi in Japan triggered a $10.0 million milestone payment to us from Roche. In December 2021, we recorded our first sales milestone of $25.0 million for the achievement of $500.0 million in worldwide annual net sales from Evrysdi. Comparatively, in the year ended December 31, 2020, the FDA approved Evrysdi for the treatment of SMA in adults and children two months and older in August 2020. The first commercial sale of Evrysdi in the United States was made in August 2020. This event triggered a $20.0 million milestone payment to us from Roche. In August 2020, the EMA accepted the MAA filed by Roche for Evrysdi for the treatment of SMA, which triggered a $15.0 million milestone payment to us from Roche. In October 2020, Chugai filed an NDA in Japan for Evrysdi for the treatment of SMA, which triggered a $7.5 million milestone payment to us from Roche.

Royalty revenue. Royalty revenue was $54.6 million for the years ended December 31, 2021, an increase of $49.9 million, or over 100%, from $4.8 million for the years ended December 31, 2020. The increase in royalty revenue was due to the FDA approval of Evrysdi in August 2020. In accordance with the SMA License Agreement, we are entitled to royalties on worldwide annual net sales of the product.

Cost of product sales, excluding amortization of acquired intangible asset. Cost of product sales, excluding amortization of acquired intangible asset, was $32.3 million for the year end December 31, 2021, an increase of $13.4 million, or 71%, from $18.9 million for the year ended December 31, 2020. Cost of product sales consist primarily of royalty payments associated with Emflaza and Translarna net product sales, excluding contingent payments to Marathon,

costs associated with Emflaza and Translarna product sold during the period, and royalty expense related to royalty revenues and collaboration milestone revenues. The increase in cost of product sales, excluding amortization of acquired intangible asset, is primarily due to the increases in net product revenue, royalty revenues, and collaboration milestone revenue.

Amortization of acquired intangible asset. Amortization of acquired intangible asset was $54.8 million for the year ended December 31, 2021, an increase of $17.9 million, or 48%, from $36.9 million for the year ended December 31, 2020. These amounts are related to the acquisition of all rights to Emflaza acquired in May 2017, Marathon contingent payments, and our Waylivra and Tegsedi intangible assets. The increase is primarily related to additional Marathon contingent payments. The amount allocated to the Emflaza intangible asset is amortized on a straight-line basis over its estimated useful life of approximately seven years from the date of the completion of the acquisition of all rights to Emflaza, the period of estimated future cash flows. The Marathon contingent payments are amortized prospectively as incurred, straight-line, over the remaining useful life of the Emflaza intangible asset. The Waylivra and Tegsedi assets are amortized on a straight-line basis over their estimated useful life of approximately ten years, respectively. Additionally, in August 2021, we made a $4.0 million milestone payment to Akcea upon regulatory approval of Waylivra from ANVISA. In accordance with the guidance for an asset acquisition, we recorded the milestone payment when it became payable to Akcea, and it increased the cost basis for the Waylivra intangible asset. This payment is being amortized to cost of product sales over the expected remaining useful life of the Waylivra asset on a straight line basis.

Research and development expense. Research and development expense was $540.7 million for the year ended December 31, 2021, an increase of $63.0 million, or 13%, compared to $477.6 million for the year ended December 31, 2020. The increase in research and development expenses is primarily related to increased investment in research programs and advancement of the clinical pipeline. This increase was partially offset by one time charges in the year ended December 31, 2020 of $53.6 million for our Censa Merger, as well as $41.4 million for our commercial manufacturing service agreement with MassBio related to dedicated manufacturing space for our lead gene therapy program, AADC deficiency.

Selling, general and administrative expense. Selling, general and administrative expense was $285.8 million for the year ended December 31, 2021, an increase of $40.6 million, or 17%, from $245.2 million for the year ended December 31, 2020. The increase reflects our continued investment to support our commercial activities including our expanding commercial portfolio, including an increase in rent and related expenses associated with entering into a long term lease for the Hopewell Facility that commenced on July 1, 2020.

Change in the fair value of deferred and contingent consideration. Change in the fair value of deferred and contingent consideration was a gain of $0.5 million for the year ended December 31, 2021, a change of $23.8 million, or over 100%, from a loss of $23.3 million for the year ended December 31, 2020. The change is related to the fair valuation of the potential future consideration to be paid to former equityholders of Agilis as a result of our merger with Agilis which closed in August 2018. Changes in the fair value were due to the re-calculation of discounted cash flows for the passage of time and changes to certain other estimated assumptions.

Settlement of deferred and contingent consideration. Settlement of deferred and contingent consideration was $0.0 million for year ended December 31, 2021, a decrease of $10.6 million, or 100%, from $10.6 million for the year ended December 31, 2020. The settlement of deferred and contingent consideration for the year ended December 31, 2020 is related to a loss upon the settlement of the deferred and contingent consideration liabilities as a result of the Rights Exchange Agreement with certain former equityholders of Agilis, whereby we exchanged their pro rata share of specific future cash milestone payments in the aggregate amount of $225.0 million for a combination of cash and equity. We paid $36.9 million in cash and issued 2,821,176 shares of common stock in exchange for the cancellation and forfeiture of the Participating Rightholders' rights to receive (i) $174.0 million, in the aggregate, of potential milestone payments based on the achievement of certain regulatory milestones and (ii) $37.6 million, in the aggregate, of $40.0 million in development milestone payments that would have been due upon the passing of the second anniversary of the closing of the Agilis Merger, regardless of whether the milestones are achieved.

Interest expense, net. Interest expense, net was $86.0 million for the year ended December 31, 2021, an increase of $29.7 million, 53%, from interest expense, net of $56.4 million for the year ended December 31, 2020. The increase in interest expense, net was primarily due to interest expense recorded from the liability for the sale of future royalties related

to the Royalty Purchase Agreement, partially offset by a decrease in interest expense recorded from the 2022 and 2026 Convertible Notes as a result of the adoption of ASU 2020-06 and interest income from our investments.

Other (expense) income, net. Other expense, net was $57.9 million for the year ended December 31, 2021, a change of $143.1 million, over 100%, from other income, net of $85.2 million for the year ended December 31, 2020. The change in other (expense) income, net resulted primarily from an unrealized foreign exchange loss of $41.0 million from the remeasurement of our intercompany loan, which is recorded on a non-U.S. subsidiary and denominated in U.S. dollars, and unrealized losses on our equity investments and convertible debt security in ClearPoint Neuro, Inc. (formerly MRI Interventions, Inc.), or ClearPoint, of $6.1 million and $8.3 million, respectively.

Income tax expense. Income tax expense was $5.6 million for the year ended December 31, 2021, a decrease of $29.7 million, or 84%, from income tax expense of $35.2 million for the year ended December 31, 2020. We recorded a state income tax provision for the year ended December 31, 2020, which is attributable to the taxable income from the sale of our right to receive sales-based royalty payments on Roche's worldwide net sales of Evrysdi. We also incurred income tax expense in various foreign jurisdictions, and our foreign tax liabilities are largely dependent upon the distribution of pre-tax earnings among these different jurisdictions.

Year ended December 31, 2020 compared to year ended December 31, 2019

The following table summarizes revenues and selected expense and other income data for the years ended December 31, 2020 and 2019:

	Year ended December 31,		Change
(in thousands)	**2020**	**2019**	**2020 vs. 2019**
Net product revenue	$ 333,401	$ 291,306	$ 42,095
Collaboration revenue	42,579	15,674	$ 26,905
Royalty revenue	4,786	—	$ 4,786
Cost of product sales, excluding amortization of acquired intangible assets	18,942	12,135	$ 6,807
Amortization of acquired intangible assets	36,892	27,650	$ 9,242
Research and development expense	477,643	257,452	$ 220,191
Selling, general and administrative expense	245,164	202,541	$ 42,623
Change in the fair value of deferred and contingent consideration	23,280	48,360	$ (25,080)
Settlement of deferred and contingent consideration	10,613	—	$ 10,613
Interest expense, net	(56,352)	(12,491)	$ (43,861)
Other income, net	85,188	13,723	$ 71,465
Income tax expense	(35,228)	(11,650)	$ (23,578)

Net product revenue. Net product revenue was $333.4 million for the year ended December 31, 2020, an increase of $42.1 million, or 14%, from net product revenue of $291.3 million for the year ended December 31, 2019. Translarna net product revenues were $191.9 million for the year ended December 31, 2020, an increase of $1.9 million, or 1%, compared to $190.0 million for the year ended December 31, 2019. The increase in Translarna net product revenues was driven by broader uptake due to new patients in existing geographies, geographic expansion, and label updates. Emflaza net product revenues were $139.0 million for the year ended December 31, 2020, an increase of $38.0 million, or 38%, compared to $101.0 million for the year ended December 31, 2019. The increase in Emflaza net product revenue was primarily due to increased new patient prescriptions and higher compliance. The remaining increase was due to an increase in net product sales of Tegsedi and the commercial launch of Waylivra in the year ended December 31, 2020.

Collaboration revenue. Collaboration revenue was $42.6 million for the year ended December 31, 2020, an increase of $26.9 million, over 100%, from collaboration revenue of $15.7 million for the year ended December 31, 2019. The increase is primarily related to three milestones that were triggered from Roche in the years ended December 31, 2020. In August 2020, the FDA approved Evrysdi for the treatment of SMA in adults and children two months and older. The first commercial sale of Evrysdi in the United States was made in August 2020. This event triggered a $20.0 million milestone

payment to us from Roche. In August 2020, the EMA accepted the MAA filed by Roche for Evrysdi for the treatment of SMA, which triggered a $15.0 million milestone payment to us from Roche. In October 2020, Chugai filed an NDA in Japan for Evrysdi for the treatment of SMA, which triggered a $7.5 million milestone payment to us from Roche. Comparatively, in the year ended December 31, 2019, a $15.0 million milestone was triggered upon the FDA's acceptance of the filing of the NDA for risdiplam for the treatment of SMA.

Royalty revenue. Royalty revenue was $4.8 million for the years ended December 31, 2020, an increase of $4.8 million, or 100%, from $0.0 million for the years ended December 31, 2019. The increase in royalty revenue was due to the FDA approval of Evrysdi in August 2020. In accordance with the SMA License Agreement, we are entitled to royalties on worldwide annual net sales of the product.

Cost of product sales, excluding amortization of acquired intangible asset. Cost of product sales, excluding amortization of acquired intangible asset, was $18.9 million for the year end December 31, 2020, an increase of $6.8 million, or 56%, from $12.1 million for the year ended December 31, 2019. Cost of product sales consist primarily of royalty payments associated with Emflaza and Translarna net product sales, excluding contingent payments to Marathon, costs associated with Emflaza and Translarna product sold during the period, and royalty expense related to royalty revenues and collaboration milestone revenues. The increase in cost of product sales, excluding amortization of acquired intangible asset, is primarily due to the increases in net product revenue, royalty revenues, and collaboration milestone revenue.

Amortization of acquired intangible asset. Amortization of acquired intangible asset was $36.9 million for the year ended December 31, 2020, an increase of $9.2 million, or 33%, from $27.7 million for the year ended December 31, 2019. These amounts are related to the acquisition of all rights to Emflaza acquired in May 2017, Marathon contingent payments, and our Waylivra and Tegsedi intangible assets. The increase is primarily related to additional Marathon contingent payments. The amount allocated to the Emflaza intangible asset is amortized on a straight-line basis over its estimated useful life of approximately seven years from the date of the completion of the acquisition of all rights to Emflaza, the period of estimated future cash flows. The Marathon contingent payments are amortized prospectively as incurred, straight-line, over the remaining useful life of the Emflaza intangible asset. The Waylivra and Tegsedi assets are amortized on a straight-line basis over their estimated useful life of approximately ten years, respectively.

Research and development expense. Research and development expense was $477.6 million for the year ended December 31, 2020, an increase of $220.2 million, or 86%, compared to $257.5 million for the year ended December 31, 2019. The increase in research and development expenses reflects costs associated with advancing the gene therapy and Bio-e platforms, increased investment in research programs, and advancement of the clinical pipeline. The increase also includes one-time charges of $53.6 million in acquisition related and other expenses from our acquisition of Censa pursuant to the Censa Merger Agreement and $41.4 million related to our commercial manufacturing services agreement with or MassBio related to dedicated manufacturing space for our lead gene therapy program, AADC deficiency.

Selling, general and administrative expense. Selling, general and administrative expense was $245.2 million for the year ended December 31, 2020, an increase of $42.6 million, or 21%, from $202.5 million for the year ended December 31, 2019. The increase was primarily due to continued investment to support our commercial activities including our expanding commercial portfolio and rent and related expenses associated with entering into a long term lease for the Hopewell Facility that commenced on July 1, 2020.

Change in the fair value of deferred and contingent consideration. Change in the fair value of deferred and contingent consideration was a loss of $23.3 million for the year ended December 31, 2020, a decrease of $25.1 million, or 52%, from a loss of $48.4 million for the year ended December 31, 2019. The change is related to the fair valuation of the potential future consideration to be paid to former equityholders of Agilis as a result of our merger with Agilis which closed in August 2018. Changes in the fair value were due to the re-calculation of discounted cash flows for the passage of time and changes to certain other estimated assumptions.

Settlement of deferred and contingent consideration. Settlement of deferred and contingent consideration was $10.6 million for year ended December 31, 2020. The settlement of deferred and contingent consideration is related to a loss upon the settlement of the deferred and contingent consideration liabilities as a result of the Rights Exchange Agreement

with certain former equityholders of Agilis, whereby we exchanged their pro rata share of specific future cash milestone payments in the aggregate amount of $225.0 million for a combination of cash and equity. We paid $36.9 million in cash and issued 2,821,176 shares of common stock in exchange for the cancellation and forfeiture of the Participating Rightholders' rights to receive (i) $174.0 million, in the aggregate, of potential milestone payments based on the achievement of certain regulatory milestones and (ii) $37.6 million, in the aggregate, of $40.0 million in development milestone payments that would have been due upon the passing of the second anniversary of the closing of the Agilis Merger, regardless of whether the milestones are achieved.

Interest expense, net. Interest expense, net was $56.4 million for the year ended December 31, 2020, an increase of $43.9 million, over 100%, from interest expense, net of $12.5 million for the year ended December 31, 2019. The increase in interest expense, net was primarily due to interest expense recorded from the liability for the sale of future royalties related to the Royalty Purchase Agreement, interest expense recorded from the 2022 and 2026 Convertible Notes and the Credit Agreement, partially offset by interest income from our investments.

Other income, net. Other income, net was $85.2 million for the year ended December 31, 2020, an increase of $71.5 million, over 100%, from other income, net of $13.7 million for the year ended December 31, 2019. The increase in other income, net resulted primarily from an unrealized foreign exchange gain of $54.6 million from the remeasurement of our intercompany loan, which is recorded on a non-U.S. subsidiary and denominated in U.S. dollars, and unrealized gains on our equity investments and convertible debt security in ClearPoint of $14.3 million and $19.3 million, respectively. These gains were partially offset by Agilis Rights Exchange transaction fees of $2.0 million.

Income tax expense. Income tax expense was $35.2 million for the year ended December 31, 2020, an increase of $23.6 million, over 100%, from income tax expense of $11.7 million for the year ended December 31, 2019. We recorded a state income tax provision in the years ended December 31, 2020, which is attributable to the taxable income from the sale of our right to receive sales-based royalty payments on Roche's worldwide net sales of Evrysdi. We also incurred income tax expense in various foreign jurisdictions, and our foreign tax liabilities are largely dependent upon the distribution of pre-tax earnings among these different jurisdictions.

Liquidity and capital resources

Sources of liquidity

Since inception, we have incurred significant operating losses.

As a growing commercial-stage biopharmaceutical company, we are engaging in significant commercialization efforts for our products while also devoting a substantial portion of our efforts on research and development related to our products, product candidates and other programs. To date, almost all of our product revenue has been attributable to sales of Translarna for the treatment of nmDMD in territories outside of the United States and from Emflaza for the treatment of DMD in the United States. Our ongoing ability to generate revenue from sales of Translarna for the treatment of nmDMD is dependent upon our ability to maintain our marketing authorizations in Brazil, Russia and in the EEA and secure market access through commercial programs following the conclusion of pricing and reimbursement terms at sustainable levels in the member states of the EEA or through EAP programs in the EEA and other territories. The marketing authorization requires annual review and renewal by the European Commission following reassessment by the EMA of the benefit-risk balance of the authorization and is subject to the specific obligation to conduct Study 041. Our ability to generate product revenue from Emflaza will largely depend on the coverage and reimbursement levels set by governmental authorities, private health insurers and other third-party payors.

We have historically financed our operations primarily through the issuance and sale of our common stock in public offerings, our "at the market offering" of our common stock, proceeds from the Royalty Purchase Agreement, the private placements of our preferred stock, collaborations, bank and institutional lender debt, convertible debt financings and grants and clinical trial support from governmental and philanthropic organizations and patient advocacy groups in the disease areas addressed by our product candidates. We expect to continue to incur significant expenses and operating losses for at least the next fiscal year. The net losses we incur may fluctuate significantly from quarter to quarter.

In August 2015, we closed a private offering of $150.0 million in aggregate principal amount of 2022 Convertible Notes, including the exercise by the initial purchasers of an option to purchase an additional $25.0 million in aggregate principal amount of the 2022 Convertible Notes. The 2022 Convertible Notes bear cash interest payable on February 15 and August 15 of each year, beginning on February 15, 2016. The 2022 Convertible Notes are senior unsecured obligations of ours and will mature on August 15, 2022, unless earlier converted, redeemed or repurchased in accordance with their terms prior to such date. We received net proceeds from the offering of approximately $145.4 million, after deducting the initial purchasers' discounts and commissions and the estimated offering expenses payable by us.

As of February 15, 2022, until the close of business on the business day immediately preceding the maturity date, holders may convert their 2022 Convertible Notes at any time. Upon conversion, we will pay or deliver, as the case may be, cash, shares of our common stock or any combination thereof at our election.

The conversion rate for the 2022 Convertible Notes was initially, and remains, 17.7487 shares of our common stock per $1,000 principal amount of the 2022 Convertible Notes, which is equivalent to an initial conversion price of approximately $56.34 per share of our common stock.

We were not permitted to redeem the 2022 Convertible Notes prior to August 20, 2018. As of August 20, 2018, we may redeem for cash all or any portion of the 2022 Convertible Notes, at our option, on or after August 20, 2018 if the last reported sale price of our common stock has been at least 130% of the conversion price then in effect on the last trading day of, and for at least 19 other trading days (whether or not consecutive) during, any 30 consecutive trading day period ending on, and including, the trading day immediately preceding the date on which we provide notice of redemption, at a redemption price equal to 100% of the principal amount of the 2022 Convertible Notes to be redeemed, plus accrued and unpaid interest to, but excluding, the redemption date. No sinking fund is provided for the 2022 Convertible Notes, which means that we are not required to redeem or retire the 2022 Convertible Notes periodically. There have been no redemptions to date.

If we undergo a "fundamental change" (as defined in the Indenture governing the 2022 Convertible Notes Indenture), subject to certain conditions, holders of the 2022 Convertible Notes may require us to repurchase for cash all or part of their 2022 Convertible Notes at a repurchase price equal to 100% of the principal amount of the 2022 Convertible Notes to be repurchased, plus accrued and unpaid interest to, but excluding, the fundamental change repurchase date.

The 2022 Convertible Notes represent senior unsecured obligations and will rank senior in right of payment to our future indebtedness that is expressly subordinated in right of payment to the notes, equal in right of payment to our existing and future unsecured indebtedness that is not so subordinated, effectively junior in right of payment to any of our secured indebtedness to the extent of the value of the assets securing such indebtedness, and structurally subordinated to all existing and future indebtedness and other liabilities (including trade payables) incurred by our subsidiaries. The 2022 Convertible Notes Indenture contains customary events of default with respect to the 2022 Convertible Notes, including that upon certain events of default (including our failure to make any payment of principal or interest on the 2022 Convertible Notes when due and payable) occurring and continuing, the 2022 Convertible Notes Trustee by notice to us, or the holders of at least 25% in principal amount of the outstanding 2022 Convertible Notes by notice to us and the 2022 Convertible Notes Trustee, may, and the 2022 Convertible Notes Trustee at the request of such holders (subject to the provisions of the 2022 Convertible Notes Indenture) will, declare 100% of the principal of and accrued and unpaid interest, if any, on all the 2022 Convertible Notes to be due and payable. In case of certain events of bankruptcy, insolvency or reorganization, involving us or a significant subsidiary, 100% of the principal of and accrued and unpaid interest on the 2022 Convertible Notes will automatically become due and payable. Upon such a declaration of acceleration, such principal and accrued and unpaid interest, if any, will be due and payable immediately.

In January 2019 and February 2019, we closed an underwritten public offering of 7,563,725 shares of our common stock and received net proceeds of approximately $224.2 million. In August 2019, we entered into the Sales Agreement, pursuant to which, we may offer and sell shares of our common stock, having an aggregate offering price of up to $125.0 million from time to time through the Sales Agents by any method that is deemed to be an "at the market offering" as defined in Rule 415(a)(4) promulgated under the Securities Act. In September 2019, we closed an underwritten public offering of 2,475,248 shares of our common stock and received net proceeds of $97.0 million. See "Item 7. Management's

Discussion and Analysis of Financial Condition and Results of Operations—Overview—Funding" for additional information regarding the transactions described in this paragraph.

In September 2019, we issued $287.5 million aggregate principal amount of 2026 Convertible Notes, which included an option to purchase up to an additional $37.5 million in aggregate principal amount of the 2026 Convertible Notes, which was exercised in full by the initial purchasers. The 2026 Convertible Notes bear cash interest at a rate of 1.50% per year, payable semi-annually on March 15 and September 15 of each year, beginning on March 15, 2020. The 2026 Convertible Notes will mature on September 15, 2026, unless earlier repurchased or converted. We received net proceeds of $279.3 million after deducting the initial purchasers' discounts and commissions and the offering expenses payable by us.

Holders may convert their 2026 Convertible Notes at their option at any time prior to the close of business on the business day immediately preceding March 15, 2026 only under the following circumstances: (1) during any calendar quarter commencing on or after December 31, 2019 (and only during such calendar quarter), if the last reported sale price of our common stock for at least 20 trading days (whether or not consecutive) during a period of 30 consecutive trading days ending on the last trading day of the immediately preceding calendar quarter is greater than or equal to 130% of the conversion price on each applicable trading day; (2) during the five business day period after any five consecutive trading day period, or the measurement period, in which the trading price (as defined in the 2026 Convertible Notes Indenture) per $1,000 principal amount of 2026 Convertible Notes for each trading day of the measurement period was less than 98% of the product of the last reported sale price of our common stock and the conversion rate on each such trading day; (3) during any period after we have issued notice of redemption until the close of business on the scheduled trading day immediately preceding the relevant redemption date; or (4) upon the occurrence of specified corporate events. On or after March 15, 2026, until the close of business on the business day immediately preceding the maturity date, holders may convert their 2026 Convertible Notes at any time, regardless of the foregoing circumstances. Upon conversion, we will pay or deliver, as the case may be, cash, shares of our common stock or any combination thereof at our election.

The conversion rate for the 2026 Convertible Notes was initially, and remains, 19.0404 shares of our common stock per $1,000 principal amount of the 2026 Convertible Notes, which is equivalent to an initial conversion price of approximately $52.52 per share of our common stock. The conversion rate may be subject to adjustment in some events but will not be adjusted for any accrued and unpaid interest.

We are not permitted to redeem the 2026 Convertible Notes prior to September 20, 2023. We may redeem for cash all or any portion of the 2026 Convertible Notes, at our option, if the last reported sale price of its common stock has been at least 130% of the conversion price then in effect on the last trading day of, and for at least 19 other trading days (whether or not consecutive) during, any 30 consecutive trading day period ending on, and including, the trading day immediately preceding the date on which we provide notice of redemption, at a redemption price equal to 100% of the principal amount of the 2026 Convertible Notes to be redeemed, plus accrued and unpaid interest to, but excluding, the redemption date. No sinking fund is provided for the 2026 Convertible Notes, which means that we are not required to redeem or retire the 2026 Convertible Notes periodically.

If we undergo a "fundamental change" (as defined in the 2026 Convertible Notes Indenture), subject to certain conditions, holders of the 2026 Convertible Notes may require us to repurchase for cash all or part of their 2026 Convertible Notes at a repurchase price equal to 100% of the principal amount of the 2026 Convertible Notes to be repurchased, plus accrued and unpaid interest to, but excluding, the fundamental change repurchase date.

The 2026 Convertible Notes represent senior unsecured obligations and will rank senior in right of payment to our future indebtedness that is expressly subordinated in right of payment to the notes, equal in right of payment to our existing and future unsecured indebtedness that is not so subordinated, effectively junior in right of payment to any of our secured indebtedness to the extent of the value of the assets securing such indebtedness, and structurally subordinated to all existing and future indebtedness and other liabilities (including trade payables) incurred by our subsidiaries. The 2026 Convertible Notes Indenture contains customary events of default with respect to the 2026 Convertible Notes, including that upon certain events of default (including our failure to make any payment of principal or interest on the 2026 Convertible Notes when due and payable) occurring and continuing, the 2026 Convertible Notes Trustee by notice to us, or the holders

of at least 25% in principal amount of the outstanding 2026 Convertible Notes by notice to us and the Convertible Notes Trustee, may, and the 2026 Convertible Notes Trustee at the request of such holders (subject to the provisions of the 2026 Convertible Notes Indenture) will, declare 100% of the principal of and accrued and unpaid interest, if any, on all the 2026 Convertible Notes to be due and payable. In case of certain events of bankruptcy, insolvency or reorganization, involving us or a significant subsidiary, 100% of the principal of and accrued and unpaid interest on the 2026 Convertible Notes will automatically become due and payable. Upon such a declaration of acceleration, such principal and accrued and unpaid interest, if any, will be due and payable immediately.

In July 2020, we entered into the Royalty Purchase Agreement. Pursuant to the Royalty Purchase Agreement, we sold to RPI the Assigned Royalty Payment in consideration for $650.0 million. See "Item 7. Management's Discussion and Analysis of Financial Condition and Results of Operations—Overview—Funding" for additional information regarding this transaction.

Cash flows

As of December 31, 2021, we had cash and cash equivalents and marketable securities of $773.4 million.

The following table provides information regarding our cash flows and our capital expenditures for the periods indicated.

	Years ended December 31,		
(in thousands)	**2021**	**2020**	**2019**
Cash (used in) provided by:			
Operating activities	$ (251,332)	$ (194,071)	$ (98,639)
Investing activities	$ 219,182	$ (561,548)	$ (387,237)
Financing activities	$ 20,877	$ 668,715	$ 613,209

Net cash used in operating activities was $251.3 million, $194.1 million, and $98.6 million for the years ended December 31, 2021, 2020, and 2019, respectively. The cash used in operating activities primarily related to supporting clinical development, including the manufacture of drug product, commercial activities for Emflaza and Translarna, and costs associated with the expansion of our international infrastructure for the years ended December 31, 2021, 2020, and 2019.

Net cash provided by investing activities was $219.2 million for the year ended December 31, 2021. Net cash used in investing activities was $561.5 million and $387.2 million for the years ended December 31, 2020 and 2019, respectively. The cash provided by investing activities for the year ended December 31, 2021 was primarily related to net sales and redemptions of marketable securities. The cash used in investing activities for the year ended December 31, 2020 was primarily related to purchases of marketable securities, the acquisition of product rights, purchases of fixed assets, and our purchase of convertible debt security, partially offset by net sales and redemptions of marketable securities. The cash used in investing activities for the year ended December 31, 2019 was primarily related to purchases of marketable securities, the acquisition of product rights, purchases of fixed assets, and our Equity Investment, partially offset by net sales and redemptions of marketable securities.

Net cash provided by financing activities was $20.9 million, $668.7 million, and $613.2 million for the years ended December 31, 2021, 2020 and 2019, respectively. The cash provided by financing activities for the year ended December 31, 2021 is primarily attributable to the exercise of options, and issuance of stock under our Employee Stock Purchase Plan, or ESPP, offset by payments of finance lease principal. Net cash provided by financing activities for the year ended December 31, 2020 is primarily attributable to proceeds from the Royalty Purchase Agreement, net proceeds received from our "at the market offering" of our common stock, the exercise of options, and issuance of stock under our ESPP, partially offset by repayment on our senior secured term loan, payments on deferred consideration obligation, and payments of finance lease principal. Net cash provided by financing activities for the year ended December 31, 2019 is primarily attributable to net proceeds received from our public stock offerings, net proceeds received

from our "at the market offering" of our common stock, net proceeds received from our convertible notes offering, the exercise of options, and issuance of stock under our ESPP, partially offset by repayment on our senior secured term loan.

Funding requirements

We anticipate that our expenses will continue to increase in connection with our commercialization efforts in the United States, the EEA, Latin America and other territories, including the expansion of our infrastructure and corresponding sales and marketing, legal and regulatory, distribution and manufacturing and administrative and employee-based expenses. In addition to the foregoing, we expect to continue to incur significant costs in connection with the research and development of our splicing, gene therapy, Bio-e, metabolic and oncology programs and our studies of emvododstat for COVID-19 as well as studies in our products for maintaining authorizations, including Study 041, label extensions and additional indications. In addition, we may incur substantial costs in connection with our efforts to advance our regulatory submissions. We continue to seek marketing authorization for Translarna for the treatment of nmDMD in territories that we do not currently have marketing authorization in. We submitted an MAA to the EMA for the treatment of AADC deficiency with PTC-AADC in the EEA and we expect an opinion from the CHMP in April 2022. We are preparing a BLA for PTC-AADC for the treatment of AADC deficiency in the United States and we expect to submit a BLA to the FDA in the second quarter of 2022. We filed for marketing authorization for Waylivra with ANVISA for the treatment of FPL and we expect a regulatory decision on approval from ANVISA in the second half of 2022. These efforts may significantly impact the timing and extent of our commercialization expenses.

