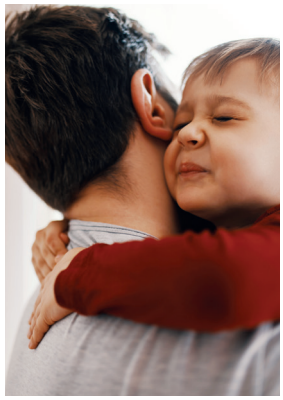
2018 Annual Report

measured by moments

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 20 years ago, he had this unique insight. That's why we're creating life-changing treatments every day.

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.

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.

Rare Resolve for Rare Disease

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

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.

measured by moments

Everyone has a different definition of progress. For the last 20 years, we've measured our progress researching rare disease in moments. Smiling ones and crying ones. Moments spent with our boys' families and ones with their friends. We know that every step forward comes after several steps backward, because we've lived it—whether spending time with families in their homes or with our scientists researching in our labs.

It can be easy to lose yourself as you progress further. Although we've grown, our heart remains in the same place, because we've never measured ourselves like larger companies do. Our biggest accomplishment has always been the time we can give to all of our families. Whether it's hours, days, months, or years, every small moment is a big win.

A Message to Our Shareholders

2018 a transformational year

Revenue guidance met

2 to 5-year-old DMD label expansion

PTC299 & PTC596 in clinical trials

Today, we are stronger than ever and have multiple technology platforms that hold the promise of a brighter future for patients suffering from rare disorders.

–Stuart W. Peltz, Ph.D., Chief Executive Officer

For more than 21 years, PTC has been relentlessly pursuing innovative technologies and therapies to help to address some of the world's greatest medical challenges for patients with rare disorders. Today, we are stronger than ever and have multiple technology platforms that hold the promise of a brighter future for patients suffering from rare disorders. Our team is determined and moving with great urgency to bring the best of PTC to patients around the world so that they will have new treatments.

2018 was a transformative year for PTC. We have expanded our talent base and increased our global footprint in key markets. We strengthened our development and commercial pipeline with two significant business development transactions. We now have a gene therapy platform that includes an advanced development program for central nervous system (CNS) gene therapy that we plan to submit to FDA this year, and we in-licensed two products from Akcea Therapeutics, an affiliate of Ionis Pharmaceuticals, that we will commercialize in Latin America.

I'm proud to say that our global teams are working hard to deliver on our five-year plan to bring to patients innovative products that make a significant difference in their lives and enable us to achieve a potential $1.5 billion in revenue by 2023.

Due to our team's continued focus on execution, we're steadily advancing toward our goals. We met our Duchenne revenue guidance, increased the commercial reach of Emflaza™ (deflazacort), achieved a label expansion for Translarna™ (ataluren), and advanced our oncology pipeline with two potential products now in the clinic.

PTC is recognized as a leader in Duchenne muscular dystrophy, and we remain committed to finding new and better solutions for the global Duchenne community. In 2018, the European Medicines Agency (EMA) approved a label expansion for Translarna in 2 to 5-year-old nonsense mutation Duchenne patients. This label expansion allows patients in countries that recognize the EMA approval to gain access to this important therapy at a younger age, which we believe maximizes the benefit to patients.

We believe Translarna has the potential to benefit all patients regardless of where they are in their disease

SMA trials enrolled; set up to file in 2019

FD program advanced to development candidate

Completed transformational BD and acquisition deals

progression. We recognize the urgent need to treat non-ambulatory patients, and with that in mind, we submitted for a label expansion for the treatment of non-ambulatory patients to the EMA and expect to finalize the regulatory process in 2019.

Our Duchenne franchise also includes Emflaza, which is commercially available in the U.S. for patients 5 years and older. We are working hard to establish Emflaza as the standard of care in the U.S. We received a request from the FDA to file for a pediatric label expansion for Emflaza and were informed that we have sufficient data to file an sNDA instead. We submitted that application at the end of last year, and our commercial team is now preparing for the potential launch of this expanded indication in 2019.

Now, I'd like to focus on the two business development deals that have changed our company's trajectory.