In addition, our expenses will increase if and as we:

- seek to satisfy contractual and regulatory obligations we assumed in connection with the Agilis Merger;
- seek to satisfy contractual and regulatory obligations in conjunction with the Tegsedi-Waylivra Agreement;
- satisfy contractual and regulatory obligations that we assumed through our other acquisitions and collaborations;
- execute our commercialization strategy for our products and product candidates that may receive marketing authorization;
- are required to complete any additional clinical trials, non-clinical studies or Chemistry, Manufacturing and Controls, or CMC, assessments or analyses in order to advance Translarna for the treatment of nmDMD in the United States or elsewhere;
- utilize the Hopewell Facility to manufacture program materials for certain of our gene therapy product candidates;
- initiate or continue the research and development of our splicing, gene therapy, Bio-e, metabolic and oncology programs and our studies of emvododstat for COVID-19 as well as studies in our products for maintaining authorizations, including Study 041, label extensions and additional indications;
- seek to discover and develop additional product candidates;
- seek to expand and diversify our product pipeline through strategic transactions;
- maintain, expand and protect our intellectual property portfolio; and
- add operational, financial and management information systems and personnel, including personnel to support our product development and commercialization efforts.

We believe that our cash flows from product sales, together with existing cash and cash equivalents, including our offerings of the Convertible Notes, public offerings of common stock, our "at the market offering" of our common stock, proceeds from the Royalty Purchase Agreement and marketable securities, will be sufficient to fund our operating expenses

and capital expenditure requirements for at least the next twelve months. We have based this estimate on assumptions that may prove to be wrong, and we could use our capital resources sooner than we currently expect.

Our future capital requirements will depend on many factors, including:

- our ability to commercialize and market our products and product candidates that may receive marketing authorization;
- our ability to negotiate, secure and maintain adequate pricing, coverage and reimbursement terms, on a timely basis, with third-party payors for our products and products candidates;
- our ability to maintain the marketing authorization for our products, including in the EEA for Translarna for the treatment of nmDMD and whether the EMA determines on an annual basis that the benefit-risk balance of Translarna supports renewal of our marketing authorization in the EEA, on the current approved label;
- the costs, timing and outcome of Study 041;
- the costs, timing and outcome of our efforts to advance Translarna for the treatment of nmDMD in the United States, including, whether we will be required to perform additional clinical trials, non-clinical studies or CMC assessments or analyses at significant cost which, if successful, may enable FDA review of an NDA re-submission by us and, ultimately, may support approval of Translarna for nmDMD in the United States;
- unexpected decreases in revenue or increase in expenses resulting from the COVID-19 pandemic;
- our ability to maintain orphan exclusivity in the United States for Emflaza;
- our ability to successfully complete all post-marketing requirements imposed by regulatory agencies with respect to our products;
- the progress and results of activities under our splicing, gene therapy, Bio-e, metabolic and oncology programs and our studies of emvododstat for COVID-19 as well as studies in our products for maintaining authorizations, label extensions and additional indications;
- the scope, costs and timing of our commercialization activities, including product sales, marketing, legal, regulatory, distribution and manufacturing, for any of our products and for any of our other product candidates that may receive marketing authorization or any additional territories in which we receive authorization to market Translarna;
- the costs, timing and outcome of regulatory review of our splicing, gene therapy, Bio-e, metabolic and oncology programs and our studies of emvododstat for COVID-19 and Translarna in other territories;
- our ability to utilize the Hopewell Facility to manufacture program materials for certain of our gene therapy product candidates;
- our ability to satisfy our obligations under the indentures governing the Convertible Notes;
- the timing and scope of growth in our employee base;
- the scope, progress, results and costs of preclinical development, laboratory testing and clinical trials for our other product candidates, including those in our splicing, gene therapy, Bio-e, metabolic and oncology programs;
- revenue received from commercial sales of our products or any of our product candidates;
- our ability to obtain additional and maintain existing reimbursed named patient and cohort EAP programs for Translarna for the treatment of nmDMD on adequate terms, or at all;
- the ability and willingness of patients and healthcare professionals to access Translarna through alternative means if pricing and reimbursement negotiations in the applicable territory do not have a positive outcome;
- the costs of preparing, filing and prosecuting patent applications, maintaining, and protecting our intellectual property rights and defending against intellectual property-related claims;
- the extent to which we acquire or invest in other businesses, products, product candidates, and technologies, including the success of any acquisition, in-licensing or other strategic transaction we may pursue, and the costs of subsequent development requirements and commercialization efforts, including with respect to our acquisitions of Emflaza, Agilis, our Bio-E platform and Censa and our licensing of Tegsedi and Waylivra; and
- our ability to establish and maintain collaborations, including our collaborations with Roche and the SMA Foundation, and our ability to obtain research funding and achieve milestones under these agreements.

With respect to our outstanding 2022 Convertible Notes, cash interest payments are payable on a semi-annual basis in arrears, which require total funding of $4.5 million annually. The 2022 Convertible Notes will mature on August 15, 2022 and we will be required to pay any outstanding principal amount of the 2022 Convertible Notes at that time, unless

earlier converted, redeemed or repurchased in accordance with their terms prior to such date. As of February 15, 2022, until the close of business on the business day immediately preceding the maturity date, holders may convert their 2022 Convertible Notes at any time. Upon conversion, we will pay or deliver, as the case may be, cash, shares of our common stock or any combination thereof at our election. With respect to our outstanding 2026 Convertible Notes, cash interest payments are payable on a semi-annual basis in arrears, which will require total funding of $4.3 million annually.

In addition, we expect to pay Marathon Pharmaceuticals, LLC (now known as Complete Pharma Holdings, LLC), or Marathon, a single $50.0 million sales-based milestone in connection with Emflaza sales in 2022. We also expect to pay the former equityholders of Agilis an aggregate of $70.0 million upon the achievement of certain development and regulatory milestones in 2022 relating to PTC-AADC.

We also have certain significant contractual obligations and commercial commitments that require funding. We lease office space for our principal office in South Plainfield, New Jersey and we occupy under leases that expire in 2024, with two consecutive five-year renewal options to renew the leases after 2024 and at 4041 Hadley Road, South Plainfield New Jersey that we occupy under a lease that will expire in May 2022. Additionally, we entered into a lease agreement for approximately 103,000 square feet of laboratory and office space in Bridgewater, New Jersey. The rental term for such facility commenced on May 1, 2020 with an initial term of seven years and two consecutive five year renewal periods at our option. We also have significant lease obligations that stem from our lease of office, manufacturing, and laboratory space in Hopewell, New Jersey. The rental term for such facility commenced on July 1, 2020, with an initial term of fifteen years and two consecutive 10-year renewal periods at our option. In addition, we lease office space, vehicles and equipment in various other locations in the U.S. and other countries for our employees and operations. We have a total of $130.8 million in obligations that stem from our operating leases.

We have a total of $33.0 million in obligations that stem from a commercial manufacturing services agreement entered into with MassBio on June 19, 2020, for a term of 12.5 years. Pursuant to the terms of the agreement, MassBio agreed to provide us with four dedicated rooms for our PTC-AADC program.

Under an Exclusive License and Supply Agreement, or the Faes Agreement, with Faes Farma, S.A., or Faes, we are required to pay royalties as a percentage of or as a fixed payment with respect to net product sales by us allocable to the Emflaza oral suspension product. We are required to pay Faes an annual minimum royalty during the first seven calendar years with a fixed percentage royalty during the remainder of the Faes Agreement term. The minimum royalty based on the euro to U.S. dollar exchange rate as of December 31, 2021 is $3.4 million, with the last minimum royalty payment due in 2023.

Under various agreements, we will be required to pay royalties and milestone payments upon the successful development and commercialization of products, including the following agreements with The Wellcome Trust Limited, or Wellcome Trust, and the SMA Foundation.

We have entered into funding agreements with Wellcome Trust for the research and development of small molecule compounds in connection with our oncology platform and antibacterial program. As we have discontinued development under our antibacterial program, we do not expect that milestone and royalty payments from us to Wellcome Trust will apply under that agreement. Under our oncology platform funding agreement, to the extent that we develop and commercialize program intellectual property, excluding emvododstat, on a for-profit basis ourselves or in collaboration with a partner (provided we retain overall control of worldwide commercialization), we may become obligated to pay to Wellcome Trust development and regulatory milestone payments and single-digit royalties on sales of any research program product. Our obligation to pay such royalties would continue on a country-by-country basis until the longer of the expiration of the last patent in the program intellectual property in such country covering the research program product and the expiration of market exclusivity of such product in such country. We made the first development milestone payment of $0.8 million to Wellcome Trust under the oncology platform funding agreement during the second quarter of 2016. Additional development and regulatory milestone payments of up to an aggregate of $22.4 million may become payable by us under this agreement. For example, in the event a Phase 2 clinical study of a research program candidate, such as unesbulin, is commenced, a milestone payment of $2.5 million would become payable by us to Wellcome Trust upon the earlier to occur of the first dose administered to the last patient enrolled in the study or the termination of dosing of all patients in the study. We expect to initiate a registration-directed Phase 2/3 trial of unesbulin for the treatment of

LMS in the second quarter of 2022 and we expect to initiate a registration-directed Phase 2 trial of unesbulin for the treatment of DIPG in the third quarter of 2022.

We have also entered into a sponsored research agreement with the SMA Foundation in connection with our spinal muscular atrophy program. We may become obligated to pay the SMA Foundation single-digit royalties on worldwide net product sales of any collaboration product that we successfully develop and subsequently commercialize or, with respect to collaboration products we outlicense, including Evrysdi, a specified percentage of certain payments we receive from our licensee. We are not obligated to make such payments unless and until annual sales of a collaboration product exceed a designated threshold. Our obligation to make such payments would end upon our payment to the SMA Foundation of an aggregate of $52.5 million.

Additionally, we have employment agreements with certain employees which require the funding of a specific level of payments, if certain events, such as a change in control or termination without cause, occur. Furthermore, since we are a public company, we have incurred and expect to continue to incur additional costs associated with operating as such, including significant legal, accounting, investor relations and other expenses.

We have never been profitable and we will need to generate significant revenues to achieve and sustain profitability, and we may never do so. We may need to obtain substantial additional funding in connection with our continuing operations. Until such time, if ever, as we can generate substantial product revenues, we expect to finance our cash needs primarily through a combination of equity offerings, debt financings, collaborations, strategic alliances, grants and clinical trial support from governmental and philanthropic organizations and patient advocacy groups in the disease areas addressed by our product and product candidates and marketing, distribution or licensing arrangements. Adequate additional financing may not be available to us on acceptable terms, or at all. To the extent that we raise additional capital through the sale of equity or convertible debt securities, our shareholders ownership interest will be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect the rights of our common stockholders. Debt financing, if available, may involve agreements that include covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, making capital expenditures or declaring dividends. If we raise additional funds through collaborations, strategic alliances or marketing, distribution or licensing arrangements with third parties, we may have to relinquish valuable rights to our technologies, future revenue streams, research programs or product candidates or to grant licenses on terms that may not be favorable to us.

If we are unable to raise additional funds through equity, debt or other financings when needed or on attractive terms, we may be required to delay, limit, reduce or terminate our product development or commercialization efforts or grant rights to develop and market product candidates that we would otherwise prefer to develop and market ourselves.

Item 7A. Quantitative and Qualitative Disclosures about Market Risk

We are exposed to market risk related to changes in interest rates. Our primary exposure to market risk is interest rate sensitivity, which is affected by changes in the general level of U.S. interest rates, particularly because our investments are in short-term securities. Our available for sale securities are subject to interest rate risk and will fall in value if market interest rates increase. At any time, sharp changes in interest rates can affect the fair value of the investment portfolio and its interest earnings. There were no investments classified as long-term at December 31, 2021. At December 31, 2021, we held $773.4 million in cash and cash equivalents and short-term investments. After a review of our marketable investment securities, we believe that in the event of a hypothetical ten percent increase in interest rates, the resulting decrease in fair value of our marketable investment securities would be insignificant to the consolidated financial statements.

Currently, we do not hedge these interest rate exposures. We maintain an investment portfolio in accordance with our investment policy. The primary objectives of our investment policy are to preserve principal, maintain proper liquidity and to meet operating needs. Although our investments are subject to credit risk, our investment policy specifies credit quality standards for our investments and limits the amount of credit exposure from any single issue, issuer or type of investment. Our investments are also subject to interest rate risk and will decrease in value if market interest rates increase. However, due to the conservative nature of our investments and relatively short duration, interest rate risk is mitigated. We do not own derivative financial instruments. Accordingly, we do not believe that there is any material market risk exposure with respect to derivative or other financial instruments.

As a result of our ex-U.S. operations, we face exposure to movements in foreign currency exchange rates, including the British Pound, Euro, Brazilian Real, and Swiss Franc against the U.S. dollar. The current exposures arise primarily from cash, accounts receivable, intercompany receivables and payables, intercompany loans and product sales denominated in foreign currencies. Both positive and negative impacts to our international product sales from movements in foreign currency exchange rates may be partially mitigated by the natural, opposite impact that foreign currency exchange rates have on our international operating expenses. For the year ended December 31, 2021, we recognized realized foreign currency transaction losses, net, of $2.1 million, which is recorded within other income, net on the Statement of Operations. A hypothetical ten percent increase or decrease in the exchange rate between the U.S. dollar and the British Pound, Euro, Brazilian Real, or Swiss Franc from the December 31, 2021 rate would not have a significant impact on our cash flows. We are not currently engaged in any foreign currency hedging activities. We will evaluate the use of derivative financial instruments to hedge our exposure as the needs and risks should arise.

In August 2015, we issued $150.0 million of 3.00% convertible senior notes due August 15, 2022, or the 2022 Convertible Notes. We do not have economic interest rate exposure on the 2022 Convertible Notes as they have a fixed annual interest rate of 3.00%. However, the fair value of the 2022 Convertible Notes is exposed to interest rate risk. We do not carry the 2022 Convertible Notes at fair value on our balance sheet but present the fair value of the principal amount for disclosure purposes. Generally, the fair value of the 2022 Convertible Notes will increase as interest rates fall and decrease as interest rates rise. The 2022 Convertible Notes are also affected by the price and volatility of our common stock and will generally increase or decrease as the market price of our common stock changes. The estimated fair value of the 2022 Convertible Notes was approximately $158.3 million as of December 31, 2021.

In September 2019, we issued $287.5 million of 1.50% convertible senior notes due September 15, 2026, or the 2026 Convertible Notes. We do not have economic interest rate exposure on the 2026 Convertible Notes as they have a fixed annual interest rate of 1.50%. However, the fair value of the 2026 Convertible Notes is exposed to interest rate risk. We do not carry the 2026 Convertible Notes at fair value on our balance sheet but present the fair value of the principal amount for disclosure purposes. Generally, the fair value of the 2026 Convertible Notes will increase as interest rates fall and decrease as interest rates rise. The 2026 Convertible Notes are also affected by the price and volatility of our common stock and will generally increase or decrease as the market price of our common stock changes. The estimated fair value of the Convertible Notes was approximately $305.3 million as of December 31, 2021.

Item 8. Financial Statements and Supplementary Data

Index to consolidated financial statements

Report of Independent Registered Public Accounting Firm

To the Stockholders and the Board of Directors of PTC Therapeutics, Inc.

Opinion on the Financial Statements

We have audited the accompanying consolidated balance sheets of PTC Therapeutics, Inc. (the Company) as of December 31, 2021 and 2020, the related consolidated statements of operations, comprehensive loss, stockholders' equity and cash flows for each of the three years in the period ended December 31, 2021, and the related notes (collectively referred to as the "consolidated financial statements"). In our opinion, the consolidated financial statements present fairly, in all material respects, the financial position of the Company at December 31, 2021 and 2020, and the consolidated results of its operations and its cash flows for each of the three years in the period ended December 31, 2021, in conformity with U.S. generally accepted accounting principles.

We also have audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States) (PCAOB), the Company's internal control over financial reporting as of December 31, 2021, based on criteria established in Internal Control-Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission (2013 framework) and our report dated February 22, 2022 expressed an unqualified opinion thereon.

Basis for Opinion

These financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on the Company's financial statements based on our audits. We are a public accounting firm registered with the PCAOB and are required to be independent with respect to the Company in accordance with the U.S. federal securities laws and the applicable rules and regulations of the Securities and Exchange Commission and the PCAOB.

We conducted our audits in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement, whether due to error or fraud. Our audits included performing procedures to assess the risks of material misstatement of the financial statements, whether due to error or fraud, and performing procedures that respond to those risks. Such procedures included examining, on a test basis, evidence regarding the amounts and disclosures in the financial statements. Our audits also included evaluating the accounting principles used and significant estimates made by management, as well as evaluating the overall presentation of the financial statements. We believe that our audits provide a reasonable basis for our opinion.

Adoption of ASU No. 2020-06

As discussed in Note 2 to the consolidated financial statements, the Company changed its method of accounting for convertible notes in 2021 due to the adoption of Accounting Standards Update (ASU) No. 2020-06, Debt— (Subtopic 470-20 & 815-40), and the related amendments.

Critical Audit Matters

The critical audit matters communicated below are matters arising from the current period audit of the financial statements that were communicated or required to be communicated to the audit committee and that: (1) relate to accounts or disclosures that are material to the financial statements and (2) involved our especially challenging, subjective or complex judgments. The communication of critical audit matters does not alter in any way our opinion on the consolidated financial statements, taken as a whole, and we are not, by communicating the critical audit matters below, providing separate opinions on the critical audit matters or on the accounts or disclosures to which they relate.

Variable consideration in contracts with customers

Description of the Matter

As discussed in Note 2 of the consolidated financial statements, the Company's revenues for product sold to its customers within the United States reflect discounts mandated by the Medicaid Drug Rebate Program. The Company includes an estimate of this variable consideration in its transaction price at the time of sale, when control of the product transfers to the customer. The Company uses the expected value or most likely amount method when estimating variable consideration, unless discount or rebate terms are specified within contracts. The estimates for variable consideration are adjusted to reflect known changes.

Auditing the amount of consideration to be paid under the Medicaid Drug Rebate Program (Medicaid) was complex and highly judgmental due to significant uncertainty about the volume of expected claims from governmental entities, the estimated amount of shipments from wholesalers that will be dispensed to eligible benefit plan participants, as well as the complexity of governmental pricing calculations in various jurisdictions. Governmental pricing calculations are complex as a result of assumptions such as patient mix, the average manufacturer price, best price, and the unit rebate amount. The reductions to gross product revenues are sensitive to these significant estimates and calculations.

How We Addressed the Matter in Our Audit

We identified, evaluated and tested controls over management's review of the calculated reductions to gross product prices related to Medicaid and the significant assumptions and data inputs utilized in the calculations.

To test the revenue adjustments related to Medicaid our audit procedures included, among others, evaluating the methodology used as well as testing the significant estimates discussed above and the underlying assumptions and data used by the Company in its analysis. We compared the assumptions used by management to historical trends, evaluated pricing adjustments recorded in the current period, and assessed the historical accuracy of management's estimates against actual results. In addition, we involved an internal governmental pricing specialist to assist with our evaluation of management's methodology and the calculations made to measure the estimated Medicaid rebates.

Valuation of acquisition-related contingent consideration liability

Description of the Matter

As discussed in Note 2 to the consolidated financial statements under the caption "Business combinations and asset acquisitions," the Company recognizes contingent consideration liabilities at their estimated fair values on the acquisition date. Subsequent changes to the fair values of the contingent consideration liabilities are recorded within the consolidated statement of operations in the period of change. At December 31, 2021, the Company recorded $239.9 million in total contingent consideration liabilities related to development, regulatory and net sales milestones.

The fair value of the contingent consideration is estimated using a combination of a probability adjusted, discounted cash flow approach and an option pricing model with Monte Carlo simulation. Certain assumptions, including development timelines, probabilities of success, and certain inputs to the weighted average cost of capital are highly subjective and the fair value estimate is sensitive to these assumptions. Auditing the valuation of contingent consideration liabilities was complex and required significant auditor judgment due to the high degree of subjectivity in evaluating these assumptions and the method used for the calculation.

How We Addressed the Matter in Our Audit

We obtained an understanding, evaluated the design and tested the operating effectiveness of controls over the Company's contingent consideration liabilities process including management's process to establish the significant assumptions and measure the liability.

To test the estimated fair value of the contingent consideration liabilities, our audit procedures included, among others, assessing the fair value methodology and testing the significant assumptions discussed above and the underlying data used in management's analyses. We evaluated the assumptions and judgments in light of observable industry and economic trends and standards, external data sources and regulatory factors. Estimated amounts of future sales and probabilities of achieving milestones were evaluated in relation to internal and external analyses, clinical development progress and timelines, probability of success benchmarks, and regulatory notices. Additionally, we compared the weighted average cost of capital that was adjusted for the Company's credit risk, to those of comparable guideline companies. Our procedures also included evaluating the data sources used by management in determining its assumptions and, where necessary, included an evaluation of available information that either corroborated or contradicted management's conclusions. We involved valuation specialists to assist with our assessment of the Company's fair value measurement methodology and to perform corroborative fair value calculations.

/s/ Ernst & Young LLP

We have served as the Company's auditor since 2010.

Iselin, New Jersey

February 22, 2022

PTC Therapeutics, Inc.

Consolidated Balance Sheets

In thousands, except shares

	December 31, 2021	December 31, 2020
Assets		
Current assets:		
Cash and cash equivalents	$ 189,718	$ 208,812
Marketable securities	583,658	894,838
Trade and royalty receivables, net	110,455	69,929
Inventory, net	15,856	18,697
Prepaid expenses and other current assets	54,681	39,469
Total current assets	954,368	1,231,745
Fixed assets, net	52,585	33,831
Intangible assets, net	724,841	715,328
Goodwill	82,341	82,341
Operating lease ROU assets	77,421	84,410
Deposits and other assets	46,500	60,623
Total assets	$ 1,938,056	$ 2,208,278
Liabilities and stockholders' equity		
Current liabilities:		
Accounts payable and accrued expenses	288,784	242,168
Current portion of long-term debt	149,540	—
Deferred revenue	—	4,151
Operating lease liabilities- current	7,273	7,465
Finance lease liabilities- current	3,000	1,276
Liability for sale of future royalties- current	59,291	21,023
Other current liabilities	1,460	1,250
Total current liabilities	509,348	277,333
Long-term debt	281,894	309,145
Contingent consideration payable	239,900	240,400
Deferred tax liability	137,110	136,735
Operating lease liabilities- noncurrent	73,619	79,499
Finance lease liabilities- noncurrent	20,053	23,053
Liability for sale of future royalties- noncurrent	674,694	658,739
Other long-term liabilities	—	1,392
Total liabilities	1,936,618	1,726,296
Stockholders' equity:		
Common stock, $0.001 par value. Authorized 250,000,000 shares; issued and outstanding 70,828,226 shares at December 31, 2021. Authorized 125,000,000 shares; issued and outstanding 69,718,096 shares at December 31, 2020.	71	70
Additional paid-in capital	2,123,606	2,171,746
Accumulated other comprehensive loss	(24,282)	(60,957)
Accumulated deficit	(2,097,957)	(1,628,877)
Total stockholders' equity	1,438	481,982
Total liabilities and stockholders' equity	$ 1,938,056	$ 2,208,278

See accompanying consolidated notes.

PTC Therapeutics, Inc.

Consolidated Statements of Operations

In thousands, except shares and per share data

	Year ended December 31,		
	2021	2020	2019
Revenues:			
Net product revenue	$ 428,904	$ 333,401	$ 291,306
Collaboration revenue	55,046	42,579	15,674
Royalty revenue	54,643	4,786	—
Total revenues	538,593	380,766	306,980
Operating expenses:			
Cost of product sales, excluding amortization of acquired intangible assets	32,328	18,942	12,135
Amortization of acquired intangible assets	54,751	36,892	27,650
Research and development	540,684	477,643	257,452
Selling, general and administrative	285,773	245,164	202,541
Change in the fair value of deferred and contingent consideration	(500)	23,280	48,360
Settlement of deferred and contingent consideration	—	10,613	—
Total operating expenses	913,036	812,534	548,138
Loss from operations	(374,443)	(431,768)	(241,158)
Interest expense, net	(86,022)	(56,352)	(12,491)
Other (expense) income, net	(57,875)	85,188	13,723
Loss before income tax expense	(518,340)	(402,932)	(239,926)
Income tax expense	(5,561)	(35,228)	(11,650)
Net loss attributable to common stockholders	$ (523,901)	$ (438,160)	$ (251,576)
Weighted-average shares outstanding:			
Basic and diluted (in shares)	70,466,393	66,027,908	58,863,185
Net loss per share—basic and diluted (in dollars per share)	$ (7.43)	$ (6.64)	$ (4.27)

See accompanying consolidated notes.

PTC Therapeutics, Inc.

Consolidated Statements of Comprehensive Loss

In thousands

	Year ended December 31,		
	2021	**2020**	**2019**
Net loss	$ (523,901)	$ (438,160)	$ (251,576)
Other comprehensive (loss) income:			
Unrealized (loss) gain on marketable securities, net of tax of $0, $0, and $165, respectively	(2,502)	1,145	724
Foreign currency translation gain (loss), net of tax of $0	39,177	(51,518)	(12,770)
Comprehensive loss	$ (487,226)	$ (488,533)	$ (263,622)

See accompanying consolidated notes.

PTC Therapeutics, Inc.

Consolidated Statements of Stockholders' Equity

In thousands, except shares

	Common stock		Additional paid-in capital	Accumulated other comprehensive income (loss)	Accumulated deficit	Total stockholders' equity
	Shares	Amount				
Balance, December 31, 2018	50,606,147	$ 51	$ 1,288,137	$ 1,462	$ (938,923)	$ 350,727
Issuance of common stock related to equity offerings	10,102,899	10	323,746	—	—	323,756
Equity component of convertible notes, net	—	—	119,482	—	—	119,482
Exercise of options	949,887	1	18,275	—	—	18,276
Restricted stock vesting and issuance, net	169,792	—	—	—	—	—
Issuance of common stock in connection with an employee stock purchase plan	107,145	—	3,577	—	—	3,577
Share-based compensation expense	—	—	42,134	—	—	42,134
Net loss	—	—	—	—	(251,576)	(251,576)
Comprehensive loss	—	—	—	(12,046)	—	(12,046)
Balance, December 31, 2019	61,935,870	$ 62	$ 1,795,351	$ (10,584)	$ (1,190,499)	$ 594,330
Issuance of common stock related to equity offerings	542,470	1	28,091	—	—	28,092
Issuance of common stock related to acquisition	845,364	1	42,868	—	—	42,869
Issuance of common stock related to rights exchange	2,821,176	3	150,525	—	—	150,528
Exercise of options	3,268,452	3	70,176	—	—	70,179
Restricted stock vesting and issuance, net	180,028	—	—	—	—	—
Issuance of common stock in connection with an employee stock purchase plan	124,736	—	5,303	—	—	5,303
Share-based compensation expense	—	—	70,325	—	—	70,325
Receivable from investor	—	—	9,107	—	—	9,107
Other	—	—	—	—	(218)	(218)
Net loss	—	—	—	—	(438,160)	(438,160)
Comprehensive loss	—	—	—	(50,373)	—	(50,373)
Balance, December 31, 2020	69,718,096	$ 70	$ 2,171,746	$ (60,957)	$ (1,628,877)	$ 481,982
Exercise of options	635,871	1	17,308	—	—	17,309
Restricted stock vesting and issuance, net	307,658	—	—	—	—	—
Issuance of common stock in connection with an employee stock purchase plan	166,601	—	5,792	—	—	5,792
Share-based compensation expense	—	—	103,513	—	—	103,513
Receivable from investor	—	—	483	—	—	483
Adjustment for the adoption of ASU 2020-06	—	—	(175,236)	—	54,796	(120,440)
Other	—	—	—	—	25	25
Net loss	—	—	—	—	(523,901)	(523,901)
Comprehensive income	—	—	—	36,675	—	36,675
Balance, December 31, 2021	70,828,226	$ 71	$ 2,123,606	$ (24,282)	$ (2,097,957)	$ 1,438

See accompanying consolidated notes.

PTC Therapeutics, Inc.

Consolidated Statements of Cash Flows

In thousands

	Year ended December 31,		
	2021	**2020**	**2019**
Cash flows from operating activities			
Net loss	$ (523,901)	$ (438,160)	$ (251,576)
Adjustments to reconcile net loss to net cash used in operating activities:			
Depreciation and amortization	64,134	43,490	32,180
Non-cash operating lease expense	7,386	6,084	3,709
Non-cash finance lease amortization expense	—	41,382	—
Non-cash royalty revenue related to sale of future royalties	(23,460)	(2,055)	—
Non-cash interest expense on liability related to sale of future royalties	77,683	31,817	—
Change in valuation of deferred and contingent consideration	(500)	23,280	48,360
Settlement of deferred and contingent consideration	—	10,613	—
Non-cash stock consideration, acquisition	—	42,869	—
Unrealized loss (gain) on ClearPoint Equity Investments	6,078	(14,310)	(2,194)
Unrealized loss (gain) on ClearPoint convertible debt security	8,281	(19,252)	—
Unrealized gain on marketable securities- equity investments	(1,673)	—	—
Amortization of premiums (discounts) on investments, net	5,299	409	(1,922)
Amortization of debt issuance costs	1,848	1,020	694
Share-based compensation expense	103,513	70,325	42,134
Non-cash interest expense	—	22,598	12,027
Disposal of asset	—	16	312
Deferred income taxes	377	5,872	8,829
Unrealized foreign currency transaction losses (gains), net	47,391	(56,980)	(11,619)
Changes in operating assets and liabilities:			
Inventory, net	1,800	1,841	(3,456)
Prepaid expenses and other current assets	(15,310)	(12,621)	(8,835)
Trade and royalty receivables, net	(44,991)	(10,483)	11,525
Deposits and other assets	(232)	(662)	(484)
Accounts payable and accrued expenses	45,659	70,798	26,836
Other liabilities	(6,704)	(3,930)	(3,771)
Deferred revenue	(4,010)	(8,032)	(1,388)
Net cash used in operating activities	(251,332)	(194,071)	(98,639)
Cash flows from investing activities			
Purchases of fixed assets	(28,213)	(17,843)	(13,757)
Purchase of convertible debt security	—	(10,000)	—
Purchases of marketable securities- available for sale	(333,148)	(1,439,665)	(494,068)
Purchases of marketable securities- equity investments	(210,018)	—	—
Sale and redemption of marketable securities- available for sale	843,498	944,094	156,270
Sale and redemption of marketable securities- equity investments	4,281	—	—
Acquisition of product rights and licenses	(57,118)	(38,134)	(31,682)
Purchase of equity investment in ClearPoint	(100)	—	(4,000)
Net cash provided by (used in) investing activities	219,182	(561,548)	(387,237)
Cash flows from financing activities			
Proceeds from issuance of convertible notes	—	—	279,267
Proceeds from exercise of options	17,309	70,179	18,276
Termination and exit fees related to payoff of secured term loan	—	(597)	—
Net proceeds from public offerings	—	28,092	323,756
Repayment of senior secured term loan	—	(28,333)	(11,667)
Payments on deferred consideration obligation	—	(38,100)	—
Proceeds from employee stock purchase plan	5,792	5,303	3,577
Payment of finance lease principal	(2,224)	(17,829)	—
Cash consideration received from Royalty Purchase Agreement	—	650,000	—
Net cash provided by financing activities	20,877	668,715	613,209
Effect of exchange rate changes on cash	(7,821)	7,688	(1,303)
Net decrease in cash and cash equivalents	(19,094)	(79,216)	126,030
Cash and cash equivalents, and restricted cash beginning of period	216,312	295,528	169,498
Cash and cash equivalents, and restricted cash end of period	$ 197,218	$ 216,312	$ 295,528
Supplemental disclosure of cash information			
Cash paid for interest	$ 9,588	$ 9,802	$ 7,693
Cash paid for income taxes	$ 7,708	$ 26,397	$ 2,109

Supplemental disclosure of non-cash investing and financing activity			
Unrealized (loss) gain on marketable securities, net of tax	$ (2,502)	$ 1,145	$ 724
Right-of-use assets obtained in exchange for operating lease obligations	$ 645	$ 76,811	$ 17,389
Right-of-use assets obtained in exchange for finance lease obligations	$ —	$ 41,382	$ —
Acquisition of product rights and licenses	$ 22,294	$ 14,191	$ 11,434
Issuance of common stock related to rights exchange	$ —	$ 150,528	$ —
Capital expenditures unpaid at the end of period	$ —	$ 1,060	$ —

See accompanying consolidated notes.

PTC Therapeutics, Inc.

Notes to consolidated financial statements

December 31, 2021

(In thousands except share and per share amount)

1. The Company

PTC Therapeutics, Inc. (the "Company" or "PTC") is a science-driven global biopharmaceutical company focused on the discovery, development and commercialization of clinically differentiated medicines that provide benefits to patients with rare disorders. PTC's ability to innovate to identify new therapies and to globally commercialize products is the foundation that drives investment in a robust and diversified pipeline of transformative medicines. PTC's mission is to provide access to best-in-class treatments for patients who have few or no treatment options. PTC's strategy is to leverage its strong scientific and clinical expertise and global commercial infrastructure to bring therapies to patients. PTC believes that this allows it to maximize value for all of its stakeholders.

The Company has two products, Translarna™ (ataluren) and Emflaza® (deflazacort), for the treatment of Duchenne muscular dystrophy ("DMD"), a rare, life threatening disorder. Translarna has marketing authorization in the European Economic Area (the "EEA") and Brazil for the treatment of nonsense mutation Duchenne muscular dystrophy ("nmDMD") in ambulatory patients aged 2 years and older and in Russia for the treatment of nmDMD in patients aged two years and older. In July 2020, the European Commission approved the removal of the statement "efficacy has not been demonstrated in non-ambulatory patients" from the indication statement for Translarna. Emflaza is approved in the United States for the treatment of DMD in patients two years and older.

The Company holds the rights for the commercialization of Tegsedi® (inotersen) and Waylivra® (volanesorsen) for the treatment of rare diseases in countries in Latin America and the Caribbean pursuant to the Collaboration and License Agreement (the "Tegsedi-Waylivra Agreement"), dated August 1, 2018, by and between the Company and Akcea Therapeutics, Inc. ("Akcea"), a subsidiary of Ionis Pharmaceuticals, Inc. Tegsedi has received marketing authorization in the United States, the European Union (the "EU") and Brazil for the treatment of stage 1 or stage 2 polyneuropathy in adult patients with hereditary transthyretin amyloidosis ("hATTR amyloidosis"). The Company has initiated its commercial launch for Tegsedi for the treatment of hATTR amyloidosis in Brazil and it continues to make Tegsedi available in certain other countries within Latin America and the Caribbean through early access programs. In August 2021, ANVISA, the Brazilian health regulatory authority, approved Waylivra as the first treatment for familial chylomicronemia syndrome ("FCS") in Brazil, and the Company has initiated its commercial launch in Brazil while continuing to make Waylivra available in certain other countries within Latin America and the Caribbean through EAP programs. Waylivra has also received marketing authorization in the EU for the treatment of FCS. Additionally, the Company submitted an application to ANVISA in December 2021 for the approval of Waylivra for the treatment of familial partial lipodystrophy, and it expects a regulatory decision on approval in the second half of 2022.

The Company also has a spinal muscular atrophy ("SMA") collaboration with F. Hoffman-La Roche Ltd and Hoffman-La Roche Inc. (referred to collectively as "Roche") and the Spinal Muscular Atrophy Foundation ("SMA Foundation"). The SMA program has one approved product, Evrysdi® (risdiplam), which was approved by the United States Food and Drug Administration ("FDA") in August 2020 for the treatment of SMA in adults and children two months and older and by the European Commission in March 2021 for the treatment of 5q SMA in patients two months and older with a clinical diagnosis of SMA Type 1, Type 2 or Type 3 or with one to four SMN2 copies. Evrysdi also received marketing authorization for the treatment of SMA in Brazil in October 2020 and Japan in June 2021. In January 2022, the FDA granted priority review of a supplemental new drug application for Evrysdi to expand the indication to include pre-symptomatic infants under two months old with SMA. In addition to the Company's SMA program, the Company's splicing platform also includes PTC518, which is being developed for the treatment of Huntington's disease ("HD"). The Company announced the results from its Phase 1 study of PTC518 in healthy volunteers in September 2021 demonstrating dose-dependent lowering of huntingtin messenger ribonucleic acid and protein levels, that PTC518 efficiently crosses the

blood brain barrier at significant levels and that PTC518 was well tolerated. The Company expects to initiate a Phase 2 study of PTC518 in the first quarter of 2022.

The Company has a pipeline of gene therapy product candidates for rare monogenic diseases that affect the central nervous system ("CNS") including PTC-AADC for the treatment of Aromatic L-Amino Acid Decarboxylase ("AADC") deficiency ("AADC deficiency"), a rare CNS disorder arising from reductions in the enzyme AADC that results from mutations in the dopa decarboxylase gene. In January 2020, the Company submitted a marketing authorization application ("MAA") to the European Medicines Agency ("EMA") for PTC-AADC for the treatment of AADC deficiency in the EEA, and the Company expects an opinion from the Committee for Medicinal Products for Human Use ("CHMP") in April 2022. The Company is also preparing a biologics license application ("BLA") for PTC-AADC for the treatment of AADC deficiency in the United States. In response to discussions with the FDA, the Company intends to provide additional information concerning the use of the commercial cannula for PTC-AADC in young patients. The Company expects to submit a BLA to the FDA in the second quarter of 2022.

The Company's Bio-e platform consists of small molecule compounds that target oxidoreductase enzymes that regulate oxidative stress and inflammatory pathways central to the pathology of a number of CNS diseases. The two most advanced molecules in the Company's Bio-e platform are vatiquinone and PTC857. The Company initiated a registration-directed Phase 2/3 placebo-controlled trial of vatiquinone in children with mitochondrial disease associated seizures in the third quarter of 2020. The Company has experienced delays in enrolling this trial due to the COVID-19 pandemic and now anticipates results from this trial to be available in the fourth quarter of 2022. The Company also initiated a registration-directed Phase 3 trial of vatiquinone in children and young adults with Friedreich ataxia in the fourth quarter of 2020 and anticipates results from this trial to be available in the second quarter of 2023. In the third quarter of 2021, the Company completed a Phase 1 trial in healthy volunteers to evaluate the safety and pharmacology of PTC857. PTC857 was found to be well-tolerated with no reported serious adverse events while demonstrating predictable pharmacology. The Company expects to initiate a Phase 2 trial of PTC857 for amyotrophic lateral sclerosis in the second quarter of 2022.

The most advanced molecule in the Company's metabolic platform is PTC923, an oral formulation of synthetic sepiapterin, a precursor to intracellular tetrahydrobiopterin, which is a critical enzymatic cofactor involved in metabolism and synthesis of numerous metabolic products. The Company initiated a registration-directed Phase 3 trial for PTC923 for phenylketonuria ("PKU") in the third quarter of 2021 and expects results from this trial to be available by the end of 2022.

The Company also has two oncology agents that are in clinical development, unesbulin and emvododstat. The Company completed its Phase 1 trials evaluating unesbulin in leiomyosarcoma ("LMS") and diffuse intrinsic pontine glioma ("DIPG") in the fourth quarter of 2021. The Company expects to initiate a registration-directed Phase 2/3 trial of unesbulin for the treatment of LMS in the second quarter of 2022, and it expects to initiate a registration-directed Phase 2 trial of unesbulin for the treatment of DIPG in the third quarter of 2022. The Company completed its Phase 1 trial evaluating emvododstat, a small molecule dihydrooratate dehydrogenase inhibitor that inhibits de novo pyrimidine nucleotide synthesis, in acute myelogenous leukemia ("AML"), in the fourth quarter of 2021. The Company expects to provide further updates regarding its emvododstat program at a later date.

In June 2020, the Company initiated a Phase 2/3 clinical trial evaluating the efficacy and safety of emvododstat in patients hospitalized with COVID-19. In February 2021, the Company announced the completion of the first stage of the Phase 2/3 trial. The Company expects results from this trial to be available in the first half of 2022.

In addition, the Company has a pipeline of product candidates and discovery programs that are in early clinical, pre-clinical and research and development stages focused on the development of new treatments for multiple therapeutic areas for rare diseases.

The Company's marketing authorization for Translarna in the EEA is subject to annual review and renewal by the European Commission following reassessment by the EMA of the benefit-risk balance of the authorization, which the Company refers to as the annual EMA reassessment. The marketing authorization in the EEA was last renewed in June 2021 and is effective, unless extended, through August 5, 2022. In February 2022, the Company submitted a marketing authorization renewal request to the EMA. This marketing authorization is further subject to the specific obligation to conduct and submit the results of a multi-center, randomized, double-blind, 18-month, placebo-controlled trial, followed by an 18-month open-label extension, according to an agreed protocol, in order to confirm the efficacy and safety of Translarna. The Company refers to the trial and open-label extension together as Study 041. The Company expects results from the placebo-controlled trial to be available in mid-2022. The Company then expects to submit a report on the placebo-controlled trial and the open-label extension data that has been collected to date to the EMA by the end of the third quarter of 2022, as required.

Translarna is an investigational new drug in the United States. During the first quarter of 2017, the Company filed a New Drug Application ("NDA") over protest with the FDA, for which the FDA granted a standard review. In October 2017, the Office of Drug Evaluation I of the FDA issued a complete response letter for the NDA, stating that it was unable to approve the application in its current form. In response, the Company filed a formal dispute resolution request with the Office of New Drugs of the FDA. In February 2018, the Office of New Drugs of the FDA denied PTC's appeal of the Complete Response Letter. In its response, the Office of New Drugs recommended a possible path forward for the ataluren NDA submission based on the accelerated approval pathway. This would involve a re-submission of an NDA containing the current data on effectiveness of ataluren with new data to be generated on dystrophin production in nmDMD patients' muscles. The Company followed the FDA's recommendation and collected, using newer technologies via procedures and methods that the Company designed, such dystrophin data in a new study, Study 045, and announced the results of Study 045 in February 2021. Study 045 did not meet its pre-specified primary endpoint. The Company expects results from the placebo-controlled trial of Study 041 to be available in mid-2022, and subject to a positive outcome in that study, the Company expects to re-submit the NDA.

As of December 31, 2021, the Company had an accumulated deficit of approximately $2,098.0 million. The Company has financed its operations to date primarily through the private offerings in September 2019 of 1.50% convertible senior notes due 2026 and in August 2015 of 3.00% convertible senior notes due 2022 (see Note 8), public offerings of common stock in February 2014, October 2014, April 2018, January 2019, and September 2019, "at the market offering" of its common stock, its initial public offering of common stock in June 2013, proceeds from the Royalty Purchase Agreement dated as of July 17, 2020, by and among the Company, RPI 2019 Intermediate Finance Trust ("RPI"), and, solely for the limited purposes set forth therein, Royalty Pharma PLC (the "Royalty Purchase Agreement") (see Note 2), private placements of its convertible preferred stock, collaborations, bank and institutional lender debt, grant funding and clinical trial support from governmental and philanthropic organizations and patient advocacy groups in the disease area addressed by the Company's product candidates. Since 2014, the Company has also relied on revenue generated from net sales of Translarna for the treatment of nmDMD in territories outside of the United States, and since May 2017, the Company has generated revenue from net sales of Emflaza for the treatment of DMD in the United States. The Company has also relied on revenue associated with milestone and royalty payments from Roche pursuant to the License and Collaboration Agreement (the "SMA License Agreement") dated as of November 23, 2011, by and among the Company, Roche and, for the limited purposes set forth therein, the SMA Foundation, under its SMA program. The Company expects that cash flows from the sales of its products, together with the Company's cash, cash equivalents and marketable securities, will be sufficient to fund its operations for at least the next twelve months.

(In thousands except share and per share amount)

2. Summary of significant accounting policies

Basis of presentation

The accompanying consolidated financial statements have been prepared in accordance with U.S. generally accepted accounting principles ("GAAP") and include all adjustments necessary for the fair presentation of the Company's financial position for the periods presented. Certain prior period balances have been reclassified to conform to the current period presentation. These reclassifications did not have a material impact on the consolidated statements of operations, consolidated balance sheets, consolidated statements of cash flows, or notes to the consolidated financial statements.

Use of estimates

The preparation of financial statements in conformity with GAAP requires management to make estimates and assumptions that affect the amounts reported in the financial statements and accompanying notes. Significant estimates in these consolidated financial statements have been made in connection with the calculation of net product sales, royalty revenue, certain accruals related to the Company's research and development expenses, valuation procedures for liability for sale of future royalties, valuation procedures for the convertible notes, indefinite lived intangible assets annual impairment assessment, fair value of the contingent consideration, and the provision for or benefit from income taxes. Actual results could differ from those estimates. Changes in estimates are reflected in reported results in the period in which they become known.

Restricted Cash

Restricted cash included in deposits and other assets on the consolidated balance sheet relates to an unconditional, irrevocable and transferable letter of credit that was entered into during the twelve-month period ended December 31, 2019 in connection with obligations under a facility lease for the Company's leased biologics manufacturing facility in Hopewell Township, New Jersey. The amount of the letter of credit is $7.5 million, is to be maintained for a term of not less than five years and has the potential to be reduced to $3.8 million if after five years the Company is not in default of its lease. The amount is classified within deposits and other assets on the consolidated balance sheet due to the long-term nature of the letter of credit.

The following table provides a reconciliation of cash, cash equivalents, and restricted cash reported within the consolidated balance sheet that sum to the total of the same amounts shown in the statement of cash flows:

	End of period- December 31, 2021	Beginning of period- December 31, 2020
Cash and cash equivalents	$ 189,718	$ 208,812
Restricted cash included in deposits and other assets	7,500	7,500
Total Cash, cash equivalents and restricted cash per statement of cash flows	$ 197,218	$ 216,312

Consolidation

The consolidated financial statements include the accounts of PTC Therapeutics, Inc. and its wholly owned subsidiaries. All inter-company accounts, transactions, and profits have been eliminated in consolidation.

Segment and geographic information

Operating segments are defined as components of an enterprise about which separate discrete information is available for evaluation by the chief operating decision maker, or decision making group, in deciding how to allocate resources and in assessing performance. The Company views its operations and manages its business in one operating and reporting segment.

Cash equivalents

The Company considers all highly liquid investments with a maturity of 90 days or less at the time of purchase to be cash equivalents. Cash equivalents are carried at cost which approximates fair value due to their short-term nature.

Marketable securities

The Company's marketable securities consists of both debt securities and equity investments. The Company considers its investments in debt securities with original maturities of greater than 90 days to be available for sale securities. Securities under this classification are recorded at fair value and unrealized gains and losses within accumulated other comprehensive income. The estimated fair value of the available for sale securities is determined based on quoted market prices or rates for similar instruments. In addition, the cost of debt securities in this category is adjusted for amortization of premium and accretion of discount to maturity. For available for sale debt securities in an unrealized loss position, the Company assesses whether it intends to sell or if it is more likely than not that the Company will be required to sell the security before recovery of its amortized cost basis. If either of the criteria regarding intent or requirement to sell is met, the security's amortized cost basis is written down to fair value. If the criteria are not met, the Company evaluates whether the decline in fair value has resulted from a credit loss or other factors. In making this assessment, management considers, among other factors, the extent to which fair value is less than amortized cost, any changes to the rating of the security by a rating agency, and adverse conditions specifically related to the security. If this assessment indicates that a credit loss exists, the present value of cash flows expected to be collected from the security are compared to the amortized cost basis of the security. If the present value of the cash flows expected to be collected is less than the amortized cost basis, a credit loss exists and an allowance for credit losses is recorded for the credit loss, limited by the amount that the fair value is less than the amortized costs basis. Any impairment that has not been recorded through an allowance for credit losses is recognized in other comprehensive income. For the years ended December 31, 2021 and 2020, no allowance was recorded for credit losses.

Marketable securities that are equity investments are measured at fair value, as it is readily available, and as such are classified as Level 1 assets. Unrealized holding gains and losses for these equity investments are components of other (expense) income, net within the consolidated statement of operations.

Concentration of credit risk

The Company's financial instruments that are exposed to credit risks consist primarily of cash and cash equivalents, available-for-sale marketable securities and accounts receivable. The Company maintains its cash and cash equivalents in bank accounts, which, at times, exceed federally insured limits. The Company has not experienced any credit losses in these accounts and does not believe it is exposed to any significant credit risk on these funds. The Company's investment policy includes guidelines on the quality of the financial institutions and financial instruments the Company is allowed to invest in, which the Company believes minimizes the exposure to concentration of credit risk.

(In thousands except share and per share amount)

The Company is subject to credit risk from its accounts receivable related to its product sales. The payment terms are predetermined and the Company evaluates the creditworthiness of each customer or distributor on a regular basis. The Company reserves all uninsured amounts billed directly to a patient until the time of cash receipt as collectability is not reasonably assured at the time the product is received. To date, the Company has not incurred any material credit losses.

Fixed assets

Fixed assets are stated at cost. Depreciation is computed starting when the asset is placed into service on a straight-line basis over the estimated useful life of the related asset as follows:

Leasehold improvements	Lesser of useful life or lease term
Computer equipment and software	3 years
Machinery and lab equipment	7 years
Furniture and fixtures	7 years

Inventory and cost of product sales

Inventory

Inventories are stated at the lower of cost and net realizable value with cost determined on a first-in, first-out basis by product. The Company capitalizes inventory costs associated with products following regulatory approval when future commercialization is considered probable and the future economic benefit is expected to be realized. Products which may be used in clinical development programs are included in inventory and charged to research and development expense when the product enters the research and development process and no longer can be used for commercial purposes. Inventory used for marketing efforts are charged to selling, general and administrative expense. Amounts related to clinical development programs and marketing efforts are immaterial.

The following table summarizes the components of the Company's inventory for the periods indicated:

	December 31, 2021	December 31, 2020
Raw materials	$ 1,418	$ 824
Work in progress	7,721	8,745
Finished goods	6,717	9,128
Total inventory	$ 15,856	$ 18,697

The Company periodically reviews its inventories for excess amounts or obsolescence and writes down obsolete or otherwise unmarketable inventory to its estimated net realizable value. The Company recorded write downs of $2.2 million and $0.5 million for the years ended December 31, 2021 and 2020, respectively, primarily related to product approaching expiration. Additionally, though the Company's product is subject to strict quality control and monitoring which it performs throughout the manufacturing processes, certain batches or units of product may not meet quality specifications resulting in a charge to cost of product sales. For the years ended December 31, 2021 and December 31, 2020, these amounts were immaterial.

Cost of product sales

Cost of product sales consists of the cost of inventory sold, manufacturing and supply chain costs, storage costs, amortization of the acquired intangible asset, royalty payments associated with net product sales, and royalty payments to

collaborative partners associated with royalty revenues and collaboration revenue related to milestones. Production costs are expensed as cost of product sales when the related products are sold or royalty revenues and collaboration revenue milestones are earned.

Accumulated other comprehensive income (loss)

Accumulated other comprehensive income (loss) consists of unrealized gains or losses on marketable securities and foreign currency translation adjustments.

Revenue recognition

Net product revenue

The Company's net product revenue primarily consists of sales of Translarna in territories outside of the U.S. for the treatment of nmDMD and sales of Emflaza in the U.S. for the treatment of DMD. The Company recognizes revenue when its performance obligations with its customers have been satisfied. The Company's performance obligations are to provide products based on customer orders from distributors, hospitals, specialty pharmacies or retail pharmacies. The performance obligations are satisfied at a point in time when the Company's customer obtains control of the product, which is typically upon delivery. The Company invoices its customers after the products have been delivered and invoice payments are generally due within 30 to 90 days of the invoice date. The Company determines the transaction price based on fixed consideration in its contractual agreements. Contract liabilities arise in certain circumstances when consideration is due for goods the Company has yet to provide. As the Company has identified only one distinct performance obligation, the transaction price is allocated entirely to product sales. In determining the transaction price, a significant financing component does not exist since the timing from when the Company delivers product to when the customers pay for the product is typically less than one year. Customers in certain countries pay in advance of product delivery. In those instances, payment and delivery typically occur in the same month.

The Company records product sales net of any variable consideration, which includes discounts, allowances, rebates related to Medicaid and other government pricing programs, and distribution fees. The Company uses the expected value or most likely amount method when estimating its variable consideration, unless discount or rebate terms are specified within contracts. The identified variable consideration is recorded as a reduction of revenue at the time revenues from product sales are recognized. These estimates for variable consideration are adjusted to reflect known changes in factors and may impact such estimates in the quarter those changes are known. Revenue recognized does not include amounts of variable consideration that are constrained. During the years ended December 31, 2021, 2020, and 2019, net product sales in the United States were $187.3 million, $139.0 million, and $101.0 million, respectively, consisting solely of sales of Emflaza, and net product sales outside of the United States were $241.6 million, $194.4 million, and $190.3 million respectively, consisting of sales of Translarna, Tegsedi, and Waylivra. Translarna net product revenues made up $236.0 million, $191.9 million, and $190.0 million of the net product sales outside of the United States for the years ended December 31, 2021, 2020, and 2019, respectively.

In relation to customer contracts, the Company incurs costs to fulfill a contract but does not incur costs to obtain a contract. These costs to fulfill a contract do not meet the criteria for capitalization and are expensed as incurred. The Company considers any shipping and handling costs that are incurred after the customer has obtained control of the product as a cost to fulfill a promise. Shipping and handling costs associated with finished goods delivered to customers are recorded as a selling expense.

Collaboration and royalty revenue

The terms of these agreements typically include payments to the Company of one or more of the following: nonrefundable, upfront license fees; milestone payments; research funding and royalties on future product sales. In addition, the Company generates service revenue through agreements that generally provide for fees for research and development services and may include additional payments upon achievement of specified events.

At the inception of a collaboration arrangement, the Company needs to first evaluate if the arrangement meets the criteria in Financial Accounting Standards Board ("FASB") Accounting Standards Codification ("ASC") Topic 808 "Collaborative Arrangements" to then determine if ASC Topic 606 is applicable by considering whether the collaborator meets the definition of a customer. If the criteria are met, the Company assesses the promises in the arrangement to identify distinct performance obligations.

For licenses of intellectual property, the Company assesses, at contract inception, whether the intellectual property is distinct from other performance obligations identified in the arrangement. If the licensing of intellectual property is determined to be distinct, revenue is recognized for nonrefundable, upfront license fees when the license is transferred to the customer and the customer can use and benefit from the license. If the licensing of intellectual property is determined not to be distinct, then the license will be bundled with other promises in the arrangement into one distinct performance obligation. The Company needs to determine if the bundled performance obligation is satisfied over time or at a point in time. If the Company concludes that the nonrefundable, upfront license fees will be recognized over time, the Company will need to assess the appropriate method of measuring proportional performance.

For milestone payments, the Company assesses, at contract inception, whether the development or sales-based milestones are considered probable of being achieved. If it is probable that a significant revenue reversal will occur, the Company will not record revenue until the uncertainty has been resolved. Milestone payments that are contingent upon regulatory approval are not considered probable of being achieved until the applicable regulatory approvals or other external conditions are obtained as such conditions are not within the Company's control. If it is probable that a significant revenue reversal will not occur, the Company will estimate the milestone payments using the most likely amount method. The Company will re-assess the development and sales-based milestones each reporting period to determine the probability of achievement. The Company recognizes royalties from product sales at the later of when the related sales occur or when the performance obligation to which the royalty has been allocated has been satisfied. If it is probable that a significant revenue reversal will not occur, the Company will estimate the royalty payments using the most likely amount method.

The Company recognizes revenue for reimbursements of research and development costs under collaboration agreements as the services are performed. The Company records these reimbursements as revenue and not as a reduction of research and development expenses as the Company has the risks and rewards as the principal in the research and development activities.

For the years ended December 31, 2021, 2020, and 2019, the Company has recognized $55.0 million, $42.6 million, and $15.2 million of collaboration revenue, respectively, related to the SMA License Agreement with Roche.

For the years ended December 31, 2021 and 2020, the Company has recognized $54.6 million and $4.8 million of royalty revenue, respectively, related to Evrysdi. No royalty revenue was recognized in 2019, as the first commercial sale of Evrysdi occurred in August 2020.

Allowance for doubtful accounts

The Company maintains an allowance for estimated losses resulting from the inability of its customers to make required payments. The Company estimates uncollectible amounts based upon current customer receivable balances, the age of customer receivable balances, the customer's financial condition and current economic trends. The Company also assesses whether an allowance for expected credit losses may be required which includes a review of the Company's receivables portfolio, which are pooled on a customer basis or country basis. In making its assessment of whether an allowance for credit losses is required, the Company considers its historical experience with customers, current balances, levels of delinquency, regulatory and legal environments, and other relevant current and future forecasted economic conditions. For the years ended December 31, 2021 and 2020, no allowance was recorded for credit losses. The allowance for doubtful accounts was $0.1 million as of December 31, 2021 and $0.1 million as of December 31, 2020. For the years ended December 31, 2021, 2020 and 2019, bad debt expense was immaterial.

Liability for sale of future royalties

On July 17, 2020, the Company, RPI Intermediate Finance Trust ("RPI"), and, for the limited purposes set forth in the agreement, Royalty Pharma PLC, entered into a Royalty Purchase Agreement (the "Royalty Purchase Agreement"). Pursuant to the Royalty Purchase Agreement, the Company sold to RPI 42.933% (the "Assigned Royalty Payment") of the Company's right to receive sales-based royalty payments (the "Royalty") on worldwide net sales of Evrysdi and any other product developed pursuant to the License and Collaboration Agreement (the "License Agreement"), dated as of November 23, 2011, by and among the Company, Roche and, for the limited purposes set forth therein, the SMA Foundation under the SMA program. In consideration for the sale of the Assigned Royalty Payments, RPI paid the Company $650.0 million in cash consideration. The Company has retained a 57.067% interest in the Royalty and all economic rights to receive the remaining potential regulatory and sales milestone payments under the License Agreement, which remaining milestone payments equal $300.0 million in the aggregate as of December 31, 2021. The Royalty Purchase Agreement will terminate 60 days following the earlier of the date on which Roche is no longer obligated to make any payments of the Royalty pursuant to the License Agreement and the date on which RPI has received $1.3 billion in respect of the Assigned Royalty Payments.

The cash consideration obtained pursuant to the Royalty Purchase Agreement is classified as debt and is recorded as "liability for sale of future royalties-current" and "liability for sale of future royalties-noncurrent" on the Company's consolidated balance sheet based on the timing of the expected payments to be made to RPI. The fair value for the liability for sale of future royalties at the time of the transaction was based on the Company's estimates of future royalties expected to be paid to RPI over the life of the arrangement, which was determined using forecasts from market data sources, which are considered Level 3 inputs. The liability will be amortized using the effective interest method over the life of the arrangement, in accordance with the respective guidance. The Company will utilize the prospective method to account for subsequent changes in the estimated future payments to be made to RPI. Refer to Note 8 for further details.

Leases

The Company determines if an arrangement is a lease at inception. This determination generally depends on whether the arrangement conveys to the Company the right to control the use of an explicitly or implicitly identified fixed asset for a period of time in exchange for consideration. Control of an underlying asset is conveyed to the Company if the Company obtains the rights to direct the use of and to obtain substantially all of the economic benefits from using the underlying asset. The Company has lease agreements which include lease and non-lease components, which the Company accounts for as a single lease component for all leases. Operating and finance leases are classified as right of use ("ROU") assets, short term lease liabilities, and long term lease liabilities. Operating and finance lease ROU assets and lease liabilities are

recognized at the commencement date based on the present value of lease payments over the lease term. ROU assets are amortized and lease liabilities accrete to yield straight-line expense over the term of the lease. Lease payments included in the measurement of the lease liability are comprised of fixed payments.