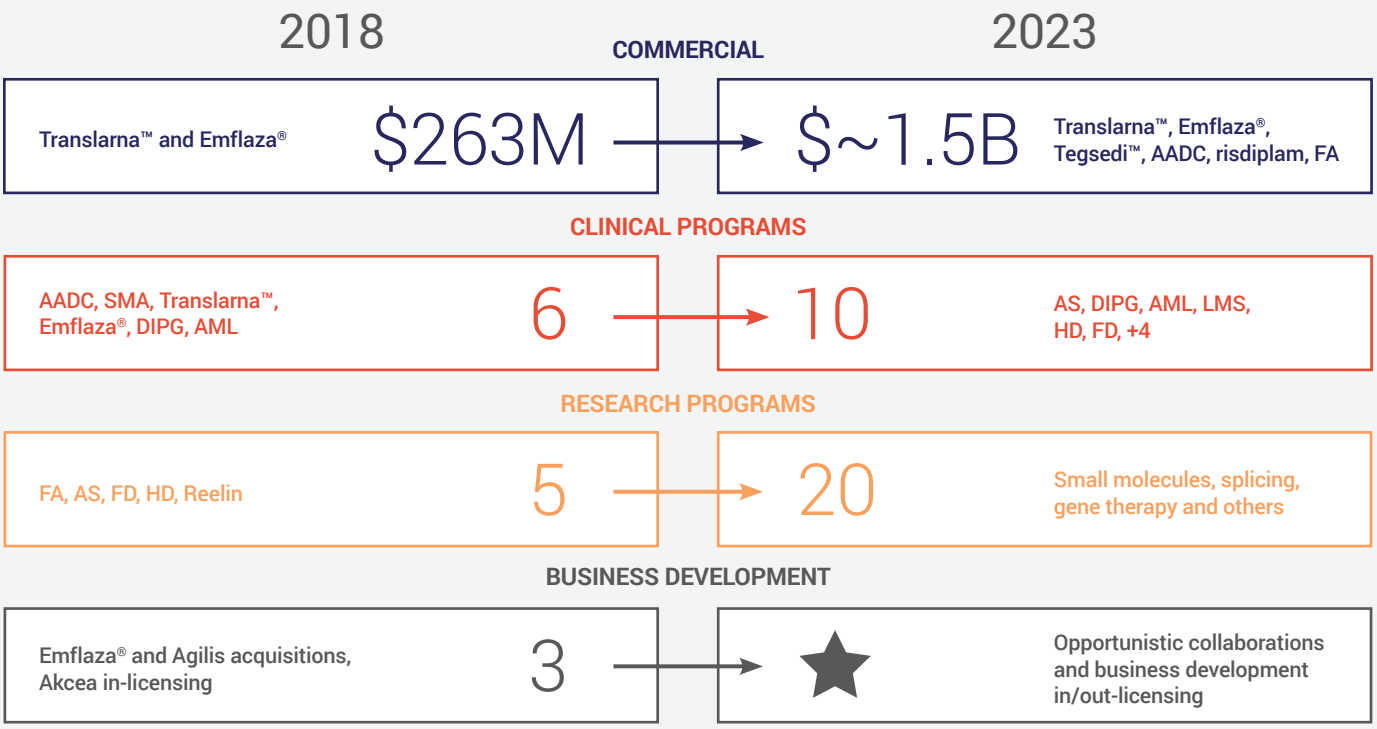
A very exciting area of focus for PTC this year is gene therapy – a technology that holds tremendous promise for some of the most debilitating and intractable rare genetic diseases. We are developing a robust pipeline of gene therapy candidates and intend to declare new candidates and secure access to a dedicated gene therapy manufacturing facility in 2019.

Our strategy in pursuing CNS-specific gene therapy includes key advantages. The first is the ability to target the specific area where the disease process is occurring, maximizing benefit/risk. Secondly, because cell turnover in the brain is low, there is the potential for durable effect and the use of small amounts of the compound (micro dosing) in the brain, which reduces the manufacturing burden. Finally, the combination of a target approach with a small dose reduces immunogenicity risk.