Variable lease payments associated with the Company's leases are recognized when the event, activity, or circumstance in the lease agreement on which those payments are assessed occurs. Variable lease payments are presented in the Company's consolidated statements of operations in the same line item as expense arising from fixed lease payments for operating leases.

Leases with an initial term of 12 months or less are not recorded on the consolidated balance sheet and the Company recognizes lease expense for these leases on a straight-line basis over the lease term. The Company applies this policy to all underlying asset categories.

A lessee is required to discount its unpaid lease payments using the interest rate implicit in the lease or, if that rate cannot be readily determined, its incremental borrowing rate. As most of the Company's leases do not provide an implicit rate, the Company uses its incremental borrowing rate based on the information available at the commencement date in determining the present value of lease payments. The Company gives consideration to its recent debt issuances as well as publicly available data for instruments with similar characteristics when calculating its incremental borrowing rates.

The lease term for all of the Company's leases includes the non-cancellable period of the lease plus any additional periods covered by either a Company option to extend (or not to terminate) the lease that the Company is reasonably certain to exercise, or an option to extend (or not to terminate) the lease controlled by the lessor. Leasehold improvements are capitalized and depreciated over the lesser of useful life or lease term. See Note 6 Leases for additional information.

Research and development costs

Research and development expenses include the clinical development costs associated with the Company's product development programs and research and development costs associated with the Company's discovery programs. These expenses include internal research and development costs and the costs of research and development conducted on behalf of the Company by third parties, including sponsored university-based research agreements and clinical study vendors. All research and development costs are expensed as incurred. Costs incurred in obtaining technology licenses are charged immediately to research and development expense if the technology licensed has not reached technological feasibility and has no alternative future uses.

Advance payments made for goods and services that will be used in future research and development activities are deferred if the contracted party has not yet performed the related activities. The amount deferred is then recognized as expense when the research and development activities are performed. The short term deferred research and development advance payments were $1.4 million and $4.7 million and are classified as prepaid expenses and other current assets on the consolidated balance sheet as of December 31, 2021 and 2020, respectively. The long term deferred research and development advance payments were $1.8 million and $1.6 million and are classified as deposits and other assets on the consolidated balance sheet as of December 31, 2021 and 2020, respectively.

Fair value of financial instruments

The Company follows the fair value measurement rules, which provides guidance on the use of fair value in accounting and disclosure for assets and liabilities when such accounting and disclosure is called for by other accounting literature. These rules establish a fair value hierarchy for inputs to be used to measure fair value of financial assets and liabilities.

This hierarchy prioritizes the inputs to valuation techniques used to measure fair value into three levels: Level 1 (highest priority), Level 2, and Level 3 (lowest priority).

- Level 1—Unadjusted quoted prices in active markets for identical assets or liabilities that the Company has the ability to access at the balance sheet date.

- Level 2—Inputs other than quoted prices included within Level 1 that are observable for the asset or liability, either directly or indirectly. Level 2 inputs include quoted prices for similar assets and liabilities in active markets, quoted prices for identical or similar assets or liabilities in markets that are not active, inputs other than quoted prices that are observable for the asset or liability (i.e., interest rates, yield curves, etc.), and inputs that are derived principally from or corroborated by observable market data by correlation or other means (market corroborated inputs).

- Level 3—Inputs are unobservable and reflect the Company's assumptions as to what market participants would use in pricing the asset or liability. The Company develops these inputs based on the best information available.

Cash equivalents, marketable securities, and equity investments are reflected in the accompanying financial statements at fair value. The carrying amount of receivables and accounts payable and accrued expenses approximates fair value due to the short-term nature of those instruments.

Share-based compensation

The Company measures the cost of employee services received in exchange for an award of equity instruments based on the grant date fair value of the award. Restricted stock awards are measured based on the fair market values of the underlying stock on the dates of grant. For service type awards, share-based compensation expense is recognized on a straight-line basis over the period during which the employee is required to provide service in exchange for the entire award. For awards that vest or begin vesting upon achievement of a performance condition, the Company estimates the likelihood of satisfaction of the performance condition and recognizes compensation expense when achievement of the performance condition is deemed probable using an accelerated attribution model.

The fair value of options is calculated using the Black-Scholes option pricing model to determine the fair value of stock options on the date of grant based on key assumptions such as expected volatility and expected term. The Company historically estimated the expected volatility of share options based on a historical volatility analysis of peers that were similar to the Company with respect to industry, stage of life cycle, size, and financial leverage. Starting in the third quarter of 2019 and continuing forward, the expected volatility of options was estimated based on the Company's historical stock volatility. The Company historically used the "simplified method" to determine the expected term of options. Under this method, the expected term represents the average of the vesting period and the contractual term. Starting in the third quarter of 2019 and continuing forward, the expected term of options was estimated based on the Company's historical exercise data. The risk-free rate of the option is based on U.S. Government Securities Treasury Constant Maturities yields at the date of grant for a term similar to the expected term of the option. In connection with the adoption of FASB Accounting Standards Update ("ASU") 2016-9, the Company made a policy election to continue its methodology for estimating its forfeiture rate.

Income taxes

On March 27, 2020, the United States enacted the Coronavirus Aid, Relief, and Economic Security Act, referred to herein as the CARES Act, as a response to the economic uncertainty resulting from a strain of novel coronavirus, COVID-19. The CARES Act includes modifications for net operating loss carryovers and carrybacks, limitations of business interest expense for tax, immediate refund of alternative minimum tax ("AMT") credit carryovers as well as a technical correction to the 2017 Tax Cuts and Jobs Act ("the 2017 Tax Act") for qualified improvement property. On December 27, 2020, the Coronavirus Response and Relief Supplemental Appropriations Act of 2021 – a $900 billion relief package to deliver the second round of economic stimulus for individuals, families, and businesses was signed into law. The bill provides relief through multiple measures and expands many of the provisions already put into place under the CARES Act. As of December 31, 2021, the Company expects that these provisions will not have a material impact. Tax provisions of the CARES Act also include the deferral of certain payroll taxes, relief for retaining employees, and other provisions. The relief for retaining employees was not material to the financial statements and the deferral of certain payroll taxes amounted to $1.3 million as of December 31, 2021, which is accrued in other current liabilities on the consolidated balance sheet.

Additionally, the Organization for Economic Co-operation and Development, or OECD, the EC, and individual taxing jurisdictions where the Company and its affiliates do business have recently focused on issues related to the taxation of multinational corporations. The OECD has released its comprehensive plan to create an agreed set of international rules for fighting base erosion and profit shifting. In addition, the OECD, the EC and individual counties are examining changes to how taxing rights should be allocated among countries considering the digital economy. As a result, the tax laws in the U.S. and other countries in which PTC and its affiliates do business could change on a prospective or retroactive basis and any such changes could materially adversely affect the Company's business.

On December 22, 2017, the U.S. government enacted the 2017 Tax Act, which significantly revises U.S. tax law by, among other provisions, lowering the U.S. federal statutory income tax rate to 21%, imposing a mandatory one-time transition tax on previously deferred foreign earnings, and eliminating or reducing certain income tax deductions. The Global Intangible Low-tax Income ("GILTI") provisions of the 2017 Tax Act require the Company to include in its U.S. income tax return foreign subsidiary earnings in excess of an allowable return on the foreign subsidiary's tangible assets. The Company has elected to account for GILTI tax in the period in which it is incurred, and therefore has not provided any deferred tax impacts of GILTI in its consolidated financial statements for the period ended December 31, 2021.

In December 2017, the SEC staff issued Staff Accounting Bulletin No. 118, Income Tax Accounting Implications of the Tax Cuts and Jobs Act (SAB 118), which allowed the Company to record provisional amounts during a measurement period not to extend beyond one year of the enactment date. As a result of the reduction in the U.S. corporate income tax rate, the Company revalued its ending net deferred tax assets as of December 31, 2017. In the fourth quarter of 2018, the Company completed its analysis to determine the effect of the Tax Act and recorded no further adjustments.

Deferred tax assets and liabilities are recognized for the future tax consequences attributable to differences between the financial statement carrying amounts of existing assets and liabilities and their respective tax bases and net operating loss and credit carryforwards. Deferred tax assets and liabilities are measured at rates expected to apply to taxable income in the years in which those temporary differences and carryforwards are expected to be recovered or settled. The effect on deferred tax assets and liabilities of a change in tax rates is recognized in the statement of operations in the period that includes the enactment date. A valuation allowance is recorded when it is not more likely than not that all or a portion of the net deferred tax assets will be realized.

On August 23, 2018, the Company completed its acquisition of Agilis Biotherapeutics, Inc. ("Agilis"), pursuant to an Agreement and Plan of Merger, dated as of July 19, 2018 (the "Agilis Merger Agreement"), by and among the Company, Agility Merger Sub, Inc., a Delaware corporation and the Company's wholly owned, indirect subsidiary, Agilis and, solely in its capacity as the representative, agent and attorney-in-fact of the equityholders of Agilis, Shareholder Representative Services LLC, (the "Agilis Merger"). The Company recorded a deferred tax liability in conjunction with the Agilis Merger of $122.0 million in 2018, related to the tax basis difference in the In-Process Research and Development, or IPR&D, indefinite-lived intangibles acquired. The Company's policy is to record a deferred tax liability related to acquired IPR&D which may eventually be realized either upon amortization of the asset when the research is completed and a product is successfully launched or the write-off of the asset if it is abandoned or unsuccessful.

Foreign currency

The functional currencies of the Company's foreign subsidiaries primarily are the local currencies of the country in which the subsidiary operates. The Company also has an intercompany loan which is recorded on a non-U.S. subsidiary and denominated in U.S. dollars. The loan is remeasured into local currency using the exchange rate as of the balance sheet date. The Company's asset and liability accounts, including the intercompany loan, are translated using the current exchange rate as of the balance sheet date. Stockholders' equity accounts are translated using historical rates at the balance sheet date. Revenue and expense accounts are translated using a weighted average exchange rate over the period ended on the balance sheet date. Adjustments resulting from the translation of the financial statements of the Company's foreign subsidiaries into U.S. dollars are accumulated as a separate component of stockholders' equity within other comprehensive income. Gains or losses resulting from transactions denominated in foreign currencies are included in other income or expense, within the consolidated statements of income. For the year ended December 31, 2021, the Company recorded an unrealized foreign exchange loss of $41.0 million from the remeasurement of the intercompany loan.

Net (loss) income per share

Basic net (loss) income per share is calculated by dividing the net (loss) income attributable to common stockholders by the weighted average number of common shares outstanding for the period, without consideration for common stock equivalents. Diluted net income per share is calculated by dividing the net income attributable to common stockholders by the weighted-average number of common share equivalents outstanding for the period determined using the treasury-stock method and the if-converted method. During periods in which the Company incurs net losses, both basic and diluted loss per share is calculated by dividing the net loss by the weighted average shares outstanding—potentially dilutive securities are excluded from the calculation because their effect would be anti-dilutive. Dilutive common stock equivalents are comprised of options and unvested restricted stock outstanding under the Company's stock option plans.

Business combinations and asset acquisitions

The Company evaluates acquisitions of assets and other similar transactions to assess whether or not the transaction should be accounted for as a business combination or asset acquisition by first applying a screen to determine if substantially all of the fair value of the gross assets acquired is concentrated in a single identifiable asset or group of similar identifiable assets. If the screen is met, the transaction is accounted for as an asset acquisition. If the screen is not met, further determination is required as to whether or not the Company has acquired inputs and processes that have the ability to create outputs, which would meet the requirements of a business. If determined to be a business combination, the Company accounts for the transaction under the acquisition method of accounting as indicated in ASU 2017-01, "Business Combinations", which requires the acquiring entity in a business combination to recognize the fair value of all assets acquired, liabilities assumed, and any non-controlling interest in the acquiree and establishes the acquisition date as the fair value measurement point. Accordingly, the Company recognizes assets acquired and liabilities assumed in business

combinations, including contingent assets and liabilities, and non-controlling interest in the acquiree based on the fair value estimates as of the date of acquisition. In accordance with ASC 805, the Company recognizes and measures goodwill as of the acquisition date, as the excess of the fair value of the consideration paid over the fair value of the identified net assets acquired.

The consideration for the Company's business acquisitions may include future payments that are contingent upon the occurrence of a particular event or events. The obligations for such contingent consideration payments are recorded at fair value on the acquisition date. The contingent consideration obligations are then evaluated each reporting period. Changes in the fair value of contingent consideration, other than changes due to payments, are recognized as a gain or loss and recorded within the change in the fair value of deferred and contingent consideration in the consolidated statements of operations.

If determined to be an asset acquisition, the Company accounts for the transaction under ASC 805-50, which requires the acquiring entity in an asset acquisition to recognize assets acquired and liabilities assumed based on the cost to the acquiring entity on a relative fair value basis, which includes transaction costs in addition to consideration given. No gain or loss is recognized as of the date of acquisition unless the fair value of noncash assets given as consideration differs from the assets' carrying amounts on the acquiring entity's books. Consideration transferred that is noncash will be measured based on either the cost (which will be measured based on the fair value of the consideration given) or the fair value of the assets acquired and liabilities assumed, whichever is more reliably measurable. Goodwill is not recognized in an asset acquisition and any excess consideration transferred over the fair value of the net assets acquired is allocated to the identifiable assets based on relative fair values.

Contingent consideration payments in asset acquisitions are recognized when the contingency is resolved and the consideration is paid or becomes payable (unless the contingent consideration meets the definition of a derivative, in which case the amount becomes part of the basis in the asset acquired). Upon recognition of the contingent consideration payment, the amount is included in the cost of the acquired asset or group of assets.

Finite-lived intangible assets

The Company records the fair value of purchased intangible assets with finite useful lives as of the transaction date of a business combination or asset acquisition. Purchased intangible assets with finite useful lives are amortized to their estimated residual values over their estimated useful lives.

Impairment of long-lived assets

The Company monitors its long-lived assets and finite-lived intangibles for indicators of impairment. If such indicators are present, the Company assesses the recoverability of affected assets by determining whether the carrying value of such assets is less than the sum of the undiscounted future cash flows of the assets. If such assets are found not to be recoverable, the Company measures the amount of such impairment by comparing the carrying value of the assets to the fair value of the assets, with the fair value generally determined based on the present value of the expected future cash flows associated with the assets. The Company believes that no impairment of long-lived assets exists as of December 31, 2021.

Indefinite-lived intangible assets

Indefinite-lived intangible assets consist of IPR&D. IPR&D acquired directly in a transaction other than a business combination is capitalized if the projects will be further developed or have an alternative future use; otherwise they are expensed. The fair values of IPR&D projects and license agreement assets acquired in business combinations are

capitalized. Several methods may be used to determine the estimated fair value of the IPR&D and license agreement asset acquired in a business combination. The Company utilizes the "income method" and uses estimated future net cash flows that are derived from projected sales revenues and estimated costs. These projections are based on factors such as relevant market size, patent protection, and expected pricing and industry trends. The estimated future net cash flows are then discounted to the present value using an appropriate discount rate. These assets are treated as indefinite-lived intangible assets until completion or abandonment of the projects, at which time the assets are amortized over the remaining useful life or written off, as appropriate. Intangible assets with indefinite lives, including IPR&D, are tested for impairment if impairment indicators arise and, at a minimum, annually. However, an entity is permitted to first assess qualitative factors to determine if a quantitative impairment test is necessary. Further testing is only required if the entity determines, based on the qualitative assessment, that it is more likely than not that an indefinite-lived intangible asset's fair value is less than its carrying amount. Otherwise, no further impairment testing is required. The indefinite-lived intangible asset impairment test consists of a one-step analysis that compares the fair value of the intangible asset with its carrying amount. If the carrying amount of an intangible asset exceeds its fair value, an impairment loss is recognized in an amount equal to that excess. The Company considers many factors in evaluating whether the value of its intangible assets with indefinite lives may not be recoverable, including, but not limited to, expected growth rates, the cost of equity and debt capital, general economic conditions, the Company's outlook and market performance of the Company's industry and recent and forecasted financial performance. The Company performed a quantitative annual test for its indefinite-lived intangible assets as of October 1, 2021 and concluded that no impairment exists as of December 31, 2021.

Goodwill

Goodwill represents the amount of consideration paid in excess of the fair value of net assets acquired as a result of the Company's business acquisitions accounted for using the acquisition method of accounting. Goodwill is not amortized and is subject to impairment testing at a reporting unit level on an annual basis or when a triggering event occurs that may indicate the carrying value of the goodwill is impaired. The Company reassess its reporting units as part of its annual segment review. As of December 31, 2021, the Company concluded that it continues to operate as one reporting unit. An entity is permitted to first assess qualitative factors to determine if a quantitative impairment test is necessary. Further testing is only required if the entity determines, based on the qualitative assessment, that it is more likely than not that the fair value of the reporting unit is less than its carrying amount. The Company performed an annual test for goodwill as of October 1, 2021 and concluded that no impairment exists as of December 31, 2021.

Impact of recently adopted accounting pronouncements

In August 2020, the FASB issued ASU 2020-06, "Debt—Debt with Conversion and Other Options (Subtopic 470-20) and Derivatives and Hedging—Contracts in Entity's Own Equity (Subtopic 815-40): Accounting for Convertible Instruments and Contracts in an Entity's Own Equity." ASU 2020-06 simplifies the accounting for convertible instruments by removing certain separation models in Subtopic 470- 20, Debt—Debt with Conversion and Other Options, for convertible instruments. Under ASU 2020-06, the embedded conversion features no longer are separated from the host contract for convertible instruments with conversion features that are not required to be accounted for as derivatives under Topic 815, Derivatives and Hedging, or that do not result in substantial premiums accounted for as paid-in capital. Consequently, a convertible debt instrument will be accounted for as a single liability measured at its amortized cost and a convertible preferred stock will be accounted for as a single equity instrument measured at its historical cost, as long as no other features require bifurcation and recognition as derivatives. By removing those separation models, the interest rate of convertible debt instruments typically will be closer to the coupon interest rate when applying the guidance in Topic 835, Interest. The amendments under ASU 2020-06 also include revisions related to the derivatives scope exception for contracts in an entity's own equity and earnings per share. The amendments under ASU 2020-06 are effective for public business entities that meet the definition of a SEC filer, excluding entities eligible to be smaller reporting companies as

defined by the SEC, for fiscal years beginning after December 15, 2021, including interim periods within those fiscal years. For all other entities, the amendments are effective for fiscal years beginning after December 15, 2023, including interim periods within those fiscal years. Early adoption is permitted, but no earlier than fiscal years beginning after December 15, 2020, including interim periods within those fiscal years. The FASB specified that an entity should adopt the guidance as of the beginning of its annual fiscal year. The Company early adopted this guidance on January 1, 2021, utilizing the modified retrospective method. The Company now accounts for its Convertible Notes as single liabilities measured at amortized cost. As a result, the adoption of the guidance had a material impact on the consolidated financial statements and accompanying notes, resulting in adjustments of $175.2 million, $54.8 million, and $120.4 million to the opening balances of additional paid-in capital, retained earnings, and long term debt, respectively, as of January 1, 2021. Additionally, due to the adoption, the Company reversed the remaining balance of the deferred tax liability of $29.6 million which was initially recorded in connection with the Convertible Notes. Additionally, the Company increased the existing valuation allowance by $29.6 million as part of the adoption adjustment. The Company concluded that the adoption of the ASU did not change its prior valuation allowance conclusions. The Company has updated its debt note (Note 8) with additional and modified disclosures as required by the standard upon adoption.

3. Acquisitions

Censa Asset Acquisition

On May 29, 2020, the Company completed its acquisition of Censa Pharmaceuticals, Inc. (“Censa”) pursuant to an Agreement and Plan of Merger, dated as of May 5, 2020 (the "Censa Merger Agreement"), by and among the Company, Hydro Merger Sub, Inc., the Company’s wholly owned, indirect subsidiary, and, solely in its capacity as the representative, agent and attorney-in-fact of the securityholders of Censa, Shareholder Representative Services LLC (the "Censa Merger").

Upon the closing of the Censa Merger, the Company paid to the Censa securityholders (i) cash consideration of $15.0 million, which consisted of an upfront payment of $10.4 million and an additional $4.6 million for the net assets on Censa’s opening balance sheet as of the date of the acquisition, and (ii) 845,364 shares of the Company’s common stock, which were valued at $42.9 million based on the closing stock price on the acquisition date. The number of shares issued was determined using a 30-day volume weighted average price (“VWAP”) pursuant to the Censa Merger Agreement.

The Company determined that substantially all of the fair value is concentrated in PTC923 and accounted for the transaction as an asset acquisition under ASC 805-50. The purchase price consisted of the cash consideration of $15.0 million and $42.9 million in the Company’s common stock, in addition to $0.7 million of acquisition costs. As such, the total consideration transferred was determined to be $58.6 million. The opening balance sheet net assets of $4.6 million, which consisted of cash of $3.8 million and other current assets of $0.8 million, were determined to be non-qualifying assets and recorded at their fair values, respectively. The remaining consideration of $54.0 million was allocated to PTC923. As PTC923 is an IPR&D asset, the Company concluded that it did not have any alternative future use, and accordingly, the fair value amount allocated to the IPR&D was expensed. Of the $54.0 million, $53.3 million is included in research and development expense and the $0.7 million related to the acquisition costs, is included in selling, general, and administrative expense within the Company’s statement of operations for the year ended December 31, 2020.

Subject to the terms and conditions of the Censa Merger Agreement, Censa securityholders may become entitled to receive contingent payments from the Company based on (i) the achievement of certain development and regulatory milestones up to an aggregate maximum amount of $217.5 million for PTC923’s two most advanced programs and receipt of a priority review voucher from the FDA as set forth in the Censa Merger Agreement, (ii) $109.0 million in development and regulatory milestones for each additional indication of PTC923, (iii) the achievement of certain net sales milestones

up to an aggregate maximum amount of $160.0 million, (iv) a percentage of annual net sales during specified terms, ranging from single to low double digits of the applicable net sales threshold amount, and (v) any sublicense fees paid to the Company in consideration of any sublicense of Censa's intellectual property to commercialize PTC923, on a country-by-country basis, which contingent payment will equal to a mid-double digit percentage of any such sublicense fees. Pursuant to the Censa Merger Agreement, the Company has the option to pay the initial $30.0 million development milestone, for the completion of enrollment of a Phase 3 clinical trial for PTC923 for PKU, if achieved, in cash or shares of the Company's common stock. The Company will record the milestone and royalty payments when they become payable. Milestone payments prior to FDA approval of PTC923 for PKU (or other indications) will be expensed accordingly and milestone payments that will only occur after PTC923 for PKU (or other indications) is FDA approved, will be capitalized and amortized over their expected useful lives.

BioElectron Asset Acquisition

On October 25, 2019, the Company completed the acquisition of substantially all of the assets of BioElectron Technology Corporation ("BioElectron"), a Delaware corporation, including certain compounds that the Company has begun to develop as part of its Bio-e platform, (the "Asset Acquisition") pursuant to an asset purchase agreement by and between the Company and BioElectron, dated October 1, 2019 (the "BioElectron Asset Purchase Agreement"). BioElectron was a private company with a pipeline focused on inflammatory and central nervous system (CNS) disorders. The lead program, vatiquinone, is in late stage development for CNS disorders with substantial unmet need and significant commercial opportunity that are complementary to PTC's existing pipeline.

Upon the closing of the Asset Acquisition, the Company paid to BioElectron total upfront consideration of $10.0 million, funded with cash on hand, less (i) transaction expenses incurred by BioElectron, (ii) the amount of outstanding indebtedness of BioElectron including a $4.0 million loan advance to BioElectron plus accrued and unpaid interest thereon and (iii) $1.5 million held in an escrow account to secure potential indemnification obligations owed to the Company. Subject to the terms and conditions of the BioElectron Asset Purchase Agreement, BioElectron may become entitled to receive contingent milestone payments of up to $200.0 million (in cash or in shares of the Company's common stock, as determined by the Company) from the Company based on the achievement of certain regulatory and net sales milestones. Subject to the terms and conditions of the BioElectron Asset Purchase Agreement, BioElectron may also become entitled to contingent payments based on a percentage of net sales of certain products.

The Company concluded that the transaction included inputs and processes that did not constitute a business under the revised guidance of ASU 2017-01, which allows for a screen to evaluate if substantially all of the fair value of the gross assets acquired is concentrated in a single identifiable asset or group of similar identifiable assets. If the screen is met, the transaction is accounted for as an asset acquisition. The Company determined that substantially all of the fair value is concentrated in vatiquinone and accounted for the transaction as an asset acquisition under ASC 805-50.

The purchase price consisted of upfront consideration of $10.0 million in cash and approximately $0.5 million of acquisition costs, resulting in $10.5 million of total consideration transferred. As vatiquinone is an IPR&D asset, the Company concluded that it did not have any alternative future use, and accordingly, the fair value amount allocated to the IPR&D asset of $10.0 million was expensed to research and development during the year ended December 31, 2019 and included within operating activities in the statement of cash flows. The remaining assets acquired and liabilities assumed were immaterial. Additionally, as noted above, BioElectron may be entitled to receive contingent milestone payment and contingent royalty payments. The Company will record the milestone and royalty payments if and when they become payable, in accordance with the applicable guidance. These payments will be capitalized and amortized over their expected useful lives.

4. Fair value of financial instruments and investments

The Company follows the fair value measurement rules, which provide guidance on the use of fair value in accounting and disclosure for assets and liabilities when such accounting and disclosure is called for by other accounting literature. Cash equivalents, marketable securities, and equity investments are reflected in the accompanying financial statements at fair value. The carrying amount of receivables and accounts payable and accrued expenses approximate fair value due to the short-term nature of those instruments.

The Company uses the market approach to measure fair value for its marketable securities. The market approach uses prices and other relevant information generated by market transactions involving identical or comparable assets. The Company's marketable securities are classified as Level 2 as they primarily utilize broker quotes in a nonactive market to value these securities.

In May 2019, the Company purchased $4.0 million of shares of ClearPoint Neuro, Inc.'s ("ClearPoint") (formerly MRI Interventions, Inc.) common stock, at a purchase price of $3.10 per share, in connection with a securities purchase agreement that the Company entered into with ClearPoint, a publicly traded medical device company. In February 2021, the Company purchased $0.1 million of shares of ClearPoint's common stock, at a purchase price of $23.50 per share, in connection with ClearPoint's underwritten public offering of common stock. The Company determined that the May 2019 and February 2021 ClearPoint equity investments (collectively, the "ClearPoint Equity Investments") represent financial instruments, and therefore, are recorded at fair value, which is readily determinable. The ClearPoint Equity Investments are components of deposits and other assets on the consolidated balance sheet. During the year ended December 31, 2021 and 2020, the Company recorded an unrealized loss of $6.1 million and an unrealized gain of $14.3 million respectively, which are components of other (expense) income, net within the consolidated statement of operations. The fair value of the equity investments was $14.5 million and $20.5 million as of December 31, 2021 and 2020, respectively. The Company classifies its equity investments in ClearPoint as a Level 1 asset within the fair value hierarchy, as the value is based on a quoted market price in an active market, which is not adjusted.

In January 2020, the Company purchased a $10.0 million convertible note from ClearPoint that the Company can convert into ClearPoint shares at a conversion rate of $6.00 per share at any point throughout the term of the loan, which matures five years from the purchase date. The Company determined that the convertible note represents an available for sale debt security and the Company has elected to record it at fair value under ASC 825. The Company classifies its ClearPoint convertible debt security as a Level 2 asset within the fair value hierarchy, as the value is based on inputs other than quoted prices that are observable. The fair value of the ClearPoint convertible debt security is determined at each reporting period by utilizing a Black-Scholes option pricing model, as well as a present value of expected cash flows from the debt security utilizing the risk free rate and the estimated credit spread as of the valuation date as the discount rate. During the year ended December 31, 2021 and 2020, the Company recorded an unrealized loss of $8.3 million and an unrealized gain of $19.3 million, respectively. These unrealized gains and losses are components of other (expense) income, net within the consolidated statement of operations. The fair value of the convertible debt security was $21.0 million and $29.3 million as of December 31, 2021 and 2020, respectively. The convertible debt security is considered to be long term and is included as a component of deposits and other assets on the consolidated balance sheet. Other than the equity investment and the convertible debt security, no other items included in deposits and other assets on the consolidated balance sheets are fair valued.

In February 2021, the Company invested $200.0 million in two mutual funds. In August 2021 and November 2021, the Company made a $5.4 million and $4.6 million investment into a third mutual fund that is denominated in a foreign currency, respectively. All of these are equity investments and are classified as marketable securities on the Company's consolidated balance sheets. These equity investments are reported at fair value, as it is readily available, and as such are

(In thousands except share and per share amount)

classified as Level 1 assets. Unrealized holding gains and losses for these equity investments are included as components of other (expense) income, net within the consolidated statement of operations. During the year ended December 31, 2021, the Company had $1.7 million unrealized net gains relating to the equity investments still held at the reporting date. During the year ended December 31, 2021, the Company had redemptions of $4.3 million. During the year ended December 31, 2021, the Company had $0.4 million foreign currency unrealized losses relating to these equity investments.

Fair value of marketable securities that are classified as available for sale debt securities is based upon market prices using quoted prices in active markets for identical assets quoted on the last day of the period. In establishing the estimated fair value of the remaining available for sale debt securities, the Company used the fair value as determined by its investment advisors using observable inputs other than quoted prices.

The following represents the fair value using the hierarchy described in Note 2 for the Company's financial assets and liabilities that are required to be measured at fair value on a recurring basis as of December 31, 2021 and 2020:

	December 31, 2021			
	Total	Quoted prices in active markets for identical assets (level 1)	Significant other observable inputs (level 2)	Significant unobservable inputs (level 3)
Marketable securities - available for sale	$ 376,685	$ —	$ 376,685	$ —
Marketable securities - equity investments	$ 206,973	$ 206,973	$ —	$ —
ClearPoint Equity Investments	$ 14,525	$ 14,525	$ —	$ —
ClearPoint convertible debt security	$ 20,971	$ —	$ 20,971	$ —
Contingent consideration payable- development and regulatory milestones	$ 139,300	$ —	$ —	$ 139,300
Contingent consideration payable- net sales milestones and royalties	$ 100,600	$ —	$ —	$ 100,600

	December 31, 2020			
	Total	Quoted prices in active markets for identical assets (level 1)	Significant other observable inputs (level 2)	Significant unobservable inputs (level 3)
Marketable securities - available for sale	$ 894,838	$ —	$ 894,838	$ —
ClearPoint Equity Investments	$ 20,503	$ 20,503	$ —	$ —
ClearPoint convertible debt security	$ 29,252	$ —	$ 29,252	$ —
Contingent consideration payable- development and regulatory milestones	$ 139,200	$ —	$ —	$ 139,200
Contingent consideration payable- net sales milestones and royalties	$ 101,200	$ —	$ —	$ 101,200

No transfers of assets between Level 1 and Level 2 of the fair value measurement hierarchy occurred during the years ended December 31, 2021 and 2020.

(In thousands except share and per share amount)

The following is a summary of marketable securities accounted for as available for sale debt securities at December 31, 2021 and 2020:

	December 31, 2021			
	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Fair Value
Commercial paper	$ 75,275	5	(1)	75,279
Corporate debt securities	268,246	81	(644)	267,683
Asset-backed securities	15,287	16	(5)	15,298
Government obligations	18,479	5	(59)	18,425
Total	$ 377,287	$ 107	$ (709)	$ 376,685

	December 31, 2020			
	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Fair Value
Commercial paper	$ 276,855	$ 19	$ (37)	$ 276,837
Corporate debt securities	474,030	1,658	(29)	475,659
Asset-backed securities	28,681	210	(3)	28,888
Government obligations	113,372	88	(6)	113,454
Total	$ 892,938	$ 1,975	$ (75)	$ 894,838

For available for sale debt securities in an unrealized loss position, the Company assesses whether it intends to sell or if it is more likely than not that the Company will be required to sell the security before recovery of its amortized cost basis. If either of the criteria regarding intent or requirement to sell is met, the security's amortized cost basis is written down to fair value. For the years ended December 31, 2021 and 2020, no write downs occurred. The Company does not intend to sell the investments and it is not more likely than not that the Company will be required to sell the investments before recovery of their amortized cost basis, which may be maturity. The Company also reviews its available for sale debt securities in an unrealized loss position and evaluates whether the decline in fair value has resulted from credit losses or other factors. This review is subjective, as it requires management to evaluate whether an event or change in circumstances has occurred in that period that may be related to credit issues. For the years ended December 31, 2021 and 2020, no allowance was recorded for credit losses. Unrealized gains and losses are reported as a component of accumulated other comprehensive (loss) income in stockholders' equity.

For the year ended December 31, 2021, the Company had $0.8 million, realized gains from the sale of available for sale debt securities. For the year ended December 31, 2020, the Company had $0.7 million, realized gains from the sale of available for sale debt securities. Realized gains and losses are reported as a component of interest expense, net in the consolidated statement of operations.

(In thousands except share and per share amount)

The unrealized losses and fair values of available for sale debt securities that have been in an unrealized loss position for a period of less than and greater than or equal to 12 months as of December 31, 2021 are as follows:

	December 31, 2021					
	Securities in an unrealized loss position less than 12 months		Securities in an unrealized loss position greater than or equal to 12 months		Total	
	Unrealized losses	Fair Value	Unrealized losses	Fair Value	Unrealized losses	Fair Value
Commercial paper	$ (1)	12,992	—	—	(1)	12,992
Corporate debt securities	(608)	217,540	(36)	4,985	(644)	222,525
Asset-backed securities	(5)	10,786	—	—	(5)	10,786
Government obligations	(59)	15,483	—	—	(59)	15,483
Total	$ (673)	$ 256,801	$ (36)	$ 4,985	$ (709)	$ 261,786

The unrealized losses and fair values of available for sale debt securities that have been in an unrealized loss position for a period of less than and greater than or equal to 12 months as of December 31, 2020 are as follows:

	December 31, 2020					
	Securities in an unrealized loss position less than 12 months		Securities in an unrealized loss position greater than or equal to 12 months		Total	
	Unrealized losses	Fair Value	Unrealized losses	Fair Value	Unrealized losses	Fair Value
Commercial paper	$ (37)	129,630	—	—	(37)	129,630
Corporate debt securities	(29)	102,426	—	—	(29)	102,426
Asset-backed securities	(3)	1,830	—	—	(3)	1,830
Government obligations	(6)	27,084	—	—	(6)	27,084
Total	$ (75)	$ 260,970	$ —	$ —	$ (75)	$ 260,970

Available for sale debt securities on the balance sheet at December 31, 2021 and 2020 mature as follows:

	December 31, 2021	
	Less Than 12 Months	More Than 12 Months
Commercial paper	$ 75,279	$ —
Corporate debt securities	131,606	136,077
Asset-backed securities	8,724	6,574
Government obligations	6,002	12,423
Total	$ 221,611	$ 155,074

	December 31, 2020	
	Less Than 12 Months	More Than 12 Months
Commercial paper	$ 276,837	$ —
Corporate debt securities	240,139	235,520
Asset-backed securities	6,363	22,525
Government obligations	65,524	47,930
Total	$ 588,863	$ 305,975

The Company classifies all of its marketable securities as current as they are all either available for sale debt securities or equity investments and are available for current operations.

Convertible senior notes

In August 2015, the Company issued $150.0 million of 3.0% convertible senior notes due August 15, 2022 (the "2022 Convertible Notes"). In September 2019, the Company issued $287.5 million of 1.5% convertible senior notes due September 15, 2026 (the "2026 Convertible Notes," together with the "2022 Convertible Notes," the "Convertible Notes"). The fair value of the Convertible Notes, which differs from their carrying values, is influenced by interest rates, the Company's stock price and stock price volatility and is determined by prices for the Convertible Notes observed in market trading which are Level 2 inputs. The estimated fair value of the 2022 Convertible Notes at December 31, 2021 and 2020 was $158.3 million and $193.2 million, respectively. The estimated fair value of the 2026 Convertible Notes at December 31, 2021 and December 31, 2020 was $305.3 million and $394.9 million.

Rights Exchange Agreement

On April 29, 2020, the Company, certain of the former equity holders of Agilis, and, for the limited purposes set forth in the agreement, Shareholder Representative Services LLC, entered into a Rights Exchange Agreement (the "Rights Exchange Agreement"). Pursuant to the terms of the Rights Exchange Agreement, in the year ended December 31, 2020, the Company issued 2,821,176 shares of its common stock (the "Common Stock Consideration") and paid $36.9 million (the "Cash Consideration"), in the aggregate, to such former equityholders of Agilis (the "Participating Rightholders") who in exchange have canceled and forfeited their rights under the Agilis Merger Agreement to receive (i) $174.0 million, in the aggregate, of potential milestone payments based on the achievement of certain regulatory milestones and (ii) $37.6 million, in the aggregate, of $40.0 million in development milestone payments, or the deferred consideration, that would have been due upon the passing of the second anniversary of the closing of the Agilis Merger. As a result of the Rights Exchange Agreement, the remaining deferred consideration payable was $2.4 million, was paid out upon the passing of the second anniversary of the closing of the Agilis Merger. Accordingly, there was no deferred consideration payable as of December 31, 2020.

The Rights Exchange Agreement has no effect on the Agilis Merger Agreement other than to provide for the cancellation and forfeiture of the Participating Rightholders' rights to receive $211.6 million, in the aggregate, of the milestone payments described above. As a result, all other rights and obligations under the Agilis Merger Agreement remain in effect pursuant to their terms. The Company's outstanding obligations under the Agilis Merger Agreement include obligations to pay up to an aggregate maximum amount of $20.0 million upon the achievement of certain development milestones, up to an aggregate maximum amount of $361.0 million upon the achievement of certain regulatory milestones, up to a maximum aggregate amount of $150.0 million upon the achievement of certain net sales milestones and a percentage of annual net sales for Friedreich ataxia and Angelman syndrome during specified terms, ranging from 2% to 6%, pursuant to the terms of the Agilis Merger Agreement.

(In thousands except share and per share amount)

As of result of the Rights Exchange Agreement, the Company recognized a gain of $0.7 million on the settlement of the development milestones related to the difference in the development milestone settled of $37.6 million and Cash Consideration of $36.9 million. Additionally, the Company recognized a loss of $11.3 million on the settlement of the regulatory milestones related to the difference in fair value of the regulatory milestones settled of $139.2 million and the fair value of the Common Stock Consideration of $150.5 million. The $0.7 million gain and $11.3 million loss are included in the settlement of deferred and contingent consideration in the Company's statement of operations for the year ended December 31, 2020. Additionally, as of the date of the Rights Exchange Agreement, the Company recognized a gain on the fair value of the contingent consideration of $1.0 million related to the portion of regulatory milestones that were forfeited, which is included in the change in fair value of the deferred and contingent liability within the Company's statement of operations for the year ended December 31, 2020. This gain on the fair value of the contingent consideration is considered a non-recurring Level 3 fair value measurement and was estimated using the same valuation methodology and unobservable input ranges for development and regulatory milestones in the Level 3 valuation section below. In conjunction with the Rights Exchange Agreement, the Company also incurred $2.0 million of transaction fees, which were included in other expense in the Company's statement of operations for the year ended December 31, 2020.

Level 3 valuation

The contingent consideration payable is fair valued each reporting period with the change in fair value recorded as a gain or loss in the consolidated statements of operations. The fair value of the development and regulatory milestones are estimated utilizing a probability adjusted, discounted cash flow approach. The discount rates are estimated utilizing Corporate B rated bonds maturing in the years of expected payments based on the Company's estimated development timelines for the acquired product candidate. On December 31, 2021, the weighted average discount rate for the development and regulatory milestones was 3.4% and the weighted average probability of success was 42%. The fair value of the net sales milestones and royalties is determined utilizing an option pricing model with Monte Carlo simulation to simulate a range of possible payment scenarios, and the average of the payments in these scenarios is then discounted to calculate present fair value. On December 31, 2021, the weighted average discount rate for the net sales milestones and royalties was 11.0% and the weighted average probability of success for the net sales milestones was 48%.

The table presented below is a summary of changes in the fair value of the Company's Level 3 valuation for the contingent consideration payables for the years ended December 31, 2021, and 2020:

	Contingent consideration payable-development and regulatory milestones - Agilis	Contingent consideration payable-net sales milestones and royalties - Agilis
Beginning balance as of December 31, 2019	290,500	65,800
Additions	—	—
Change in fair value	(12,120)	35,400
Payments	—	—
Rights Exchange settlement	(139,180)	—
Ending balance as of December 31, 2020	139,200	101,200
Additions	—	—
Change in fair value	100	(600)
Payments	—	—
Rights Exchange settlement	—	—
Ending balance as of December 31, 2021	$ 139,300	$ 100,600

(In thousands except share and per share amount)

The following significant unobservable inputs were used in the valuation of the contingent consideration payables for the years ended December 31, 2021 and 2020:

	December 31, 2021			
	Fair Value	Valuation Technique	Unobservable Input	Range
Contingent consideration payable- development and regulatory milestones	$139,300	Probability-adjusted discounted cash flow	Potential development and regulatory milestones Probabilities of success Discount rates Projected years of payments	$0 - $381 million 25% - 94% 1.7% - 4.7% 2022 - 2028
Contingent considerable payable- net sales milestones and royalties	$100,600	Option-pricing model with Monte Carlo simulation	Potential net sales milestones Probabilities of success Potential percentage of net sales for royalties Discount rate Projected years of payments	$0 - $150 million 25% - 94% 2% - 6% 11.0% 2023 - 2040

	December 31, 2020			
	Fair Value	Valuation Technique	Unobservable Input	Range
Contingent consideration payable- development and regulatory milestones	$139,200	Probability-adjusted discounted cash flow	Potential development and regulatory milestones Probabilities of success Discount rates Projected years of payments	$0 - $381 million 25% - 94% 2.2% - 4.5% 2021 - 2028
Contingent considerable payable- net sales milestones and royalties	$101,200	Option-pricing model with Monte Carlo simulation	Potential net sales milestones Probabilities of success Potential percentage of net sales for royalties Discount rate Projected years of payments	$0 - $150 million 25% - 94% 2% - 6% 11.5% 2022 - 2040

The contingent consideration payables are classified Level 3 liabilities as their valuation requires substantial judgment and estimation of factors that are not currently observable in the market. If different assumptions were used for the various inputs to the valuation approaches, including but not limited to, assumptions involving probability adjusted sales estimates for the gene therapy platform and estimated discount rates, the estimated fair value could be significantly higher or lower than the fair value determined.

5. Fixed assets

Fixed assets, net were as follows at December 31, 2021 and 2020:

	December 31,	
	2021	2020
Leasehold improvements	$ 19,937	$ 8,072
Computer equipment and software	13,812	11,471
Machinery and lab equipment	33,187	23,430
Furniture and fixtures	3,805	3,844
Assets in process	9,017	5,076
	79,758	51,893
Less accumulated depreciation	(27,173)	(18,062)
Total	$ 52,585	$ 33,831

Depreciation expense was approximately $9.4 million, $6.6 million, and $4.7 million for the years ended December 31, 2021, 2020, and 2019, respectively.

6. Leases

The Company leases office space in South Plainfield, New Jersey for its principal office under three noncancelable operating leases through May 2022 and August 2024, in addition to office and laboratory space in Bridgewater, New Jersey and office space in various countries for international employees primarily through workspace providers.

The Company also leases approximately 220,500 square feet of office, manufacturing and laboratory space at a facility located in Hopewell Township, New Jersey (the "Campus") pursuant to a Lease Agreement (the "Lease") with Hopewell Campus Owner LLC (the "Landlord"). The rental term of the Lease commenced on July 1, 2020 and has an initial term of fifteen years (the "Initial Term"), with two consecutive ten year renewal periods, each at the Company's option. The aggregate rent for the Initial Term will be approximately $111.5 million. The rental rate for the renewal periods will be 95% of the Prevailing Market Rate (as defined in the Lease) and determined at the time of the exercise of the renewal. The Company is also responsible for maintaining certain insurance and the payment of proportional taxes, utilities and common area operating expenses. The Lease contains customary events of default, representations, warranties and covenants.

Subject to the terms of the Lease, the Company has a right of first refusal to rent certain other space of the Campus, which would be triggered upon the Landlord's issuance of a second round proposal or letter of intent to another tenant for such space. The Company also may seek to build a new separate building on the Campus, which may not contain less than 75,000 square feet (the "New Building"). Upon receipt of notice of the Company's intention to build the New Building, the Landlord may, in its sole discretion, construct and lease the New Building to the Company or enter into a ground lease with the Company permitting the Company to construct the New Building. Rent terms for the New Building would be determined based on the land value, construction and project costs subject to whether the Landlord or Company constructs the New Building.

On June 19, 2020, the Company entered into a commercial manufacturing service agreement for a term of 12.5 years with MassBiologics of the University of Massachusetts Medical School ("MassBio"). The agreement will expire on December 31, 2032 unless the Company terminates it on 24 months prior written notice to MassBio. Pursuant to the terms of the agreement, MassBio agreed to provide the Company with four dedicated rooms for its gene therapy AADC program. The Company concluded that the agreement contains an embedded lease as the Company controls the use of the four dedicated rooms and the equipment therein. The agreement included guaranteed lease payments of $15.0 million at the onset of the agreement and $3.0 million annually thereafter. The present value of the guaranteed lease payments was determined to be $41.4 million, which exceeded the assessed fair value of the Company's share of the building. Therefore, the Company determined that the agreement was a finance lease, for which the Company recorded a finance lease ROU asset and corresponding finance lease liability at the onset of the lease agreement. Given that the leased asset is designed for the production of PTC's AADC program and would not have an alternate use outside the PTC gene therapy platform without incurring significant costs, the Company determined that the lease should be treated as research and development expense under ASC 730. Accordingly, the full $41.4 million relating to the finance lease ROU asset was written off and expensed to research and development during the year ended December 31, 2020. The remaining balance for the finance lease ROU asset related to this arrangement is $0 as of December 31, 2021 and as of December 31, 2020. As of December 31, 2021, the balance of the finance lease liabilities-current and finance lease liabilities-non-current are $3.0 million and $20.1 million, respectively, and are directly related to the Company's MassBio agreement. As of December 31, 2020, the balance of the finance lease liabilities-current and finance lease liabilities non-current were $1.3 million and $23.1 million, respectively. Additionally, during the years ended December 30, 2021 and December 30, 2020, the Company recorded finance lease costs of $1.7 million and $0.9 million, respectively, related to interest on the lease liability.

The Company also leases certain vehicles, lab equipment, and office equipment under operating leases. The Company's operating leases have remaining lease terms ranging from 0.1 years to 13.5 years and certain leases include

(In thousands except share and per share amount)

renewal options to extend the lease for up to 10 years. Rent expense was approximately $21.4 million, $15.3 million, and $6.0 million for the years ended December 31, 2021, 2020 and 2019.

The components of lease expense were as follows:

	Year Ended December 31, 2021	Year Ended December 31, 2020	Year Ended December 31, 2019
Operating Lease Cost			
Fixed lease cost	$ 16,411	$ 12,368	$ 4,929
Variable lease cost	4,361	2,448	694
Short-term lease cost	656	450	350
Total operating lease cost	$ 21,428	$ 15,266	$ 5,973

Total operating lease cost is a component of operating expenses on the consolidated statements of operations.

The Company did not enter into any new material leases during the year ended December 31, 2021. The decrease in the operating lease ROU asset and operating lease liability during the year ended December 31, 2021 resulted from the termination of the Company's office leases in Sweden and Washington DC.

Supplemental lease term and discount rate information related to leases was as follows:

	December 31, 2021	December 31, 2020
Weighted-average remaining lease terms - operating leases (years)	10.87	11.49
Weighted-average discount rate - operating leases	8.91 %	8.86 %
Weighted-average remaining lease terms - finance lease (years)	11.00	12.00
Weighted-average discount rate - finance lease	7.80 %	7.80 %

Supplemental cash flow information related to leases was as follows:

	Year Ended December 31, 2021	2020	2019
Cash paid for amounts included in the measurement of lease liabilities:			
Operating cash flows from operating leases	$ 13,683	$ 8,462	$ 4,466
Financing cash flows from finance lease	2,224	17,829	—
Operating cash flows from finance leases	776	171	—
Right-of-use assets obtained in exchange for lease obligations:			
Operating leases	$ 645	$ 76,811	$ 17,389
Finance lease	—	41,382	—

(In thousands except share and per share amount)

Future minimum lease payments under non-cancelable leases as of December 31, 2021 were as follows:

	Operating Leases	Finance Lease
2022	$ 13,443	$ 3,000
2023	13,068	3,000
2024	12,343	3,000
2025	11,221	3,000
2026 and thereafter	80,771	21,000
Total lease payments	130,846	33,000
Less: Imputed Interest expense	49,954	9,947
Total	$ 80,892	$ 23,053

In conjunction with the BioElectron Asset Purchase Agreement by and between the Company and BioElectron, the Company acquired BioElectron's lease in Mountain View, California. As substantially all of the fair value of the gross assets acquired was related to vatiquinone, the relative fair value allocated to the right of use asset and corresponding lease liability for the Mountain View lease was determined to be immaterial, and accordingly is not included in the tables above. The future minimum lease payments for the Mountainview lease are $1.4 million for 2022 and $0 thereafter.

7. Accounts payable and accrued expenses

Accounts payable and accrued expenses at December 31, 2021 and 2020 consist of the following:

	December 31,	
	2021	2020
Employee compensation, benefits, and related accruals	$ 55,733	$ 53,291
Income tax payable	1,287	4,315
Consulting and contracted research	26,434	18,250
Professional fees	3,547	3,614
Sales allowance	61,662	54,327
Sales rebates	68,770	63,774
Royalties	35,679	16,575
Accounts payable	23,033	18,665
Other	12,639	9,357
Total	$ 288,784	$ 242,168

8. Debt

Liability for sale of future royalties

In July 2020, the Company entered into the Royalty Purchase Agreement. As RPI's interest is explicitly limited, the $650.0 million cash consideration was classified as debt and is recorded as "liability for sale of future royalties-current" and "liability for sale of future royalties-noncurrent" on the Company's consolidated balance sheet based on the timing of the expected payments to be made to RPI. The fair value for the liability for sale of future royalties at the time of the transaction was based on the Company's estimates of future royalties expected to be paid to RPI over the life of the arrangement, which was determined using forecasts from market data sources, which are considered Level 3 inputs. The liability will be amortized using the effective interest method over the life of the arrangement, in accordance ASC 470 and ASC 835. The initial annual effective interest rate was determined to be 11.0%. The Company will utilize the prospective

(In thousands except share and per share amount)

method to account for subsequent changes in the estimated future payments to be made to RPI and will update the effective interest rate on a quarterly basis. Issuance costs related to the transaction were determined to be immaterial.

The following table shows the activity within the "liability for sale of future royalties- current" and "liability for sale of future royalties- noncurrent" accounts for the year ended December 31, 2021:

	Year Ended December 31,	
Liability for sale of future royalties- (current and noncurrent)	**2021**	
Beginning balance as of December 31, 2020	$	679,762
Less: Non-cash royalty revenue payable to RPI		(23,460)
Plus: Non-cash interest expense recognized		77,683
Ending balance	$	733,985
Effective interest rate as of December 31, 2021		10.9 %

Non-cash interest expense is recorded in the statement of operations within "Interest expense, net".

2026 Convertible Notes

In September 2019, the Company issued, at par value, $287.5 million aggregate principal amount of 1.50% convertible senior notes due 2026, which included an option to purchase up to an additional $37.5 million in aggregate principal amount of the 2026 Convertible Notes, which was exercised in full by the initial purchasers. The 2026 Convertible Notes bear cash interest at a rate of 1.50% per year, payable semi-annually on March 15 and September 15 of each year, beginning on March 15, 2020. The 2026 Convertible Notes will mature on September 15, 2026, unless earlier repurchased or converted. The net proceeds to the Company from the offering were $279.3 million after deducting the initial purchasers' discounts and commissions and the offering expenses payable by the Company.

The 2026 Convertible Notes are governed by an indenture (the "2026 Convertible Notes Indenture") with U.S Bank National Association as trustee (the "2026 Convertible Notes Trustee").

Holders of the 2026 Convertible Notes may convert their 2026 Convertible Notes at their option at any time prior to the close of business on the business day immediately preceding March 15, 2026 only under the following circumstances:

- during any calendar quarter commencing on or after December 31, 2019 (and only during such calendar quarter), if the last reported sale price of the Company's common stock for at least 20 trading days (whether or not consecutive) during a period of 30 consecutive trading days ending on the last trading day of the immediately preceding calendar quarter is greater than or equal to 130% of the conversion price on each applicable trading day;

- during the five business day period after any five consecutive trading day period (the "measurement period") in which the trading price (as defined in the 2026 Convertible Notes Indenture) per $1,000 principal amount of 2026 Convertible Notes for each trading day of the measurement period was less than 98% of the product of the last reported sale price of the Company's common stock and the conversion rate on each such trading day;

- during any period after the Company has issued notice of redemption until the close of business on the scheduled trading day immediately preceding the relevant redemption date; or

- upon the occurrence of specified corporate events.

On or after March 15, 2026, until the close of business on the business day immediately preceding the maturity date, holders may convert their 2026 Convertible Notes at any time, regardless of the foregoing circumstances. Upon conversion, the Company will pay or deliver, as the case may be, cash, shares of the Company's common stock or any combination thereof at the Company's election.

The conversion rate for the 2026 Convertible Notes was initially, and remains, 19.0404 shares of the Company's common stock per $1,000 principal amount of the 2026 Convertible Notes, which is equivalent to an initial conversion price of approximately $52.52 per share of the Company's common stock. The conversion rate may be subject to adjustment in some events but will not be adjusted for any accrued and unpaid interest.

The Company is not permitted to redeem the 2026 Convertible Notes prior to September 20, 2023. The Company may redeem for cash all or any portion of the 2026 Convertible Notes, at its option, if the last reported sale price of its common stock has been at least 130% of the conversion price then in effect on the last trading day of, and for at least 19 other trading days (whether or not consecutive) during, any 30 consecutive trading day period ending on, and including, the trading day immediately preceding the date on which the Company provides notice of redemption, at a redemption price equal to 100% of the principal amount of the 2026 Convertible Notes to be redeemed, plus accrued and unpaid interest to, but excluding, the redemption date. No sinking fund is provided for the 2026 Convertible Notes, which means that the Company is not required to redeem or retire the 2026 Convertible Notes periodically.

If the Company undergoes a "fundamental change" (as defined in the 2026 Convertible Notes Indenture), subject to certain conditions, holders of the 2026 Convertible Notes may require the Company to repurchase for cash all or part of their 2026 Convertible Notes at a repurchase price equal to 100% of the principal amount of the 2026 Convertible Notes to be repurchased, plus accrued and unpaid interest to, but excluding, the fundamental change repurchase date.

The 2026 Convertible Notes represent senior unsecured obligations and will rank senior in right of payment to the Company's future indebtedness that is expressly subordinated in right of payment to the notes, equal in right of payment to the Company's existing and future unsecured indebtedness that is not so subordinated, effectively junior in right of payment to any of the Company's secured indebtedness to the extent of the value of the assets securing such indebtedness, and structurally subordinated to all existing and future indebtedness and other liabilities (including trade payables) incurred by the Company's subsidiaries. The 2026 Convertible Notes Indenture contains customary events of default with respect to the 2026 Convertible Notes, including that upon certain events of default (including the Company's failure to make any payment of principal or interest on the 2026 Convertible Notes when due and payable) occurring and continuing, the 2026 Convertible Notes Trustee by notice to the Company, or the holders of at least 25% in principal amount of the outstanding 2026 Convertible Notes by notice to the Company and the Convertible Notes Trustee, may, and the 2026 Convertible Notes Trustee at the request of such holders (subject to the provisions of the 2026 Convertible Notes Indenture) will, declare 100% of the principal of and accrued and unpaid interest, if any, on all the 2026 Convertible Notes to be due and payable. In case of certain events of bankruptcy, insolvency or reorganization, involving the Company or a significant subsidiary, 100% of the principal of and accrued and unpaid interest on the 2026 Convertible Notes will automatically become due and payable. Upon such a declaration of acceleration, such principal and accrued and unpaid interest, if any, will be due and payable immediately.

(In thousands except share and per share amount)

Prior to the adoption of ASU 2020-06, the Company accounted for the 2026 Convertible Notes as a liability and equity component where the carrying value of the liability component was valued based on a similar instrument. In accounting for the issuance of the 2026 Convertible Notes, the Company separated the 2026 Convertible Notes into liability and equity components. The carrying amount of the liability component was calculated by measuring the fair value of a similar liability that did not have an associated convertible feature. The carrying amount of the equity component representing the conversion option was determined by deducting the fair value of the liability component from the par value of the 2026 Convertible Notes as a whole. The excess of the principal amount of the liability component over its carrying amount, referred to as the debt discount, was amortized to interest expense over the seven-year term of the 2026 Convertible Notes. The equity component was not re-measured as long as it continued to meet the conditions for equity classification. The equity component recorded at issuance related to the 2026 Convertible Notes was $123.0 million and was recorded in additional paid-in capital.

In accounting for the transaction costs related to the issuance of the 2026 Convertible Notes, the Company allocated the total costs incurred to the liability and equity components of the 2026 Convertible Notes based on their relative values. Transaction costs attributable to the liability component were amortized to interest expense over the seven-year term of the 2026 Convertible Notes, and transaction costs attributable to the equity component were netted with the equity components in stockholders' equity. Additionally, the Company initially recorded a net deferred tax liability of $25.3 million in connection with the 2026 Convertible Notes.

Effective January 1, 2021 the Company adopted ASU 2020-06. After adoption, the Company now accounts for the 2026 Convertible Notes as a single liability measured at amortized cost. As the equity component is no longer required to be split into a separate component, the Company recorded an adjustment for the initial $123.0 million that was allocated to additional paid in capital and $16.1 million of life to date interest expense recorded as amortization of debt discount. Additionally, the net deferred tax liability recorded for the 2026 Convertible Notes was reversed. The principal amount of the liability over its carrying amount is amortized to interest expense over the seven-year term of the 2026 Convertible Notes. Since the 2026 Convertible Notes are classified as a single liability, there is no debt discount required to be amortized.

The 2026 Convertible Notes consist of the following:

	Year ended December 31,	
Liability component	**2021**	**2020**
Principal	$ 287,500	$ 287,500
Less: Debt issuance costs	(5,606)	(4,058)
Less: Debt discount, net(1)	—	(106,065)
Net carrying amount	$ 281,894	$ 177,377

(1) Included in the consolidated balance sheets within convertible senior notes (due 2026) and amortized to interest expense over the remaining life of the 2026 Convertible Notes using the effective interest rate method.

As of December 31, 2021, the remaining contractual life of the 2026 Convertible Notes is approximately 4.7 years.

(In thousands except share and per share amount)

The following table sets forth total interest expense recognized related to the 2026 Convertible Notes:

	Year ended December 31,	
	2021	2020
Contractual interest expense	$ 4,313	$ 4,319
Amortization of debt issuance costs	1,128	508
Amortization of debt discount	—	13,285
Total	$ 5,441	$ 18,112
Effective interest rate of the liability component	1.9 %	10.2 %

2022 Convertible Notes

In August 2015, the Company issued, at par value, $150.0 million aggregate principal amount of 3.00% convertible senior notes due 2022. The Convertible Notes bear cash interest at a rate of 3.00% per year, payable semi-annually on February 15 and August 15 of each year, beginning on February 15, 2016. The 2022 Convertible Notes will mature on August 15, 2022, unless earlier repurchased or converted. The net proceeds to the Company from the offering were $145.4 million after deducting the initial purchasers' discounts and commissions and the offering expenses payable by the Company.