Our most advanced gene therapy to address AADC deficiency is expected to be submitted to the FDA in 2019. We have started pre-commercial efforts ahead of the BLA filing and have identified patients through early KOL interactions.

We plan to submit an IND in 2019 for our next gene therapy program, which is the most advanced program for the underlying cause of Friedreich ataxia. The next most-advanced discovery program is our gene therapy candidate for Angelman syndrome and we are planning to file an IND with the FDA for that program in 2020.

Looking Forward: Our Growth Vision for the Next Five Years

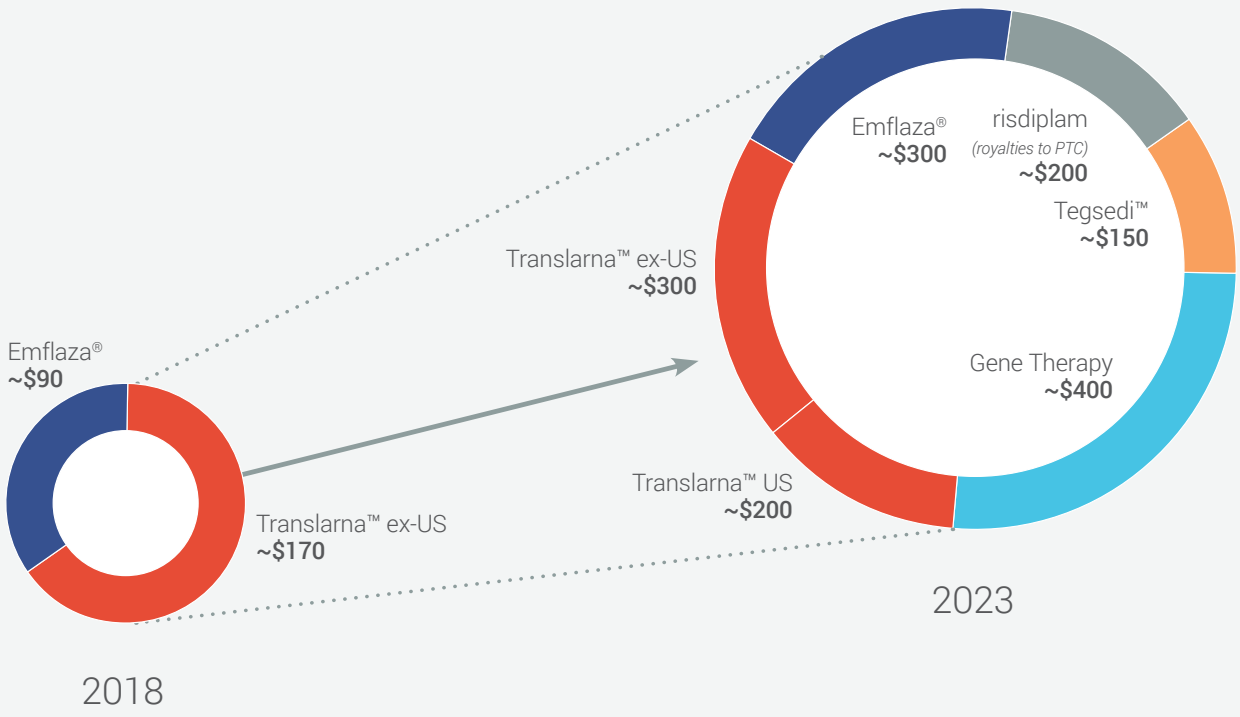


See glossary for all PTC definitions

While the progress we have made across our research, clinical and commercial fronts is impressive, we will continue to strive to identify the best therapies for patients. We know that every moment counts for rare disease patients and we are driven every day to bring meaningful improvements to the lives of patients around the world.

–Stuart W. Peltz, Ph.D., Chief Executive Officer

$1.5B Potential Revenue by 2023 ($Millions*)



*Revenue based on PTC current assumptions and estimates

We have also built a strong commercial team in rare disorders with a global footprint. We wanted to leverage our commercial platform to bring rare disease therapies to patients in all parts of the world. We recently completed our first in-licensed deal and have Latin American commercial rights to two products from Akcea; Tegsedi™ and Waylivra™. We have positioned ourselves for success in the region and have established the necessary processes to support patients, including an exclusive partnership with a nursing support team.

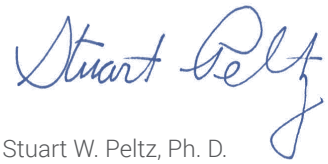
We're advancing our oncology programs in our DIPG trial with PTC596 and making great progress in our AML trial with PTC299. We expect both trials to complete enrollment by the end of 2019.

I am especially proud of the progress we've made on our splicing programs, an area of innovation in which we are both the pioneers and leading the field. An emerging area of therapeutic focus is the ability to modulate splicing with a small molecule, in which our technology produced the most advanced compound, risdiplam. This compound, which we are pursuing in collaboration with Roche and the SMA Foundation, is planned for an NDA submission to the FDA in the second half of 2019 for spinal muscular atrophy- or SMA- Types 1, 2, and 3.

This is great news for patients with SMA and it is a powerful validation of our splicing platform technology. We are applying our splicing platform to other diseases with high unmet needs, including Familial Dysautonomia (FD) and Huntington's disease. At the end of 2018, we declared the development candidate for FD and we expect to enter the clinic in 2019.

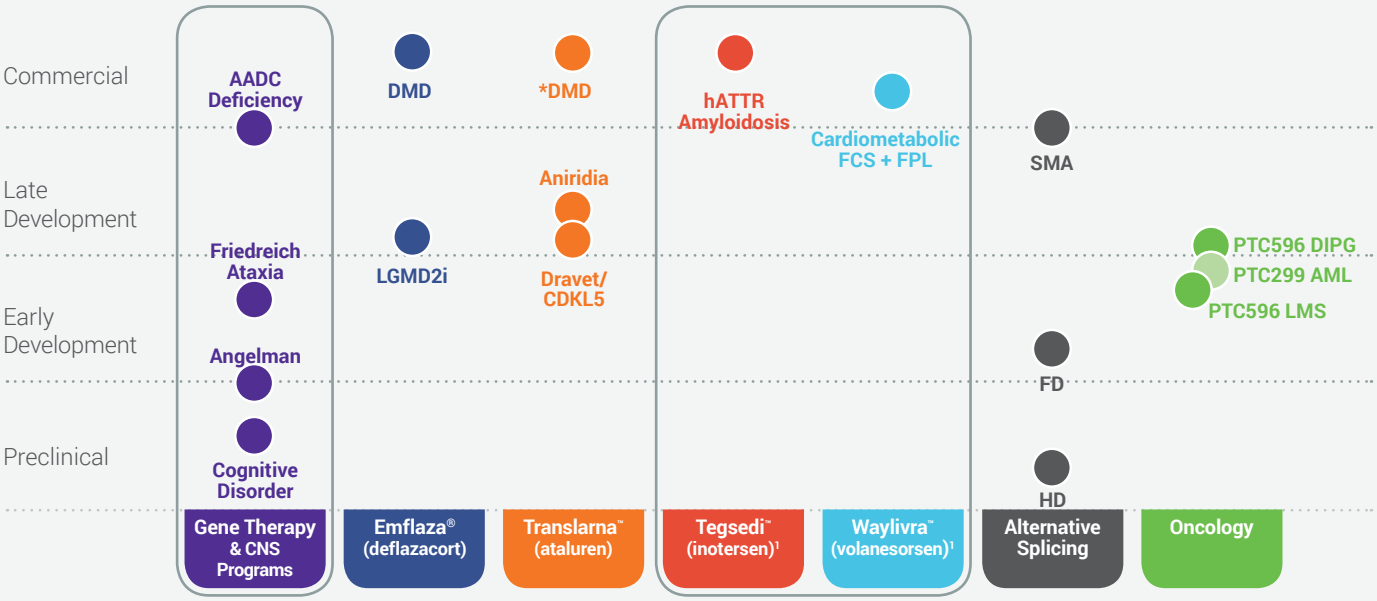
While the progress we have made across our research, clinical and commercial fronts is impressive, we will continue to strive to identify the best therapies for patients. We know that every moment counts for rare disease patients and we are driven every day to bring meaningful improvements to the lives of patients around the world.