The 2022 Convertible Notes are governed by an indenture (the "2022 Convertible Notes Indenture") with U.S Bank National Association as trustee (the "2022 Convertible Notes Trustee").

Holders of the 2022 Convertible Notes may have converted their 2022 Convertible Notes at their option at any time prior to the close of business on the business day immediately preceding February 15, 2022 only under the following circumstances:

- during any calendar quarter commencing on or after September 30, 2015 (and only during such calendar quarter), if the last reported sale price of the Company's common stock for at least 20 trading days (whether or not consecutive) during a period of 30 consecutive trading days ending on the last trading day of the immediately preceding calendar quarter is greater than or equal to 130% of the conversion price on each applicable trading day;

- during the five business day period after any five consecutive trading day period (the "measurement period") in which the trading price (as defined in the Convertible Notes Indenture) per $1,000 principal amount of Convertible Notes for each trading day of the measurement period was less than 98% of the product of the last reported sale price of the Company's common stock and the conversion rate on each such trading day;

- during any period after the Company has issued notice of redemption until the close of business on the scheduled trading day immediately preceding the relevant redemption date; or

- upon the occurrence of specified corporate events.

As of February 15, 2022, until the close of business on the business day immediately preceding the maturity date, holders may convert their 2022 Convertible Notes at any time, regardless of the foregoing circumstances. Upon conversion, the Company will pay or deliver, as the case may be, cash, shares of the Company's common stock or any combination thereof at the Company's election.

The conversion rate for the 2022 Convertible Notes was initially, and remains, 17.7487 shares of the Company's common stock per $1,000 principal amount of the 2022 Convertible Notes, which is equivalent to an initial conversion price of approximately $56.34 per share of the Company's common stock.

The Company was not permitted to redeem the 2022 Convertible Notes prior to August 20, 2018. As of August 20, 2018, the Company may redeem for cash all or any portion of the Convertible Notes, at its option, if the last reported sale price of its common stock has been at least 130% of the conversion price then in effect on the last trading day of, and for at least 19 other trading days (whether or not consecutive) during, any 30 consecutive trading day period ending on, and including, the trading day immediately preceding the date on which the Company provides notice of redemption, at a redemption price equal to 100% of the principal amount of the 2022 Convertible Notes to be redeemed, plus accrued and unpaid interest to, but excluding, the redemption date. No sinking fund is provided for the 2022 Convertible Notes, which means that the Company is not required to redeem or retire the 2022 Convertible Notes periodically. There have been no redemptions to date.

If the Company undergoes a "fundamental change" (as defined in the 2022 Convertible Notes Indenture), subject to certain conditions, holders of the 2022 Convertible Notes may require the Company to repurchase for cash all or part of their 2022 Convertible Notes at a repurchase price equal to 100% of the principal amount of the 2022 Convertible Notes to be repurchased, plus accrued and unpaid interest to, but excluding, the fundamental change repurchase date.

The 2022 Convertible Notes represent senior unsecured obligations and will rank senior in right of payment to the Company's future indebtedness that is expressly subordinated in right of payment to the notes, equal in right of payment to the Company's existing and future unsecured indebtedness that is not so subordinated, effectively junior in right of payment to any of the Company's secured indebtedness to the extent of the value of the assets securing such indebtedness, and structurally subordinated to all existing and future indebtedness and other liabilities (including trade payables) incurred by the Company's subsidiaries. The 2022 Convertible Notes Indenture contains customary events of default with respect to the 2022 Convertible Notes, including that upon certain events of default (including the Company's failure to make any payment of principal or interest on the 2022 Convertible Notes when due and payable) occurring and continuing, the 2022 Convertible Notes Trustee by notice to the Company, or the holders of at least 25% in principal amount of the outstanding 2022 Convertible Notes by notice to the Company and the Convertible Notes Trustee, may, and the 2022 Convertible Notes Trustee at the request of such holders (subject to the provisions of the 2022 Convertible Notes Indenture) will, declare 100% of the principal of and accrued and unpaid interest, if any, on all the 2022 Convertible Notes to be due and payable. In case of certain events of bankruptcy, insolvency or reorganization, involving the Company or a significant subsidiary, 100% of the principal of and accrued and unpaid interest on the 2022 Convertible Notes will automatically become due and payable. Upon such a declaration of acceleration, such principal and accrued and unpaid interest, if any, will be due and payable immediately.

Prior to the adoption of ASU 2020-06, the Company accounted for the 2022 Convertible Notes as a liability and equity component where the carrying value of the liability component was valued based on a similar instrument. In accounting for the issuance of the 2022 Convertible Notes, the Company separated the 2022 Convertible Notes into liability and equity components. The carrying amount of the liability component was calculated by measuring the fair value of a similar liability that did not have an associated convertible feature. The carrying amount of the equity component representing the conversion option was determined by deducting the fair value of the liability component from the par value of the 2022 Convertible Notes as a whole. The excess of the principal amount of the liability component over its carrying amount, referred to as the debt discount, was amortized to interest expense over the seven-year term of the 2022 Convertible Notes. The equity component was not re-measured as long as it continued to meet the conditions for equity classification. The equity component recorded at issuance related to the 2022 Convertible Notes was $57.5 million and was recorded in additional paid-in capital.

(In thousands except share and per share amount)

In accounting for the transaction costs related to the issuance of the 2022 Convertible Notes, the Company allocated the total costs incurred to the liability and equity components of the 2022 Convertible Notes based on their relative values. Transaction costs attributable to the liability component were amortized to interest expense over the seven-year term of the 2022 Convertible Notes, and transaction costs attributable to the equity component are netted with the equity components in stockholders' equity. Additionally, the Company initially recorded a net deferred tax liability of $22.3 million in connection with the 2022 Convertible Notes.

Effective January 1, 2021 the Company adopted ASU 2020-06. After adoption, the Company now accounts for the 2022 Convertible Notes as a single liability measured at amortized cost. As the equity component is no longer required to be split into a separate component, the Company recorded an adjustment for the initial $57.5 million that was allocated to additional paid in capital and $38.7 million of life to date interest expense recorded as amortization of debt discount. Additionally, the net deferred tax liability recorded for the 2022 Convertible Notes was reversed. The principal amount of the liability over its carrying amount is amortized to interest expense over the seven-year term of the 2022 Convertible Notes. Since the 2022 Convertible Notes are classified as a single liability, there is no debt discount required to be amortized.

The 2022 Convertible Notes consist of the following:

	Year ended December 31,	
Liability component	**2021**	**2020**
Principal	$ 150,000	$ 150,000
Less: Debt issuance costs	(460)	(865)
Less: Debt discount, net (1)	—	(17,372)
Net carrying amount	$ 149,540	$ 131,763

(1) Included in the consolidated balance sheets within convertible senior notes (due 2022) and amortized to interest expense over the remaining life of the 2022 Convertible Notes using the effective interest rate method.

As of December 31, 2021, the remaining contractual life of the 2022 Convertible Notes is approximately 0.6 years.

The following table sets forth total interest expense recognized related to the 2022 Convertible Notes:

	Year ended December 31,	
	2021	**2020**
Contractual interest expense	$ 4,500	$ 4,500
Amortization of debt issuance costs	720	464
Amortization of debt discount	—	9,314
Total	$ 5,220	$ 14,278
Effective interest rate of the liability component	3.5 %	11.0 %

9. Capital structure

Common stock

In January 2019, the Company closed an underwritten public offering of its common stock. The Company issued and sold an aggregate of 7,563,725 shares of common stock at a public offering price of $30.20 per share, including 843,725 shares issued upon exercise by the underwriter of its option to purchase additional shares in February 2019. The Company received net proceeds of $224.2 million after deducting underwriting discounts and commissions and other offering expenses payable by the Company.

In August 2019, the Company entered into an At the Market Offering Sales Agreement (the "Sales Agreement") with Cantor Fitzgerald and RBC Capital Markets, LLC (together, the "Sales Agents"), pursuant to which, the Company may offer and sell shares of its common stock, having an aggregate offering price of up to $125.0 million from time to time through the Sales Agents by any method that is deemed to be an "at the market offering" as defined in Rule 415(a)(4) promulgated under the Securities Act of 1933, as amended. During the year ended December 31, 2019, the Company issued and sold an aggregate of 63,926 shares of common stock pursuant to the Sales Agreement at a weighted average public offering price of $46.60 per share. The Company received net proceeds of $2.6 million after deducting agent discounts and commissions and other offering expenses payable by the Company.

In September 2019, the Company closed an underwritten public offering of its common stock. The Company issued and sold an aggregate of 2,475,248 shares of common stock at a public offering price of $40.40 per share. The offering included an option to purchase up to an additional 371,287 shares for a period of 30 days following the offering. This option was not exercised by the underwriter. The Company received net proceeds of $97.0 million after deducting underwriting discounts and commissions and other offering expenses payable by the Company.

During the year ended December 31, 2020, the Company issued and sold an aggregate of 542,470 shares of common stock pursuant to the Sales Agreement at a weighted average public offering price of $53.37 per share. During the year ended December 31, 2020, the Company received net proceeds of $28.1 million after deducting agent discounts and commissions and other offering expenses payable by the Company. No shares were sold during the year ended December 31, 2021. The remaining shares of the Company's common stock available to be issued and sold, under the Sales Agreement, have an aggregate offering price of up to $93.0 million as of December 31, 2021.

As a result of the Rights Exchange Agreement, during the year ended December 31, 2020, the Company issued 2,821,176 shares of its common stock to Participating Rightholders. The shares had a fair value of $150.5 million upon issuance.

As a result of the Censa Merger, during the year ended December 31, 2020, the Company issued 845,364 shares of the Company's common stock to Censa securityholders, which were valued at $42.9 million based on the closing stock price on the acquisition date. The number of shares issued was determined using a 30-day VWAP pursuant to the Censa Merger Agreement.

In June 2021, the Company filed a Certificate of Amendment to its Restated Certificate of Incorporation, which increased the number of authorized shares of the Company's common stock from 125,000,000 to 250,000,000 shares.

As of December 31, 2021, the Company's number of authorized shares of common stock was 250,000,000.

(In thousands except share and per share amount)

10. Net loss per share

Basic and diluted net loss per share is computed by dividing net loss available to common stockholders by the weighted-average number of common shares outstanding. Potentially dilutive securities were excluded from the diluted calculation because their effect would be anti-dilutive.

The following table sets forth the computation of basic and diluted net loss per share for common stockholders:

	Year ended December 31,		
	2021	2020	2019
Numerator			
Net loss	$ (523,901)	$ (438,160)	$ (251,576)
Denominator			
Denominator for basic and diluted net loss per share	70,466,393	66,027,908	58,863,185
Net loss per share:			
Basic and diluted	$ (7.43)*	$ (6.64)*	$ (4.27)*

* For the years ended December 31, 2021, 2020, and 2019, the Company experienced a net loss and therefore did not report any dilutive share impact.

The following table shows historical dilutive common share equivalents outstanding, which are not included in the above historical calculation, as the effect of their inclusion is anti-dilutive during each period.

	As of December 31,		
	2021	2020	2019
Stock Options	10,772,582	9,663,677	11,043,939
Unvested restricted stock awards and units	1,519,831	982,058	642,419
Total	12,292,413	10,645,735	11,686,358

11. Stock award plan

In May 2013, the Company's Board of Directors and stockholders approved the 2013 Long Term Incentive Plan, which became effective upon the closing of the Company's IPO. The 2013 Long Term Incentive Plan provides for the grant of incentive stock options, nonstatutory stock options, restricted stock awards and other stock-based awards. The number of shares of common stock reserved for issuance under the 2013 Long Term Incentive Plan is the sum of (1) 122,296 shares of common stock available for issuance under the Company's 2009 Equity and Long Term Incentive Plan and 2013 Stock Incentive Plan, (2) the number of shares (up to 3,040,444 shares) equal to the sum of the number of shares of common stock subject to outstanding awards under the Company's 1998 Employee, Director and Consultant Stock Option Plan, 2009 Equity and Long Term Incentive Plan and 2013 Stock Incentive Plan that expire, terminate or are otherwise surrendered, cancelled, forfeited or repurchased by the Company at their original issuance price pursuant to a contractual repurchase right plus (3) an annual increase, to be added on the first day of each fiscal year until the expiration of the 2013 Long Term Incentive Plan, equal to the lowest of 2,500,000 shares of common stock, 4% of the number of shares of common stock outstanding on the first day of the fiscal year and an amount determined by the Company's Board of Directors. As of December 31, 2021, awards for 995,368 shares of common stock were available for issuance under the 2013 Long Term Incentive Plan.

There are no additional shares of common stock available for issuance under the Company's 1998 Employee, Director and Consultant Stock Option Plan, 2009 Equity and Long Term Incentive Plan or 2013 Stock Incentive Plan.

In January 2020, the Company's Board of Directors approved the 2020 Inducement Stock Incentive Plan. The 2020 Inducement Stock Incentive Plan provides for the grant of incentive stock options, nonstatutory stock options, restricted stock awards and other stock-based awards, initially up to an aggregate of 1,000,000 shares of common stock. Any grants made under the 2020 Inducement Stock Incentive Plan must be made pursuant to the Nasdaq Listing Rule 5635(c)(4) inducement grant exception as a material component of the Company's new hires' employment compensation. In December 2020, the Company's Board of Directors approved an additional 1,000,000 shares of common stock that may be issued under the 2020 Inducement Stock Incentive Plan. As of December 31, 2021, awards for 794,436 shares of common stock are available for issuance under the 2020 Inducement Stock Incentive Plan.

The Board of Directors has the authority to select the individuals to whom options are granted and determine the terms of each option, including (i) the number of shares of common stock subject to the option; (ii) the date on which the option becomes exercisable; (iii) the option exercise price, which, in the case of incentive stock options, must be at least 100% (110% in the case of incentive stock options granted to a stockholder owning in excess of 10% of the Company's stock) of the fair market value of the common stock as of the date of grant; and (iv) the duration of the option (which, in the case of incentive stock options, may not exceed ten years). Options typically vest over a four-year period.

Inducement stock option awards

Pursuant to the Nasdaq inducement grant exception, during the year ended December 31, 2021, the Company issued options to purchase an aggregate of 392,845 shares of common stock to certain new hire employees at a weighted-average exercise price of $42.32 per share. Additionally, during the year ended December 31, 2021, the Company issued 128,635 restricted stock units under the 2020 Inducement Stock Incentive Plan. An aggregate of 335,020 of options and 14,810 of restricted stock units previously granted as inducement awards were forfeited during the year ended December 31, 2021 in connection with employee separations from the Company.

A summary of stock option activity is as follows:

	Number of options	Weighted-average exercise price	Weighted-average remaining contractual term	Aggregate intrinsic value(in thousands)
Outstanding at December 31, 2018	8,534,358	$ 28.58		
Granted	3,977,995	$ 35.81		
Exercised	(949,887)	$ 19.25		
Forfeited	(518,527)	$ 35.27		
Outstanding at December 31, 2019	11,043,939	$ 31.67		
Granted	2,777,975	$ 51.06		
Exercised	(3,268,452)	$ 24.25		
Forfeited	(889,785)	$ 42.14		
Outstanding at December 31, 2020	9,663,677	$ 38.72		
Granted	2,487,234	61.36		
Exercised	(635,871)	28.01		
Forfeited/Cancelled	(742,458)	52.04		
Outstanding at December 31, 2021	10,772,582	$ 43.66	6.91 years	$ 50,564
Vested or Expected to vest at December 31, 2021	4,409,301	$ 51.05	8.34 years	$ 7,022
Exercisable at December 31, 2021	5,958,347	$ 37.53	5.74 years	$ 43,249

The fair values of grants made in the years ended December 31, 2021, 2020 and 2019 were contemporaneously estimated on the date of grant using the following assumptions:

	2021	2020	2019
Risk-free interest rate	0.51% - 1.24%	0.34% - 1.45%	1.58% - 2.63%
Expected volatility	74% - 89%	87% - 89%	62% - 92%
Expected term	5.5 years	5.75 years	5.75 - 6.11 years

The Company assumed no expected dividends for all grants. The weighted average grant date fair value of options granted during the years ended December 31, 2021, 2020 and 2019 was $43.05, $36.94, and $23.05 per share, respectively.

Restricted Stock Awards and Restricted Stock Units—Restricted stock awards and Restricted stock units are granted subject to certain restrictions, including in some cases service conditions (restricted stock). The grant-date fair value of restricted stock awards, which has been determined based upon the market value of the Company's shares on the grant date, is expensed over the vesting period.

(In thousands except share and per share amount)

The following table summarizes information on the Company's restricted stock awards and units:

	Restricted Stock Awards and Units	
	Number of Shares	Weighted Average Grant Date Fair Value
Unvested at December 31, 2020	982,058	$ 41.78
Granted	1,018,228	62.54
Vested	(335,114)	36.09
Forfeited	(145,341)	57.71
Unvested at December 31, 2021	1,519,831	$ 55.43

Employee Stock Purchase Plan—In June 2016, the Company established an Employee Stock Purchase Plan (as amended, "ESPP" or the "Plan") for certain eligible employees. The Plan is administered by the Company's Board of Directors or a committee appointed by the Board. In June 2021, the Plan was amended to increase the total number of shares available for purchase under the Plan from one million shares to two million shares of the Company's common stock. Employees may participate over a six-month period through payroll withholdings and may purchase, at the end of the six-month period, the Company's common stock at a purchase price of at least 85% of the closing price of a share of the Company's common stock on the first business day of the offering period or the closing price of a share of the Company's common stock on the last business day of the offering period, whichever is lower. No participant will be granted a right to purchase the Company's common stock under the Plan if such participant would own more than 5% of the total combined voting power of the Company or any subsidiary of the Company after such purchase. For the period ending December 31, 2021, the Company recorded $2.3 million in compensation expense related to the ESPP.

The Company recorded share-based compensation expense in the statement of operations related to incentive stock options, nonstatutory stock options, restricted stock awards, restricted stock units and the ESPP as follows:

	Year ended December 31,		
	2021	2020	2019
Research and development	$ 53,632	$ 38,716	$ 20,836
Selling, general and administrative	49,881	31,609	21,298
Total	$ 103,513	$ 70,325	$ 42,134

As of December 31, 2021, there was approximately $198.8 million of total unrecognized compensation cost related to unvested share-based compensation arrangements granted under the Company's Plans. This cost is expected to be recognized as compensation expense over the weighted average remaining service period of approximately 2.54 years.

12. Other comprehensive income (loss) and accumulated other comprehensive items

Other comprehensive income (loss) includes changes in equity that are excluded from net loss, such as unrealized gains and losses on marketable securities.

(In thousands except share and per share amount)

The following table summarizes other comprehensive income (loss) and the changes in accumulated other comprehensive items, by component, for the years ended December 31, 2021, 2020, and 2019, respectively.

	Unrealized Gains (Losses) On Marketable Securities, net of tax	Foreign Currency Translation	Total Accumulated Other Comprehensive Items
Balance at December 31, 2018	$ 31	$ 1,431	$ 1,462
Other comprehensive income (loss) before reclassifications	724	(12,770)	(12,046)
Amounts reclassified from other comprehensive items	—	—	—
Other comprehensive income (loss)	724	(12,770)	(12,046)
Balance at December 31, 2019	$ 755	$ (11,339)	$ (10,584)
Other comprehensive income (loss) before reclassifications	479	(51,518)	(51,039)
Amounts reclassified from other comprehensive items	666	—	666
Other comprehensive income (loss)	1,145	(51,518)	(50,373)
Balance at December 31, 2020	$ 1,900	$ (62,857)	$ (60,957)
Other comprehensive (loss) income before reclassifications	(3,279)	39,177	35,898
Amounts reclassified from other comprehensive items	777	—	777
Other comprehensive (loss) income	(2,502)	39,177	36,675
Balance at December 31, 2021	$ (602)	$ (23,680)	$ (24,282)

Reclassified amounts from other comprehensive items were determined using the actual realized gains and losses from the sales of marketable securities.

13. Revenue recognition

Net product sales

The Company views its operations and manages its business in one operating segment. During the years ended December 31, 2021, 2020 and 2019, net product sales in the United States were $187.3 million, $139.0 million, and $101.0 million, respectively, consisting solely of sales of Emflaza, and net product sales outside of the United States were $241.6 million, $194.4 million, and $190.3 million respectively, consisting of sales of Translarna, Tegsedi, and Waylivra. Translarna net product revenues made up $236.0 million, $191.9 million, and $190.0 million of the net product sales outside the United States for the years ended December 31, 2021, 2020, and 2019, respectively. For the years ended December 31, 2021, 2020, and 2019, two of the Company's distributors each accounted for over 10% of the Company's net product sales.

As of December 31, 2021, the Company does not have a contract liabilities balance. As of December 31, 2020, the Company's contract liabilities balance was $4.2 million. The Company did not have any contract assets for the years ended December 31, 2021 and 2020. During the years ended December 31, 2021 and 2020, the Company recognized revenues of $4.0 million and $8.1 million, respectively, related to amounts included in contract liability balance at the beginning of each period. The Company has not made significant changes to the judgments made in applying ASC Topic 606 for the years ended December 31, 2021 and 2020.

Remaining performance obligations

Remaining performance obligations represent the transaction price for goods the Company has yet to provide. As of December 31, 2021, the Company does not have any remaining performance obligations relating to Translarna net product revenue. As of December 31, 2020, the aggregate amount of transaction price allocated to remaining performance obligations relating to Translarna net product revenue was $4.2 million.

Collaboration revenue and Royalty revenue

In November 2011, the Company and the Spinal Muscular Atrophy Foundation ("SMA Foundation") entered into a licensing and collaboration agreement with F. Hoffman-La Roche Ltd and Hoffman- La Roche Inc. (collectively, "Roche"). Under the terms of the SMA License Agreement, Roche acquired an exclusive worldwide license to the Company's SMA program.

Under the agreement, the Company is eligible to receive additional payments from Roche if specified events are achieved with respect to each licensed product, including up to $135.0 million in research and development event milestones, up to $325.0 million in sales milestones upon achievement of certain sales events, and up to double digit royalties on worldwide annual net sales of a commercial product.

In November 2019, the Company announced the filing of an NDA in the United States, which triggered a $15.0 million payment to the Company from Roche. Under ASC Topic 606, the acceptance of the NDA filing by the FDA resolved the uncertainty of whether the milestone was probable of being achieved, and the Company recorded it as collaboration revenue for the year ended December 31, 2019.

The SMA program currently has one approved product, Evrysdi™ (risdiplam), which was approved in August 2020 by the FDA for the treatment of SMA in adults and children two months and older. The first commercial sale of Evrysdi in the United States was made in August 2020. This event triggered a $20.0 million milestone payment to the Company from Roche. In August 2020, the EMA accepted the MAA filed by Roche for Evrysdi for the treatment of SMA, which triggered a $15.0 million milestone payment to the Company from Roche. In October 2020, Chugai, a subsidiary of Roche, filed an NDA in Japan for Evrysdi for the treatment of SMA, which triggered a $7.5 million milestone payment to the Company from Roche. Under ASC Topic 606, the acceptance of the NDA filing resolved the uncertainty of whether the milestone was probable of being achieved. The Company recorded the three milestone payments as collaboration revenue for the year ended December 31, 2020.

The first commercial sale of Evrysdi in the EU was made in March 2021. This event triggered a $20.0 million milestone payment to the Company from Roche. The first commercial sale in Japan was made in August 2021, which was the final research and development milestone received by the Company. This event triggered a $10.0 million payment to the Company from Roche. As of December 31, 2021, the Company does not have any remaining research and development milestones that can be received.

In December 2021, the Company recorded its first sales milestone of $25.0 million for the achievement of $500.0 million in worldwide annual net sales from Evrysdi, which is recorded on the balance sheet within prepaid expenses and other current assets as of December 31, 2021. The remaining potential sales milestones as of December 31, 2021 is $300.0 million upon achievement of certain sales events.

For the years ended December 31, 2021, 2020, and 2019, the Company recognized revenue related to the licensing and collaboration agreement with Roche of $55.0 million, $42.6 million, and $15.2 million, respectively.

(In thousands except share and per share amount)

In addition to research and development and sales milestones, the Company is eligible to receive up to double-digit royalties on worldwide annual net sales of a commercial product under the SMA License Agreement. For the year ended December 31, 2021, the Company has recognized $54.6 million of royalty revenue related to Evrysdi. For the year ended December 31, 2020, the Company has recognized $4.8 million of royalty revenue related to Evrysdi. No royalty revenue was recognized in the years prior, as the first commercial sale of Evrysdi occurred in August 2020.

14. Income taxes

The loss from operations before tax (expense) benefit consisted of the following for the years ended December 31, 2021, 2020, and 2019:

	2021	2020	2019
Domestic	$ (487,726)	$ (452,475)	$ (231,915)
Foreign	(30,614)	49,543	(8,011)
Total	$ (518,340)	$ (402,932)	$ (239,926)

The Income Tax Provision consisted of the following for the years ended December 31, 2021, 2020 and 2019:

	2021	2020	2019
Current:			
U.S. Federal	$ —	$ —	$ —
U.S. State and Local	(3,844)	(24,984)	(61)
Foreign	(1,340)	(4,372)	(2,041)
Deferred:			
U.S. Federal	—	—	—
U.S. State and Local	(377)	(5,872)	(8,812)
Foreign	—	—	(736)
Total tax expense	$ (5,561)	$ (35,228)	$ (11,650)

A reconciliation of the U.S. statutory income tax rate to the Company's effective tax rate is as follows:

	December 31,		
	2021	2020	2019
Federal income tax provision at statutory rate	21.00 %	21.00 %	21.00 %
State income tax provision, net of federal benefit	(0.74)	(3.31)	1.08
Permanent differences	(4.06)	(6.66)	(6.17)
Research and development	4.50	4.93	4.38
Change in valuation allowances	(29.03)	(26.40)	(35.49)
Change in deferred tax assets	12.05	2.93	15.89
Foreign tax rate differential	0.01	0.72	(1.88)
Tax rate change	0.01	(1.46)	(3.67)
(Accrual) Release of uncertain tax positions	(4.78)	(0.61)	—
Other	(0.03)	0.12	—
Effective income tax rate	(1.07)%	(8.74)%	(4.86)%

Accounting for income taxes under U.S. GAAP requires that individual tax-paying entities of the company offset all deferred tax liabilities and assets within each particular tax jurisdiction and present them as a noncurrent deferred tax

(In thousands except share and per share amount)

liability or asset. Amounts in different tax jurisdictions cannot be offset against each other. The noncurrent deferred income tax asset is recorded within deposits and other assets on the balance sheet. The amount of deferred income taxes are as follows:

	December 31,	
	2021	2020
Assets:		
Noncurrent deferred income taxes	$ —	$ —
Liabilities:		
Noncurrent deferred income taxes	(137,110)	(136,735)
Deferred income taxes - net	$ (137,110)	$ (136,735)

The significant components of the Company's deferred tax assets and liabilities at December 31, 2021 and 2020 are as follows:

	2021	2020
Deferred tax assets:		
Accrued expense	$ 8,208	$ 5,528
Amortization	87,998	80,677
Depreciation	—	—
Federal tax credits	142,595	123,405
State tax credits	8,054	—
Federal net operating losses	76,589	16,999
State net operating losses	9,159	1,428
Foreign net operating losses	3,316	—
Capitalized research and development costs	241	661
Share based compensation and other	15,273	14,612
Liability for sale of future royalties	148,503	161,204
Noncash interest expense	26,040	—
Other comprehensive loss	143	7,624
Total gross deferred tax assets	526,119	412,138
Less valuation allowance	(525,570)	(379,608)
Total deferred tax assets, net of valuation allowance	$ 549	$ 32,530
Deferred tax liabilities:		
Depreciation	$ (549)	$ (2,904)
Convertible debt	—	(29,626)
Indefinite lived intangible	(137,110)	(136,735)
Total gross deferred tax liabilities	(137,659)	(169,265)
Net deferred tax assets (liabilities)	$ (137,110)	$ (136,735)

For the year ended December 31, 2021, the Company generated taxable loss in the U.S. of $306.9 million. The Company has not recorded any federal income tax provision after considering the federal NOL. The Company recorded a state income tax provision of $3.8 million which is primarily attributable to state income taxes paid in the current year related to prior year's state tax liability.

At December 31, 2021 and 2020, the Company recorded valuation allowance against its net deferred tax assets of $525.6 million and $379.6 million, respectively. The change in the valuation allowance during the years ended December 31,

2021 and 2020 was $146.0 million and $112.5 million, respectively. A valuation allowance has been recorded since, in the judgment of management, these assets are not more likely than not to be realized. The ultimate realization of deferred tax assets is dependent upon the generation of future taxable income during periods in which those temporary differences and carryforwards become deductible or are utilized. As of December 31, 2021, the Company had $364.7 million and $136.7 million of federal and state net operating loss carryforwards, respectively. As a result of the adoption of ASU 2016-09, the Company no longer excludes tax benefits that arose directly from equity compensation in excess of compensation recognized for financial reporting in its U.S. federal and U.S. state net operating loss carryforwards.

During 2018, the Company acquired IPR&D as part of the acquisition of Agilis. This asset is currently considered an indefinite-lived intangible with no related book amortization and tested for impairment, annually. As the IPR&D has no tax basis and is an indefinite-lived intangible, the deferred tax liability created at the time of acquisition is not considered positive evidence of future income and is presented as a deferred tax liability in the balance sheet.

As of December 31, 2021, research and development credit carryforward for federal purposes is $28.0 million. In addition, the Orphan Drug Credit Carryover available as of December 31, 2021 is $114.6 million. The Company's federal credit carryforwards begin to expire in 2022.