Sincerely,



Stuart W. Peltz, Ph. D.
Chief Executive Officer

Pipeline Evolution: January 2019



Key 2018 Additions

*MA requires annual renewal following reassessment by the European Medicines Agency (EMA)

[1]In-licensed Latin American rights from Akcea Therapeutics, an affiliate of Ionis Pharmaceutics.

Leveraging PTC's Commercial Footprint in Latin America

When Akcea wanted to collaborate in Latin America, finding the right partner was a critical component. It had to be a partner with a well-established footprint and strong infrastructure in the region, as well as a documented track record of success.

It had to be PTC.

Ever since we opened our first office in the region less than five years ago, PTC in Brazil has experienced an incredible trajectory of growth and success that has made it a leader in the region.

"There was hardly any awareness of Duchenne before PTC started working in Brazil: very few physicians knew about Duchenne muscular dystrophy and there were few advocacy organizations focused on it," said Rogério Silva, Vice President and General Manager of PTC's Brazil office. "Now, all that has changed: physician awareness is high and there are more than two dozen advocacy organizations supporting patients. I'm very proud of what we have done."

This success was a key factor for Akcea, an affiliate of Ionis Pharmaceticals, with the in-licensing deal it signed with PTC in August 2018 that gave PTC two of Akcea's rare disease drugs in Latin America: TEGSEDI™ (inotersen) and WAYLIVRA™ (volanesorsen).

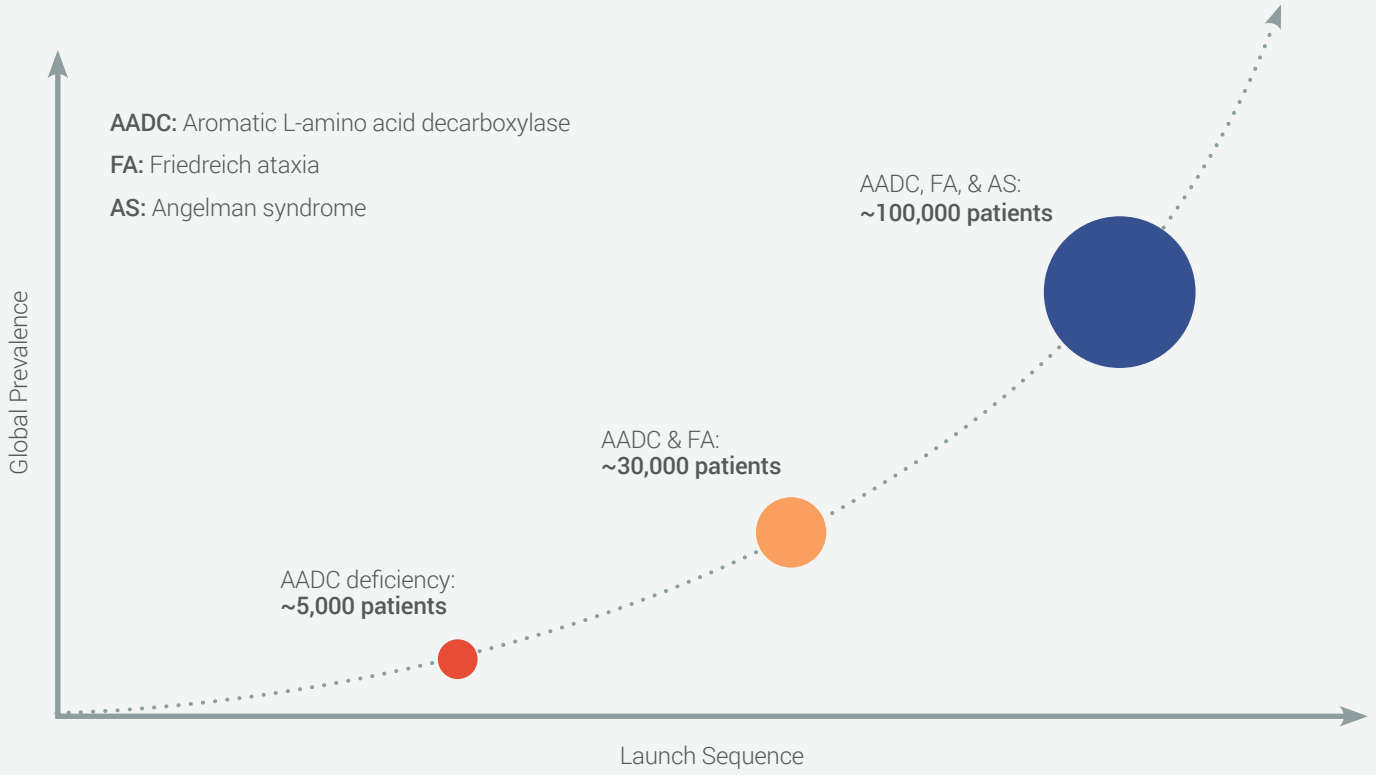
At the time the deal was announced, Akcea leadership noted several factors that sealed the deal, including PTC's commitment to patients and its established foothold in the region. Also, PTC had a proven record of success with patient identification, strong physician and patient education and support programs and success obtaining market access.