As a result of U.S. tax reform legislation, federal net operating losses generated in 2018 carryforward indefinitely. State net operating loss carryforwards begin to expire in 2037. Sections 382 and 383 of the Internal Revenue Code of 1986 subject the future utilization of net operating losses and certain other tax attributes, such as research and development tax credits, to an annual limitation in the event of certain ownership changes, as defined. The Company has undergone an ownership change and has determined that a "change in ownership" as defined by IRC Section 382 of the Internal Revenue Code of 1986, as amended, and the rules and regulations promulgated thereunder, did occur in June of 2013. Accordingly, about $231.5 million of the Company's NOL carryforwards are limited and the Company can only use $16.7 million for the first five years from the ownership change and $5.7 million per year going forward. Therefore, $169.2 million of the NOL's will be freed up over the next 20 years and $62.3 million are expected to expire unused which are not included in the deferred tax assets listed above. At December 31, 2020, the Company utilized $364.1 million NOLs of which $97.7 million is the Section 382 NOL. At December 31, 2021, there is $361.7 million available for immediate use and an additional $5.7 million will free up in 2022.

The income tax expense for the years ended December 31, 2021 and 2020 differed from the amounts computed by applying the U.S. federal income tax rate of 21% to loss before tax expense as a result of foreign taxes, the impact of permanent differences, including "global intangible low-taxed income" ("GILTI"), tax credits generated, true up of net operating loss carryforwards, and increase in the Company's valuation allowance.

The Company applies the elements of FASB ASC 740-10 regarding accounting for uncertainty in income taxes. This clarifies the accounting for uncertainty in income taxes recognized in financial statements and required impact of a tax position to be recognized in the financial statements if that position is more likely than not of being sustained by the taxing authority. As of December 31, 2021, the Company recorded unrecognized tax benefits in the amount of $27.2 million including interest and penalties through 2021. The Company's policy is to recognize interest and penalties related to tax matters within the income tax provision. Tax years beginning in 2014 are generally subject to examination by taxing authorities, although net operating losses from all years are subject to examinations and adjustments for at least three years following the year in which the attributes are used. The Company concluded the examination from the United States Internal Revenue Service for tax year 2014 noting adjustments to the U.S. federal net operating loss carryforwards and research and development credit carryforwards. No other examinations are in process.

(In thousands except share and per share amount)

For all years through December 31, 2016, the Company generated research credits but has not conducted a study to document the qualified activities. This study may result in an adjustment to the Company's research and development credit carryforwards; however, until a study is completed and any adjustment is known, no amounts are being presented as an uncertain tax position. A full valuation allowance has been provided against the Company's research and development credits and, if an adjustment is required, this adjustment would be offset by an adjustment to the deferred tax asset established for the research and development credit carryforwards and the valuation allowance.

As a result of U.S. tax reform legislation, distributions of profits from non-U.S. subsidiaries are not expected to cause a significant incremental U.S. tax impact in the future. However, distributions may be subject to non-U.S. withholding taxes if profits are distributed from certain jurisdictions. As of December 31, 2021, for purposes of ASC 740-10-25-3, the Company had $48.0 million of undistributed earnings from non-U.S. subsidiaries that it intends to reinvest permanently in its non-U.S. operations. As these ASC 740-10-25-3 earnings are considered permanently reinvested, no tax provision has been accrued. It is not feasible to estimate the amount of tax that might be payable on the eventual remittance of such earnings.

Unrecognized Tax Benefits

A reconciliation of the gross amount of unrecognized tax benefits, excluding accrued interest and penalties, is as follows:

	Unrecognized Tax Benefits
Balance at December 31, 2020	2,446
Additions based on tax positions related to the current year	24,771
Balance at December 31, 2021	$ 27,217

Uncertain tax positions, for which management's assessment is that there is a more than 50% probability of sustaining the position upon challenge by a taxing authority based upon its technical merits, are subject to certain recognition and measurement criteria. The nature of the uncertain tax positions is often very complex and subject to change, and the amounts at issue can be substantial. The Company develops its cumulative probability assessment of the measurement of uncertain tax positions using internal experience, judgment and assistance from professional advisors. The Company re-evaluates these uncertain tax positions on a quarterly basis based on a number of factors including, but not limited to, changes in facts or circumstances, changes in tax law, and effectively settled issues under audit and new audit activity. Any change in these factors could result in the recognition of a tax benefit or an additional charge to the tax provision.

For the year ended December 31, 2021, the Company recorded $24.8 million of unrecognized tax benefits. While it is reasonably possible that a further change in the unrecognized tax benefits may occur within the next twelve months, the Company is unable to estimate the amount of any such change.

The Company records penalties and tax-related interest expense on unrecognized tax benefits as a component of the provision for income taxes in the accompanying consolidated statement of operations. The Company has recorded $0.1 million of interest and penalties related to uncertain tax positions for the years ended December 31, 2021 in the accompanying consolidated balance sheet. Future changes in the Company's unrecognized tax benefits will affect the Company's annual effective tax rate.

15. Commitments and contingencies

Under various agreements, the Company will be required to pay royalties and milestone payments upon the successful development and commercialization of products. The Company has entered into funding agreements with The Wellcome Trust Limited ("Wellcome Trust") for the research and development of small molecule compounds in connection with its oncology and antibacterial programs. As the Company has discontinued development under its antibacterial program, it no longer expects that milestone and royalty payments from the Company to Wellcome Trust will apply under that agreement, resulting in a change to the total amount of development and regulatory milestone payments the Company may become obligated to pay for this program. Under the oncology platform funding agreement, to the extent that the Company develops and commercializes program intellectual property, excluding emvododstat, on a for-profit basis itself or in collaboration with a partner (provided the Company retains overall control of worldwide commercialization), the Company may become obligated to pay to Wellcome Trust development and regulatory milestone payments and single-digit royalties on sales of any research program product. The Company's obligation to pay such royalties would continue on a country-by-country basis until the longer of the expiration of the last patent in the program intellectual property in such country covering the research program product and the expiration of market exclusivity of such product in such country. The Company made the first development milestone payment of $0.8 million to Wellcome Trust under the oncology platform funding agreement during the second quarter of 2016. Additional milestone payments up to an aggregate of $22.4 million may become payable by the Company to Wellcome Trust under this agreement.

The Company has also entered into a collaboration agreement with the SMA Foundation. The Company may become obligated to pay the SMA Foundation single-digit royalties on worldwide net product sales of any collaboration product that is successfully developed and subsequently commercialized or, with respect to collaboration products the Company outlicenses, including Evrysdi, a specified percentage of certain payments the Company receives from its licensee. The Company is not obligated to make such payments unless and until annual sales of a collaboration product exceed a designated threshold. The Company's obligation to make such payments would end upon its payment to the SMA Foundation of an aggregate of $52.5 million.

Pursuant to the asset purchase agreement ("Asset Purchase Agreement") between the Company and Marathon Pharmaceuticals, LLC (now known as Complete Pharma Holdings, LLC) ("Marathon"), Marathon is entitled to receive contingent payments from the Company based on annual net sales of Emflaza up to a specified aggregate maximum amount over the expected commercial life of the asset. In addition, Marathon has the opportunity to receive a single $50.0 million sales-based milestone.

Pursuant to the Agilis Merger Agreement with Agilis, Agilis equityholders were previously entitled to receive contingent consideration payments from the Company based on (i) the achievement of certain development milestones up to an aggregate maximum amount of $60.0 million, (ii) the achievement of certain regulatory approval milestones together with a milestone payment following the receipt of a priority review voucher up to an aggregate maximum amount of $535.0 million, (iii) the achievement of certain net sales milestones up to an aggregate maximum amount of $150.0 million, and (iv) a percentage of annual net sales for Friedreich Ataxia and Angelman Syndrome during specified terms, ranging from 2%-6%. The Company was required to pay $40.0 million of the development milestone payments upon the passing of the second anniversary of the closing of the Agilis Merger, regardless of whether the applicable milestones have been achieved.

Pursuant to the terms of the Rights Exchange Agreement, the Participating Rightholders canceled and forfeited their rights under the Agilis Merger Agreement to receive (i) $174.0 million, in the aggregate, of potential milestone payments based on the achievement of certain regulatory milestones and (ii) $37.6 million, in the aggregate, of $40.0 million in

development milestone payments that would have been due upon the passing of the second anniversary of the closing of the Agilis Merger, regardless of whether the milestones are achieved.

The Rights Exchange Agreement has no effect on the Agilis Merger Agreement other than to provide for the cancellation and forfeiture of the Participating Rightholders' rights to receive $211.6 million, in the aggregate, of the milestone payments described above. As a result, all other rights and obligations under the Agilis Merger Agreement remain in effect pursuant to their terms, including the Company's obligation to pay up to an aggregate maximum amount of $20.0 million upon the achievement of certain development milestones (representing the remaining portion of potential development milestone payments for which rights were not canceled and forfeited pursuant to the Rights Exchange Agreement while excluding the remaining $2.4 million milestone payment that was due and paid upon the passing of the second anniversary of the closing of the Agilis Merger), up to an aggregate maximum amount of $361.0 million upon the achievement of certain regulatory milestones (representing the remaining portion of potential regulatory milestone payments for which rights were not canceled and forfeited pursuant to the Rights Exchange Agreement), up to a maximum aggregate amount of $150.0 million upon the achievement of certain net sales milestones and a percentage of annual net sales for Friedreich ataxia and Angelman syndrome during specified terms, ranging from 2% to 6%, pursuant to the terms of the Agilis Merger Agreement.

Subject to the terms and conditions of the BioElectron Asset Purchase Agreement, BioElectron may become entitled to receive contingent milestone payments of up to $200.0 million (in cash or in shares of the Company's common stock, as determined by the Company) from the Company based on the achievement of certain regulatory and net sales milestones. Subject to the terms and conditions of the BioElectron Asset Purchase Agreement, BioElectron may also become entitled to receive contingent payments based on a percentage of net sales of certain products.

Subject to the terms and conditions of the Censa Merger Agreement, Censa securityholders may become entitled to receive contingent payments from the Company based on (i) the achievement of certain development and regulatory milestones up to an aggregate maximum amount of $217.5 million for PTC923's two most advanced programs and receipt of a priority review voucher from the FDA as set forth in the Censa Merger Agreement, (ii) $109.0 million in development and regulatory milestones for each additional indication of PTC923, (iii) the achievement of certain net sales milestones up to an aggregate maximum amount of $160.0 million, (iv) a percentage of annual net sales during specified terms, ranging from single to low double digits of the applicable net sales threshold amount, and (v) any sublicense fees paid to the Company in consideration of any sublicense of Censa's intellectual property to commercialize PTC923, on a country-by-country basis, which contingent payment will equal to a mid-double digit percentage of any such sublicense fees. Pursuant to the Censa Merger Agreement, the Company has the option to pay the initial $30.0 million development milestone, for the completion of enrollment of a Phase 3 clinical trial for PTC923 for PKU, if achieved, in cash or shares of the Company's common stock.

The Company also has the Tegsedi-Waylivra Agreement for the commercialization of Tegsedi and Waylivra, and products containing those compounds in countries in Latin America and the Caribbean. Pursuant to the Tegsedi-Waylivra Agreement, the Company paid Akcea an upfront licensing fee, which included an initial payment of $12.0 million. In 2019, a $6.0 million milestone was paid upon receipt of regulatory approval of Waylivra from the EMA and a $4.0 million milestone was paid upon regulatory approval of Tegsedi from ANVISA, the Brazilian health regulatory authority. In addition, a $4.0 million milestone was paid upon receipt of regulatory approval for Waylivra from ANVISA in August 2021. Akcea is also entitled to receive royalty payments subject to certain terms set forth in the Tegsedi-Waylivra Agreement.

The Company has employment agreements with certain employees which require the funding of a specific level of payments, if certain events, such as a change in control or termination without cause, occur. Additionally, the Company

(In thousands except share and per share amount)

has royalty payments associated with Translarna and Emflaza product net sales, payable quarterly or annually in accordance with the terms of the related agreements.

From time to time in the ordinary course of its business, the Company is subject to claims, legal proceedings and disputes. The Company is not currently aware of any material legal proceedings against it.

16. Geographic information

The Company views its operations and manages its business in one operating segment. The following table presents financial information based on the geographic location of the facilities of the Company as of and for the years ended:

	Year Ended December 31, 2021		
	United States	Non-US	Total
Total assets	$ 1,744,225	$ 193,831	$ 1,938,056
Fixed assets, net	$ 51,626	$ 959	$ 52,585
Revenue	$ 297,005	$ 241,588	$ 538,593

	Year Ended December 31, 2020		
	United States	Non-US	Total
Total assets	$ 2,073,404	$ 134,874	$ 2,208,278
Fixed assets, net	$ 32,352	$ 1,479	$ 33,831
Revenue	$ 186,396	$ 194,370	$ 380,766

17. 401(k) plan

The Company maintains a 401(k) plan for its employees. Employee contributions are voluntary. The Company may match employee contributions in amounts to be determined at the Company's sole discretion. The Company provided an 100%, 100% and 100% matching contribution for up to the first 6% of each contributing employee's base salary contributions for the years ended December 31, 2021, 2020 and 2019, respectively. The Company made matching contributions to the 401(k) plan and recorded expense of approximately $6.6 million, $5.3 million, and $3.5 million for the years ended December 31, 2021, 2020 and 2019, respectively.

18. Intangible assets and goodwill

Definite-lived intangibles

On April 20, 2017, the Company completed its previously announced acquisition of all rights to Emflaza pursuant to the Asset Purchase Agreement, dated March 15, 2017, and amended on April 20, 2017, by and between the Company and Marathon. The assets acquired by the Company in the Transaction include intellectual property rights related to Emflaza, inventories of Emflaza, and certain contractual rights related to Emflaza. In accordance with ASU 2017-01, the Company determined that substantially all of the fair value is concentrated in the Emflaza rights intangible asset and as such accounted for the transaction as an asset acquisition under ASC 805-50 and recorded an intangible asset of $148.4 million, which is being amortized to cost of product sales over its expected useful life of approximately seven years on a straight line basis.

Marathon is entitled to receive contingent payments from the Company based on annual net sales of Emflaza beginning in 2018, up to a specified aggregate maximum amount over the expected commercial life of the asset. In

(In thousands except share and per share amount)

accordance with the guidance for an asset acquisition, the Company will record the milestone payment when it becomes payable to Marathon and increase the cost basis for the Emflaza rights intangible asset. For the years ended December 31, 2021, 2020, and 2019, milestone payments of $61.1 million, $40.9 million, and $27.1 million were recorded, respectively. These payments are being amortized over the remaining useful life of the Emflaza rights asset on a straight line basis. As of December 31, 2021, a milestone payable to Marathon of $22.1 million was recorded on the balance sheet within accounts payable and accrued expenses.

Pursuant to the Tegsedi-Waylivra Agreement, in May 2019 the Company made a $6.0 million milestone payment to Akcea upon regulatory approval of Waylivra from the EMA. In December 2019, the Company made a $4.0 million milestone payment to Akcea upon regulatory approval of Tegsedi from ANVISA. Both payments were recorded as intangible assets and are being amortized to cost of product sales over their expected useful life of approximately ten years on a straight line basis. Additionally, in August 2021, the Company made a $4.0 million milestone payment to Akcea upon regulatory approval of Waylivra from ANVISA. In accordance with the guidance for an asset acquisition, the Company recorded the milestone payment when it became payable to Akcea, and it increased the cost basis for the Waylivra intangible asset. This payment is being amortized to cost of product sales over the expected remaining useful life of the Waylivra asset on a straight line basis.

Akcea is also entitled to receive royalty payments subject to certain terms set forth in the Tegsedi-Waylivra Agreement related to sales of Waylivra and Tegsedi. In accordance with the guidance for an asset acquisition, the Company will record royalty payments when they become payable to Akcea and increase the cost basis for the Waylivra and Tegsedi intangible assets, respectively. For the year ended December 31, 2021, royalty payments of $0.2 million were recorded for Tegsedi. No royalty payments were recorded in 2020 and 2019. As of December 31, 2021, a royalty payable of $0.2 million for Tegesdi was recorded on the balance sheet within accounts payable and accrued expenses.

For the years ended December 31, 2021, 2020, and 2019, the Company recognized amortization expense of $54.8 million, $36.9 million, and $27.7 million respectively, related to the Emflaza rights, Waylivra, and Tegsedi intangible assets. The estimated future amortization of the Emflaza rights, Waylivra, and Tegsedi intangible assets is expected to be as follows:

	As of December 31, 2021
2022	$ 65,286
2023	65,286
2024	11,233
2025	1,508
2026 and thereafter	5,028
Total	$ 148,341

The weighted average remaining amortization period of the definite-lived intangibles as of December 31, 2021 is 2.5 years.

Indefinite-lived intangibles

In connection with the acquisition of the Company's gene therapy platform from Agilis, the Company acquired rights to PTC-AADC, for the treatment of AADC deficiency. AADC deficiency is a rare CNS disorder arising from reductions in the enzyme AADC that result from mutations in the dopa decarboxylase gene. The gene therapy platform also includes an asset targeting Friedreich ataxia, a rare and life-shortening neurodegenerative disease caused by a single defect in the FXN gene which causes reduced production of the frataxin protein. Additionally, the gene therapy platform includes two

other programs targeting CNS disorders, including Angelman syndrome, a rare, genetic, neurological disorder characterized by severe developmental delays.

In accordance with the acquisition method of accounting, the Company allocated the acquisition cost for the Agilis Merger to the underlying assets acquired and liabilities assumed, based upon the estimated fair values of those assets and liabilities at the date of acquisition. The Company classified the fair value of the acquired IPR&D as indefinite lived intangible assets until the successful completion or abandonment of the associated research and development efforts. The value allocated to the indefinite lived intangible assets was $576.5 million. There have been no changes to the balance of the indefinite-lived intangibles since the Agilis Merger. The Company performed a quantitative annual impairment test for its indefinite-lived intangible assets as of October 1, 2021 and concluded that no impairment exists as of December 31, 2021.

Goodwill

As a result of the Agilis Merger on August 23, 2018, the Company recorded $82.3 million of goodwill, which included a measurement period adjustment of $18.0 million recorded during the three month period ended December 31, 2018. This adjustment was related to the finalization of the fair values assigned to the intangible assets and corresponding deferred tax liability, the contingent consideration, and the deferred consideration. There have been no changes to the balance of goodwill since the date of the Agilis Merger. Accordingly, the goodwill balance as of December 31, 2021 and 2020 was $82.3 million. The Company performed an annual impairment test for goodwill as of October 1, 2021 and concluded that no impairment exists as of December 31, 2021.

19. Subsequent events

The Company has evaluated all subsequent events and transactions through the filing date. There were no material events that impacted the audited consolidated financial statements or disclosures.

Item 9. Changes in and Disagreements with Accountants on Accounting and Financial Disclosure

None.

Item 9A. Controls and Procedures.

Evaluation of Disclosure Controls and Procedures

Our management, with the participation of our Chief Executive Officer (principal executive officer) and Chief Financial Officer (principal financial officer), evaluated the effectiveness of our disclosure controls and procedures as of December 31, 2021. The term "disclosure controls and procedures", as defined in Rules 13a-15(e) and 15d-15(e) under the Securities Exchange Act of 1934, as amended, or the Exchange Act, means controls and other procedures of a company that are designed to ensure that information required to be disclosed by a company in the reports that it files or submits under the Exchange Act is recorded, processed, summarized and reported, within the time periods specified in the SEC's rules and forms. Disclosure controls and procedures include, without limitation, controls and procedures designed to ensure that information required to be disclosed by a company in the reports that it files or submits under the Exchange Act is accumulated and communicated to the company's management, including its principal executive and principal financial officers, as appropriate to allow timely decisions regarding required disclosure. Management recognizes that any controls and procedures, no matter how well designed and operated, can provide only reasonable assurance of achieving their objectives and management necessarily applies its judgment in evaluating the cost-benefit relationship of possible controls and procedures. Based on the evaluation of our disclosure controls and procedures as of December 31, 2021, our Chief Executive Officer and Chief Financial Officer concluded that, as of such date, our disclosure controls and procedures were effective at the reasonable assurance level.

Management's Report on Internal Control over Financial Reporting

Our management is responsible for establishing and maintaining adequate internal control over financial reporting for our company. Internal control over financial reporting is defined in Rule 13a-15(f) or 15d-15(f) promulgated under the Exchange Act as a process designed by, or under the supervision of, the company's principal executive and principal financial officers and effected by the company's board of directors, management and other personnel, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with GAAP and includes those policies and procedures that: (i) pertain to the maintenance of records that, in reasonable detail, accurately and fairly reflect the transactions and dispositions of the assets of the company; (ii) provide reasonable assurance that transactions are recorded as necessary to permit preparation of financial statements in accordance with generally accepted accounting principles, and that receipts and expenditures of our company are being made only in accordance with authorizations of management and directors of the company; and (iii) provide reasonable assurance regarding prevention or timely detection of unauthorized acquisition, use, or disposition of our company's assets that could have a material effect on the financial statements.

Internal control over financial reporting is designed to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements prepared for external purposes in accordance with generally accepted accounting principles. Because of its inherent limitations, internal control over financial reporting may not prevent or detect misstatements. Also, projections of any evaluation of effectiveness to future periods are subject to the risk that controls may become inadequate because of changes in conditions, or that the degree of compliance with the policies or procedures may deteriorate.

Our management, with the participation of our Chief Executive Officer (principal executive officer) and Chief Financial Officer (principal financial officer), assessed the effectiveness of our internal control over financial reporting as of December 31, 2021. In making this assessment, our management used the criteria set forth in the *Internal Control—Integrated Framework (2013)* issued by the Committee of Sponsoring Organizations of the Treadway Commission. Based on its assessment, management concluded that our internal control over financial reporting was effective as of December 31, 2021 based on those criteria.

The effectiveness of our internal control over financial reporting as of December 31, 2021, has been audited by Ernst & Young LLP, an independent registered public accounting firm, as stated in their report which appears herein.

Changes in Internal Control over Financial Reporting

No change in our internal control over financial reporting occurred during the year ended December 31, 2021 that has materially affected, or is reasonably likely to materially affect, our internal control over financial reporting.

Report of Independent Registered Public Accounting Firm

To the Stockholders and the Board of Directors of PTC Therapeutics, Inc.

Opinion on Internal Control over Financial Reporting

We have audited PTC Therapeutics, Inc.'s internal control over financial reporting as of December 31, 2021, based on criteria established in Internal Control-Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission (2013 framework) (the COSO criteria). In our opinion, PTC Therapeutics, Inc. (the Company) maintained, in all material respects, effective internal control over financial reporting as of December 31, 2021, based on the COSO criteria.

We also have audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States) (PCAOB), the accompanying consolidated balance sheets of the Company as of December 31, 2021 and 2020, the related consolidated statements of operations, comprehensive loss, stockholders' equity and cash flows for each of the three years in the period ended December 31, 2021, and the related notes and our report dated February 22, 2022 expressed an unqualified opinion thereon.

Basis for Opinion

The Company's management is responsible for maintaining effective internal control over financial reporting and for its assessment of the effectiveness of internal control over financial reporting included in the accompanying Management's Report on Internal Control Over Financial Reporting. Our responsibility is to express an opinion on the Company's internal control over financial reporting based on our audit. We are a public accounting firm registered with the PCAOB and are required to be independent with respect to the Company in accordance with the U.S. federal securities laws and the applicable rules and regulations of the Securities and Exchange Commission and the PCAOB.

We conducted our audit in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether effective internal control over financial reporting was maintained in all material respects.

Our audit included obtaining an understanding of internal control over financial reporting, assessing the risk that a material weakness exists, testing and evaluating the design and operating effectiveness of internal control based on the assessed risk, and performing such other procedures as we considered necessary in the circumstances. We believe that our audit provides a reasonable basis for our opinion.

Definition and Limitations of Internal Control Over Financial Reporting

A company's internal control over financial reporting is a process designed to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles. A company's internal control over financial reporting includes those policies and procedures that (1) pertain to the maintenance of records that, in reasonable detail, accurately and fairly reflect the transactions and dispositions of the assets of the company; (2) provide reasonable assurance that transactions are recorded as necessary to permit preparation of financial statements in accordance with generally accepted accounting principles, and that receipts and expenditures of the company are being made only in accordance with authorizations of management and directors of the company; and (3) provide reasonable assurance regarding prevention or timely detection of unauthorized acquisition, use, or disposition of the company's assets that could have a material effect on the financial statements.

Because of its inherent limitations, internal control over financial reporting may not prevent or detect misstatements. Also, projections of any evaluation of effectiveness to future periods are subject to the risk that controls may become inadequate because of changes in conditions, or that the degree of compliance with the policies or procedures may deteriorate.

/s/ Ernst & Young LLP
Iselin, New Jersey
February 22, 2022

Item 9B. Other Information.

None.

Item 9C. Disclosure Regarding Foreign Jurisdictions that Prevent Inspections.

None.

PART III

Item 10. Directors, Executive Officers and Corporate Governance

The information required by this item as set forth under the captions "Proposal 1—Election of Directors", "Executive Officers", "Delinquent Section 16(a) Reports", "Corporate Governance—Code of Conduct", "Corporate Governance—Director Nominations", "Corporate Governance—Board Committees and Audit Committee", and "Stockholder Proposals and Nominations for Director" in our Proxy Statement for the 2022 Annual Meeting of Shareholders is incorporated in this Annual Report on Form 10-K by reference.

Code of Ethics

We have adopted a written Code of Business Conduct and Ethics, which is a code of ethics that applies to our directors, officers and employees, including our principal executive officer, principal financial officer, principal accounting officer or controller, or persons performing similar functions. We have posted a current copy of the Code of Business Conduct and Ethics on the Corporate Governance page of the Investors section of our website, *www.ptcbio.com*, and it is available in print to any person who requests it. We intend to post on our website all disclosures that are required by applicable law, the rules of the Securities and Exchange Commission or the Nasdaq Global Select Market concerning any amendment to, or waiver from, any provision of the Code of Business Conduct and Ethics.

Item 11. Executive Compensation

The information required by this item as set forth in under the captions "Executive Compensation", "2021 Director Compensation", "Corporate Governance—Risk Oversight" and "Corporate Governance—Compensation Committee Interlocks and Insider Participation" in our Proxy Statement for the 2022 Annual Meeting of Shareholders is incorporated in this Annual Report on Form 10-K by reference.

Item 12. Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters

The information required by this item as set forth under the captions "Equity Compensation Plan Information" and "Principal Stockholders" in our Proxy Statement for the 2022 Annual Meeting of Shareholders is incorporated in this Annual Report on Form 10-K by reference.

Item 13. Certain Relationships and Related Transactions, and Director Independence

The information required by this item as set forth under the captions "Corporate Governance—Policies and Procedures for Related Person Transactions", "Corporate Governance—Related Person Transactions", and "Corporate Governance—Director Independence" in our Proxy Statement for the 2022 Annual Meeting of Shareholders is incorporated in this Annual Report on Form 10-K by reference.

Item 14. Principal Accountant Fees and Services

The information required by this item as set forth under the caption "Proposal 2—Ratification of Election of Independent Registered Public Accounting Firm" in our Proxy Statement for the 2022 Annual Meeting of Shareholders is incorporated in this Annual Report on Form 10-K by reference.

PART IV

Item 15. Exhibits and Financial Statement Schedules

Financial Statements

The following statements and supplementary data are included in Part II, Item 8. of the Annual Report on Form 10-K.

- Reports of independent registered public accounting firm
- Consolidated Balance Sheets as of December 31, 2021 and 2020
- Consolidated Statements of Operations for the years ended December 31, 2021, 2020 and 2019
- Consolidated Statements of Comprehensive Loss for the years ended December 31, 2021, 2020 and 2019
- Consolidated Statements of Stockholders' Equity for the years ended December 31, 2021, 2020 and 2019
- Consolidated Statements of Cash Flows for the years ended December 31, 2021, 2020 and 2019
- Notes to Consolidated Financial Statements

Exhibits

Those exhibits required to be filed by Item 601 of Regulation S-K are listed in the Exhibit Index immediately preceding the exhibits hereto and such listing is incorporated herein by reference.

Exhibit Index

Exhibit Number	Description of Exhibit
2.1††	Asset Purchase Agreement, dated March 15, 2017, between PTC Therapeutics, Inc. and Complete Pharma Holdings, LLC (f/k/a Marathon Pharmaceuticals, LLC) (incorporated by reference to Exhibit 2.1 to the Current Report on Form 8-K filed by the Registrant on March 16, 2017)
2.2	Amendment to Asset Purchase Agreement, dated April 20, 2017, between PTC Therapeutics, Inc. and Complete Pharma Holdings, LLC (f/k/a Marathon Pharmaceuticals, LLC) (incorporated by reference to Exhibit 2.1 to the Current Report on Form 8-K filed by the Registrant on April 20, 2017)
2.3†	Agreement and Plan of Merger, dated July 19, 2018, by and among PTC Therapeutics, Inc., Agility Merger Sub, Inc., Agilis Biotherapeutics, Inc. and, solely in its capacity as equityholder representative, Shareholder Representative Services LLC (incorporated by reference to Exhibit 2.1 to the Current Report on Form 8-K filed by the Registrant on July 19, 2018)
2.4*	Asset Purchase Agreement by and between PTC Therapeutics, Inc. and BioElectron Technology Corporation, dated October 1, 2019 (incorporated by reference to Exhibit 2.1 to the Current Report on Form 8-K filed by the Registrant on October 30, 2019)
2.5*	Agreement and Plan of Merger, dated May 5, 2020, by and among PTC Therapeutics, Inc., Hydro Merger Sub, Inc., Censa Pharmaceuticals Inc. and, solely in its capacity as securityholder representative, Shareholder Representative Services LLC (incorporated by reference to Exhibit 2.1 to the Current Report on Form 8-K filed by the Registrant on May 6, 2020)

Exhibit Number	Description of Exhibit
3.1	Restated Certificate of Incorporation of the Registrant, as amended (incorporated by reference to Exhibit 3.1 to the Quarterly Report on Form 10-Q filed by the Registrant on July 29, 2021)
3.2	Amended and Restated Bylaws of the Registrant (incorporated by reference to Exhibit 3.1 to the Current Report on Form 8-K filed by the Registrant on April 21, 2017)
4.1	Description of Registered Securities
4.2	Specimen Stock Certificate evidencing the shares of common stock (incorporated by reference to Exhibit 4.1 to the Registration Statement on Form S-1, as amended (File No. 333-188657), of the Registrant)
4.3	Indenture (including Form of Notes), dated as of August 14, 2015, by and between PTC Therapeutics, Inc. and U.S. Bank National Association, a national banking association, as trustee (incorporated by reference to Exhibit 4.1 to the Current Report on Form 8-K filed by the Registrant on August 14, 2015)
4.4	Indenture (including Form of Notes), dated as of September 20, 2019, by and between PTC Therapeutics, Inc. and U.S. Bank National Association, a national banking association, as trustee (incorporated by reference to Exhibit 4.1 to the Current Report on Form 8-K filed by the Registrant on September 20, 2019)
10.1+	2009 Equity and Long Term Incentive Plan, as amended (incorporated by reference to Exhibit 10.4 to the Registration Statement on Form S-1, as amended (File No. 333-188657), of the Registrant)
10.2+	Form of Notice of Award for Incentive Stock Option under 2009 Equity and Long Term Incentive Plan (incorporated by reference to Exhibit 10.5 to the Registration Statement on Form S-1, as amended (File No. 333-188657), of the Registrant)
10.3+	Form of Notice of Award for Nonstatutory Stock Option under 2009 Equity and Long Term Incentive Plan (incorporated by reference to Exhibit 10.6 to the Registration Statement on Form S-1, as amended (File No. 333-188657), of the Registrant)
10.4+	Form of Restricted Stock Agreement under 2009 Equity and Long Term Incentive Plan (incorporated by reference to Exhibit 10.19 to the Registration Statement on Form S-1, as amended (File No. 333-188657), of the Registrant)
10.5+	2013 Stock Incentive Plan (incorporated by reference to Exhibit 10.7 to the Registration Statement on Form S-1, as amended (File No. 333-188657), of the Registrant)
10.6+	Form of Restricted Stock Agreement under 2013 Stock Incentive Plan (incorporated by reference to Exhibit 10.8 to the Registration Statement on Form S-1, as amended (File No. 333-188657), of the Registrant)
10.7+	Form of Nonstatutory Stock Option Agreement under 2013 Stock Incentive Plan (incorporated by reference to Exhibit 10.9 to the Registration Statement on Form S-1, as amended (File No. 333-188657), of the Registrant)
10.8+	2013 Long Term Incentive Plan (incorporated by reference to Exhibit 10.10 to the Registration Statement on Form S-1, as amended (File No. 333-188657), of the Registrant)
10.9+	Form of Incentive Stock Option Agreement under 2013 Long Term Incentive Plan—2013/2014 (incorporated by reference to Exhibit 10.11 to the Registration Statement on Form S-1, as amended (File No. 333-188657), of the Registrant)

Exhibit Number	Description of Exhibit
10.10+	Form of Nonstatutory Stock Option Agreement under 2013 Long Term Incentive Plan—2013/2014 (incorporated by reference to Exhibit 10.12 to the Registration Statement on Form S-1, as amended (File No. 333-188657), of the Registrant)
10.11+	Form of Nonqualified Stock Option Agreement Inducement Grant Agreement—2014-2022 (incorporated by reference to Exhibit 10.14 to the Annual Report on Form 10-K filed by the Registrant on March 2, 2015)
10.12+	Form of Incentive Stock Option Agreement under 2013 Long Term Incentive Plan—2014-2022 (incorporated by reference to Exhibit 10.15 to the Annual Report on Form 10-K filed by the Registrant on March 2, 2015)
10.13+	Form of Nonstatutory Stock Option Agreement under 2013 Long Term Incentive Plan—2014-2022 (incorporated by reference to Exhibit 10.16 to the Annual Report on Form 10-K filed by the Registrant on March 2, 2015)
10.14+	Form of Nonstatutory Stock Option Agreement under 2013 Long Term Incentive Plan—Non-employee Director (incorporated by reference to Exhibit 10.31 to the Annual Report on Form 10-K filed by the Registrant on February 29, 2016)
10.15+	Form of Restricted Stock Unit Agreement under 2013 Long Term Incentive Plan —2016-2022 (incorporated by reference to Exhibit 10.32 to the Annual Report on Form 10-K filed by the Registrant on February 29, 2016)
10.16+	Form of Restricted Stock Agreement under 2013 Long Term Incentive Plan —2017-2022 (incorporated by reference to Exhibit 10.19 to the Annual Report on Form 10-K filed by the Registrant on March 16, 2017)
10.17+	Form of Nonqualified Restricted Stock Award Agreement Inducement Grant Agreement-2018 (incorporated by reference to Exhibit 99.3 to the Registration Statement on Form S-8 (File No. 333-229126), of the Registrant)
10.18	Lease Agreement, dated as of July 11, 2000, as amended, between the Registrant and 46.24 Associates L.P. (incorporated by reference to Exhibit 10.13 to the Registration Statement on Form S-1, as amended (File No. 333-188657), of the Registrant)
10.19†	License and Collaboration Agreement, dated as of November 23, 2011, as amended, by and among the Registrant, F. Hoffmann-La Roche Ltd and Hoffmann-La Roche, Inc. and Spinal Muscular Atrophy Foundation (incorporated by reference to Exhibit 10.14 to the Registration Statement on Form S-1, as amended (File No. 333-188657), of the Registrant)
10.20†	Sponsored Research Agreement, as amended dated as of June 1, 2006, by and between the Registrant and Spinal Muscular Atrophy Foundation (incorporated by reference to Exhibit 10.15 to the Registration Statement on Form S-1, as amended (File No. 333-188657), of the Registrant)
10.21†	Funding Agreement, dated as of May 26, 2010, by and between the Registrant and The Wellcome Trust Limited (incorporated by reference to Exhibit 10.16 to the Registration Statement on Form S-1, as amended (File No. 333-188657), of the Registrant)
10.22+	Amended and Restated Employment Agreement between the Registrant and Stuart W. Peltz (incorporated by reference to Exhibit 10.20 to the Registration Statement on Form S-1, as amended (File No. 333-188657), of the Registrant)

Exhibit Number	Description of Exhibit
10.23+	Amended and Restated Employment Agreement between the Registrant and Mark E. Boulding (incorporated by reference to Exhibit 10.22 to the Registration Statement on Form S-1, as amended (File No. 333-188657), of the Registrant)
10.24+	Amended and Restated Employment Agreement between the Registrant and Neil Almstead (incorporated by reference to Exhibit 10.24 to the Registration Statement on Form S-1, as amended (File No. 333-188657), of the Registrant)
10.25†	Exclusive License and Supply Agreement, dated as of May 12, 2015, as amended, by and between Faes Farma, S.A. and Complete Pharma Holdings, LLC (f/k/a Marathon Pharmaceuticals, LLC), as assigned by Complete Pharma Holdings, LLC to the Registrant on April 20, 2017 (incorporated by reference to Exhibit 10.1 to the Quarterly Report on Form 10-Q filed by the Registrant on August 9, 2017)
10.26†	Commercial Manufacturing Agreement, dated as of September 18, 2015, as amended, by and between Alcami Corporation (f/k/a/ AAI Pharma Services Corp.) and Complete Pharma Holdings, LLC (f/k/a Marathon Pharmaceuticals, LLC), as assigned by Complete Pharma Holdings, LLC to the Registrant on April 20, 2017 (incorporated by reference to Exhibit 10.2 to the Quarterly Report on Form 10-Q filed by the Registrant on August 9, 2017)
10.27+	Employment Agreement, as amended, between the Registrant and Christine Utter (incorporated by reference to Exhibit 10.2 to the Quarterly Report on Form 10-Q filed by the Registrant on August 6, 2019)
10.28†	Collaborative Research Agreement, dated September 30, 2015, as amended, by and between National Taiwan University and Agilis Biotherapeutics, Inc. (formerly Agilis Biotherapeutics, LLC) (incorporated by reference to Exhibit 10.3 on Form 10-Q filed by Registrant on November 5, 2018)
10.29†	License and Technology Transfer Agreement, dated December 23, 2015, by and among National Taiwan University, Professor Wuh-Lian(Paul) Hwu and Agilis Biotherapeutics, Inc. (formerly Agilis Biotherapeutics, LLC) (incorporated by reference to Exhibit 10.3 on Form 10-Q filed by Registrant on November 5, 2018)
10.30*	License and Technology Transfer Agreement Amendment No. 2, dated December 1, 2019, by and among National Taiwan University, Professor Wu-Lian (Paul) Hwu and PTC Therapeutics GT, Inc. (incorporated by reference to Exhibit 10.42 on Form 10-K filed by Registrant on March 2, 2020)
10.31†	Collaboration and License Agreement, dated August 1, 2018, by and between PTC Therapeutics International Limited and Akcea Therapeutics, Inc. (incorporated by reference to Exhibit 10.3 on Form 10-Q filed by Registrant on November 5, 2018)
10.32	Amended and Restated 2016 Employee Stock Purchase Plan (incorporated by reference to Exhibit 10.1 to the Current Report on Form 8-K filed by the Registrant on June 9, 2021)
10.33+	Employment Agreement, as amended, between the Registrant and Emily Hill (incorporated by reference to Exhibit 10.1 to the Quarterly Report on Form 10-Q filed by the Registrant on August 6, 2019)
10.34*	Lease Agreement dated as of August 3, 2019, by and between Bristol-Myers Squibb Company and PTC Therapeutics, Inc. (incorporated by reference to Exhibit 10.5 to the Quarterly Report on Form 10-Q filed by the Registrant on October 30, 2019)
10.35	Irrevocable Standby Letter of Credit, dated September 3, 2019, issued by HSBC Bank USA, N.A. in favor of Bristol-Myers Squibb Company for the Account of PTC Therapeutics, Inc., as amended (incorporated by reference to Exhibit 10.6 to the Quarterly Report on Form 10-Q filed by the Registrant on October 30, 2019)

Exhibit Number	Description of Exhibit
10.36+	2020 Inducement Stock Incentive Plan (incorporated by reference to Exhibit 99.3 to the Registration Statement on Form S-8 (File No. 333-235823), of the Registrant)
10.37+	Form of Inducement Option Agreement under the 2020 Inducement Stock Incentive Plan (incorporated by reference to Exhibit 99.4 to the Registration Statement on Form S-8 (File No. 333-235823), of the Registrant)
10.38+	Form of Inducement Restricted Stock Agreement under the 2020 Inducement Stock Incentive Plan (incorporated by reference to Exhibit 99.5 to the Registration Statement on Form S-8 (File No. 333-235823), of the Registrant)
10.39+	Amendment No. 1 to 2020 Inducement Stock Incentive Plan (incorporated by reference to Exhibit 99.3 to the Registration Statement on Form S-8 (File No. 333-251878), of the Registrant)
10.40*	First Amendment to Lease Agreement dated as of October 7, 2019 by and between Bristol-Myers Squibb Company and PTC Therapeutics, Inc. (incorporated by reference to Exhibit 10.51 to the Annual Report on Form 10-K filed by the Registrant on March 2, 2020)
10.41*	Second Amendment to Lease Agreement dated as of March 25, 2020 by and between Bristol-Myers Squibb Company and PTC Therapeutics, Inc. (incorporated by reference to Exhibit 10.1 to the Quarterly Report on Form 10-Q filed by the Registrant on April 30, 2020)
10.42*	License Agreement dated as of February 8, 2016, as amended, by and between Shiratori Pharmaceutical Co. Ltd. and Censa Pharmaceuticals Inc. (incorporated by reference to Exhibit 10.1 to the Quarterly Report on Form 10-Q filed by the Registrant on August 5, 2020)
10.43*	Royalty Purchase Agreement, dated as of July 17, 2020, by and among PTC Therapeutics, Inc., RPI 2019 Intermediate Finance Trust, and, solely for the limited purposes set forth therein, Royalty Pharma PLC (incorporated by reference to Exhibit 10.2 to the Quarterly Report on Form 10-Q filed by the Registrant on August 5, 2020)
10.44+	Employment Agreement, as amended, between the Registrant and Matthew Klein
10.45+	Employment Agreement, as amended, between the Registrant and Eric Pauwels (incorporated by reference to Exhibit 10.4 to the Quarterly Report on Form 10-Q filed by the Registrant on August 5, 2020)
10.46*	Rights Exchange Agreement, by and among PTC Therapeutics, Inc., the Rightholders set forth therein, and, for the limited purposes set forth therein, Shareholder Representatives Services LLC, dated as of April 29, 2020 (incorporated by reference to Exhibit 10.1 to the Current Report on Form 8-K filed by the Registrant on April 30, 2020)
10.47*	Collaborative Research Agreement Amendment 5, dated as of January 17, 2020 by and between National Taiwan University and PTC Therapeutics GT, Inc. (incorporated by reference to Exhibit 10.1 to the Quarterly Report on Form 10-Q filed by the Registrant on October 29, 2020)
10.48*	Collaborative Research Agreement Amendment 6, dated as of May 30, 2020 by and between National Taiwan University and PTC Therapeutics GT, Inc. (incorporated by reference to Exhibit 10.1 to the Quarterly Report on Form 10-Q filed by the Registrant on October 29, 2020)
10.49	At the Market Offering Sales Agreement, dated August 7, 2019, among PTC Therapeutics, Inc., Cantor Fitzgerald & Co. and RBC Capital Markets, LLC (incorporated by reference to Exhibit 1.1 to the Current Report on Form 8-K filed by the Registrant on August 7, 2019)

Exhibit Number	Description of Exhibit
10.50*	Collaborative Research Agreement Amendment 7, dated as of September 14, 2020 by and between National Taiwan University and PTC Therapeutics GT, Inc. (incorporated by reference to Exhibit 10.50 to the Annual Report on Form 10-K filed by the Registrant on February 25, 2021)
10.51*	Collaborative Research Agreement Amendment 8, dated as of December 5, 2020 by and between National Taiwan University and PTC Therapeutics GT, Inc. (incorporated by reference to Exhibit 10.51 to the Annual Report on Form 10-K filed by the Registrant on February 25, 2021)
10.52*	Collaborative Research Agreement Amendment 9, dated as of March 21, 2021 by and between National Taiwan University and PTC Therapeutics GT, Inc. (incorporated by reference to Exhibit 10.1 to the Quarterly Report on Form 10-Q filed by the Registrant on May 4, 2021)
10.53*	Collaborative Research Agreement Amendment 10, dated as of November 1, 2021 by and between National Taiwan University and PTC Therapeutics GT, Inc.
21.1	Subsidiaries of the Registrant (incorporated by reference to Exhibit 21.1 to the Annual Report on Form 10-K filed by the Registrant on March 2, 2020)
23.1	Consent of Independent Registered Public Accounting Firm
24.1	Power of attorney (included on the signature page to this Form 10-K)
31.1	Certification of Principal Executive Officer pursuant to Rule 13a-14(a) or Rule 15d-14(a) of the Securities Exchange Act of 1934, as adopted pursuant to Section 302 of the Sarbanes-Oxley Act of 2002
31.2	Certification of Principal Financial Officer pursuant to Rule 13a-14(a) or Rule 15d-14(a) of the Securities Exchange Act of 1934, as adopted pursuant to Section 302 of the Sarbanes-Oxley Act of 2002
32.1	Certification of Principal Executive Officer pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002
32.2	Certification of Principal Financial Officer pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002
101.INS	Inline XBRL Instance Document**
101.SCH	Inline XBRL Taxonomy Extension Schema Document**
101.CAL	Inline XBRL Taxonomy Extension Calculation Linkbase Document**
101.LAB	Inline XBRL Taxonomy Extension Label Linkbase Database**
101.PRE	Inline XBRL Taxonomy Extension Presentation Linkbase Document**
101.DEF	Inline XBRL Taxonomy Extension Definition Linkbase Document**
104	Cover Page Interactive Data File (formatted Inline XBRL and contained in Exhibit 101)

†† Confidential treatment has been granted as to certain portions, which portions have been omitted and separately filed with the Securities and Exchange Commission.

† Confidential treatment has been granted for certain portions that are omitted from this exhibit. The omitted information has been filed separately with the U.S. Securities and Exchange Commission (the "SEC") pursuant to the registrant's

application for confidential treatment. In addition, schedules have been omitted from this exhibit pursuant to Item 601(b)(2) of Regulation S-K. A copy of any omitted schedule will be furnished supplementally to the SEC upon request; provided, however, that the registrant may request confidential treatment for any document so furnished.

+ Management contract, compensatory plan or arrangement.

* Portions of this exhibit have been omitted pursuant to Item 601(b)(10)(iv) of Regulation S-K.

** Submitted electronically herewith.

Stockholders may obtain (without charge) a copy of this Annual Report on Form 10-K (including the financial statements and financial statement schedules) and a copy of any exhibit thereto (upon payment of a fee limited to our reasonable expenses in furnishing such exhibit) by writing to PTC Therapeutics, Inc., 100 Corporate Court, South Plainfield, New Jersey 07080.

Item 16. Form 10-K Summary

None.

SIGNATURES

Pursuant to the requirements to the requirements of Section 13 or 15(d) of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized.

PTC THERAPEUTICS, INC.

Date: February 22, 2022

By: /s/ STUART W. PELTZ
Stuart W. Peltz, Ph.D.
Chief Executive Officer
(Principal Executive Officer)

POWER OF ATTORNEY

We, the undersigned officers and directors of PTC Therapeutics, Inc., hereby severally constitute and appoint Stuart W. Peltz and Mark E. Boulding, and each of them singly (with full power to each of them to act alone), our true and lawful attorneys-in-fact and agents, with full power of substitution and resubstitution in each of them for him and in his name, place and stead, and in any and all capacities, to sign any and all amendments to this Annual Report on Form 10-K, and to file the same, with all exhibits thereto and other documents in connection therewith, with the Securities and Exchange Commission, granting unto said attorneys-in-fact and agents, and each of them, full power and authority to do and perform each and every act and thing requisite or necessary to be done in and about the premises, as full to all intents and purposes as he might or could do in person, hereby ratifying and confirming all that said attorneys-in-fact and agents or any of them, or their or his substitute or substitutes, may lawfully do or cause to be done by virtue hereof.

Pursuant to the requirements to the requirements of the Securities Exchange Act of 1934, this report has been signed below by the following persons on behalf of the registrant and in the capacities and on the dates indicated.

Dated: February 22, 2022

By: /s/ STUART W. PELTZ
Stuart W. Peltz
Chief Executive Officer and Director

Dated: February 22, 2022

By: /s/ EMILY HILL
Emily Hill
Chief Financial Officer
(Principal Financial Officer)

Dated: February 22, 2022

By: /s/ CHRISTINE UTTER
Christine Utter
Chief Accounting Officer
(Principal Accounting Officer)

Dated: February 22, 2022

By: /s/ MICHAEL SCHMERTZLER
Michael Schmertzler
Director

Dated: February 22, 2022

By: /s/ ALLAN JACOBSON
Allan Jacobson
Director

Dated: February 22, 2022

By: /s/ STEPHANIE S. OKEY
Stephanie S. Okey
Director

Dated: February 22, 2022	By:	/s/ EMMA REEVE Emma Reeve *Director*
Dated: February 22, 2022	By:	/s/ MARY SMITH Mary Smith *Director*
Dated: February 22, 2022	By:	/s/ DAVID P. SOUTHWELL David P. Southwell *Director*
Dated: February 22, 2022	By:	/s/ GLENN D. STEELE Glenn D. Steele *Director*
Dated: February 22, 2022	By:	/s/ DAWN SVORONOS Dawn Svoronos *Director*
Dated: February 22, 2022	By:	/s/ JEROME B. ZELDIS Jerome B. Zeldis *Director*

Exhibit 23.1

CONSENT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

We consent to the incorporation by reference in the following Registration Statements:

(1) Registration Statement (Form S-8 No. 333-194323) pertaining to the 2013 Long Term Incentive Plan, and the Inducement Stock Option Award,
(2) Registration Statement (Form S-8 No. 333-189962) pertaining to the 2013 Long Term Incentive Plan, the 2013 Stock Incentive Plan, the 2009 Equity and Long Term Incentive Plan, as amended, and the 1998 Employee, Director and Consultant Stock Option Plan, as amended,
(3) Registration Statement (Form S-8 No. 333-203485) pertaining to the Inducement Stock Option Awards (April 2014 - January 2015),
(4) Registration Statement (Form S-8 No. 333-208830) pertaining to the 2013 Long Term Incentive Plan and Inducement Stock Option Awards (February 2015 – October 2015),
(5) Registration Statement (Form S-8 No. 333-211997) pertaining to the 2016 Employee Stock Purchase Plan and the Inducement Stock Option Awards (December 2015 – April 2016),
(6) Registration Statement (Form S-8 No. 333-215407) pertaining to the 2013 Long Term Incentive Plan and the Inducement Stock Option Awards (September 2016 – December 2016),
(7) Registration Statement (Form S-8 No. 333-222391) pertaining to the 2013 Long Term Incentive Plan and the Inducement Stock Option Awards (January 2017 – December 2017),
(8) Registration Statement (Form S-8 No. 333-229126) pertaining to the 2013 Long Term Incentive Plan and the Inducement Grant Awards (January 2018 – December 2018),
(9) Registration Statement (Form S-8 No. 333-235823) pertaining to the 2013 Long Term Incentive Plan, the Inducement Grant Awards (January 2019 – December 2019) and the 2020 Inducement Stock Incentive Plan,
(10) Registration Statement (Form S-3 No. 333-243712) of PTC Therapeutics Inc.
(11) Registration Statement (Form S-8 No. 333-251878) pertaining to the 2013 Long Term Incentive Plan and the 2020 Inducement Stock Incentive Plan.
(12) Registration Statement (Form S-8 No. 333-262018) pertaining to the 2013 Long Term Incentive Plan and the Amended and Restated 2016 Employee Stock Purchase Plan.

of our reports dated February 22, 2022, with respect to the consolidated financial statements of PTC Therapeutics, Inc. and the effectiveness of internal control over financial reporting of PTC Therapeutics, Inc. included in this Annual Report (Form 10-K) of PTC Therapeutics, Inc. for the year ended December 31, 2021.

/s/ Ernst & Young LLP

Iselin, New Jersey
February 22, 2022

Exhibit 31.1

CERTIFICATIONS

I, Stuart W. Peltz, certify that:

1. I have reviewed this Annual Report on Form 10-K of PTC Therapeutics, Inc.;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

   (a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

   (b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

   (c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

   (d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

   (a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

   (b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: February 22, 2022

By: /s/ STUART W. PELTZ
Stuart W. Peltz
Chief Executive Officer
(Principal Executive Officer)

Exhibit 31.2

CERTIFICATIONS

I, Emily Hill, certify that:

1. I have reviewed this Annual Report on Form 10-K of PTC Therapeutics, Inc.;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

   (a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

   (b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

   (c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

   (d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

   (a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

   (b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: February 22, 2022

By: /s/ EMILY HILL
Emily Hill
Chief Financial Officer
(Principal Financial Officer)

Exhibit 32.1

CERTIFICATION PURSUANT TO 18 U.S.C. SECTION 1350,
AS ADOPTED PURSUANT TO
SECTION 906 OF THE SARBANES-OXLEY ACT OF 2002

In connection with the Annual Report on Form 10-K of PTC Therapeutics, Inc. (the "Company") for the period ended December 31, 2021 as filed with the Securities and Exchange Commission on the date hereof (the "Report"), the undersigned, Stuart W. Peltz, Chief Executive Officer of the Company, hereby certifies, pursuant to 18 U.S.C. Section 1350, that to his knowledge:

(1) the Report fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934; and

(2) the information contained in the Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

Date: February 22, 2022

By: /s/ STUART W. PELTZ
Stuart W. Peltz
Chief Executive Officer
(Principal Executive Officer)

Exhibit 32.2

CERTIFICATION PURSUANT TO 18 U.S.C. SECTION 1350,
AS ADOPTED PURSUANT TO
SECTION 906 OF THE SARBANES-OXLEY ACT OF 2002

In connection with the Annual Report on Form 10-K of PTC Therapeutics, Inc. (the "Company") for the period ended December 31, 2021 as filed with the Securities and Exchange Commission on the date hereof (the "Report"), the undersigned, Emily Hill, Principal Financial Officer of the Company, hereby certifies, pursuant to 18 U.S.C. Section 1350, that to her knowledge:

(1) the Report fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934; and

(2) the information contained in the Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

Date: February 22, 2022

By: /s/ EMILY HILL
Emily Hill
Chief Financial Officer
(Principal Financial Officer)

Board of Directors

Michael Schmertzler
Chairman of the Board
PTC Therapeutics, Inc.

Allan Jacobson, Ph.D.
Gerald L. and Zelda S. Haidak Distinguished Professor of Cell Biology
University of Massachusetts Medical School

Stephanie Okey
Former Senior Vice President, Head of North America, Rare Diseases & U.S. General Manager, Rare Disease Business Unit
Genzyme

Stuart W. Peltz, Ph.D.
Chief Executive Officer
PTC Therapeutics, Inc.

Emma Reeve
Former Chief Financial Officer
Constellation Pharmaceuticals, Inc.

Mary L. Smith
Vice Chairman
The VENG Group

David P. Southwell
Chief Executive Officer
TScan Therapeutics, Inc.

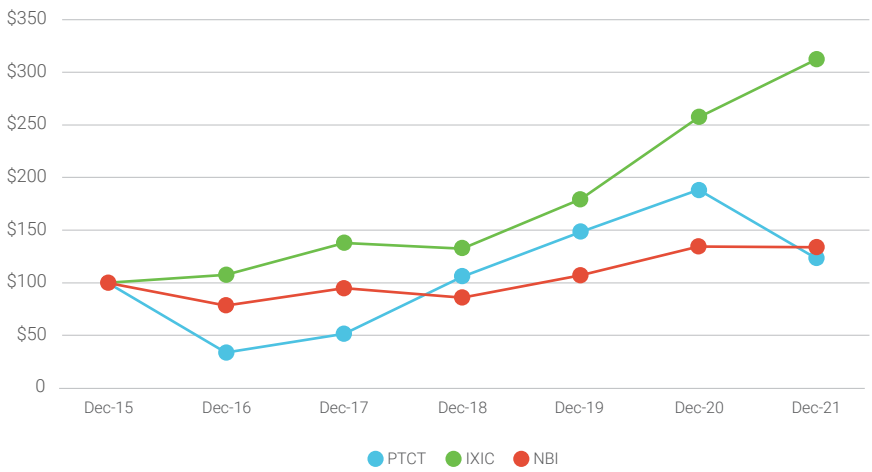
Glenn D. Steele, Jr., M.D., Ph.D.
Chairman
GSteele Health Solutions

Dawn Svoronos
Former President of Europe/Canada
Merck

Jerome B. Zeldis, M.D., Ph.D.
Executive Vice President and Head of R&D
NexImmune, Inc.

Stock Performance Graph*

The following graph illustrates a comparison of the total cumulative stockholder return on the Common Stock of PTC Therapeutics' Stock from investing on January 1, 2015 through December 31, 2021 in two indices: The NASDAQ Biotechnology Index (NBI) and the NASDAQ Composite Index (IXIC). Data for the NASDAQ Biotechnology Index (NBI) and the NASDAQ Composite Index (IXIC) assume reinvestment of dividends. The stockholder return shown in the graph below is not necessarily indicative of future performance, and we do not make or endorse any predictions as to future stockholder returns.



** The information contained in this Stock Performance Graph shall not be deemed "soliciting material" or to be "filed" with the SEC, for purposes of Section 18 of the Securities Exchange Act of 1934, as amended, or the Exchange Act, or otherwise subject to the liabilities under that Section, and shall not be deemed to be incorporated by reference into any filing of under the Securities Act of 1933 or Securities Exchange Act of 1934, each as amended, except to the extent that we specifically incorporate it by reference into such filing*

$100 Investment in Stock or Index	Dec 31, 2015	Dec 31, 2016	Dec 31, 2017	Dec 31, 2018	Dec 31, 2019	Dec 31, 2020	Dec 31, 2021
PTC Therapeutics, Inc. (PTCT)	$100	$34	$51	$106	$148	$188	$123
NASDAQ Composite (IXIC)	$100	$108	$138	$133	$179	$257	$312
NASDAQ Biotechnology Index (NBI)	$100	$78	$95	$86	$107	$134	$134

Executive Committee

Stuart W. Peltz, Ph.D.
Founder and Chief Executive Officer

Neil Almstead, Ph.D.
Chief Technical Operations Officer

Mark E. Boulding
Executive Vice President and Chief Legal Officer

Timothy Dyer
Senior Vice President, Global Operations and Chief of Staff to the Chief Executive Officer

Mary Frances Harmon
Senior Vice President Corporate and Patient Relations

Emily Hill
Chief Financial Officer

Matthew Klein, M.D., M.S., F.A.C.S.
Chief Operating Officer

Kylie O'Keefe
Senior Vice President, Commercial and Corporate Strategy

Eric Pauwels
Chief Business Officer

Martin Rexroad
Chief Culture and Community Officer

Hege Sollie-Zetlmayer
Senior Vice President, Human Resources

Christine Utter
Senior Vice President, Chief Accounting Officer and Head of People Services

Ellen Welch, Ph.D.
Chief Scientific Officer

Stockholder Information

Market Information
PTC's common stock trades on the NASDAQ Global Market under the ticker symbol PTCT.

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PTC Therapeutics, Inc.
100 Corporate Court
South Plainfield, NJ 07080

PTC Therapeutics International Limited
5th Floor
3 Grand Canal Plaza
Grand Canal Street Upper
Dublin D04 EE70 Ireland

Annual Meeting
The Annual Meeting of the Stockholders will be held on Wednesday, June 8 at 9am. Due to uncertainties of the novel Covid-19 pandemic and health restrictions, the meeting will be held virtually.

Transfer Agent
American Stock Transfer
6201 15th Avenue
Brooklyn, NY 11219

Independent Registered Public Accounting Firm
Ernst and Young
99 Wood Avenue South
Iselin, NJ 08830

Annual Report Design: Shelley Signature Design / www.shelleysignaturedesign.com

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For more information visit
www.ptcbio.com

PTC THERAPEUTICS™