"To be successful, it's essential to have the right process and the right team in place. Leveraging our Latin American infrastructure, we completed all necessary steps to support TEGSEDI and WAYLIVRA," said Marcio Souza, Chief Operating Officer at PTC. "In addition, we added an exclusive partnership with a nursing support team to complement our efforts in the region."

Patient finding, diagnosis, and market access were the three priorities for PTC when it opened its first Latin American regional office in Brazil in 2015.

"We had to focus on disease awareness and build the market access team because there wasn't anyone to do it," said Eric Pauwels, Senior Vice President and General Manager of the Americas at PTC. "Now, we have more than 30 employees, supply chain infrastructure, and no indication that things are slowing down."

Potential Addressable Market in Excess of $5B



PTC THERAPEUTICS IN GENE THERAPY

Gene therapy holds tremendous promise for some of the most debilitating and intractable rare, genetic diseases. PTC is at the forefront of this exciting and transformative area.

PROMISE OF GENE THERAPY

01

Genetic diseases arise when a defective or missing gene stops the body producing a critical protein properly.[1]

Genes provide instructions for the body to make proteins. These are essential for the body to develop and function normally.[1]

80% of rare diseases are based on genetic mutations.[2]

02

Gene therapy works by replacing or correcting a defective gene. **In-vivo gene therapy** involves administering the corrective gene in the body.

03

Vectors are the vehicle used to carry the therapeutic gene to the correct cells in the body. Vectors are delivered to the body by local injection or intravenously. This is in-vivo gene therapy.

Modified viruses or **AAV** are not harmful and make excellent vectors.[1]

04

One-time therapy potential for a single dose to confer lifelong improvement instead of a lifetime of ongoing treatment.

x1

05

1989
First human gene therapy trial.[3]

2012
First EU approval of a gene therapy.[4]

2017
First US appproval of a gene therapy.[5]

PTC AT THE FOREFRONT

01 PTC has an **advanced gene therapy pipeline** for central nervous system (CNS) disorders.

GENE THERAPY	DISEASE	PRE-CLINICAL	CLINICAL DEVELOPMENT / PRE-REGISTRATION
PTC-AADC	AADC Deficiency		✓
PTC-FA	Friedreich ataxia		✓
PTC-AS	Angelman syndrome	✓	

02 **Targeted micro-dosing directly to specific areas of the central nervous system means:**

- Greater efficacy
- Durability of effect
- Lower risk of immunogenicity & off-target effects
- Efficient, scalable manufacturing

03 **Enhancing internal research and in-house manufacturing capabilities with fully dedicated resources to maximize current and future programs:**

- End-to-end in-house capabilities
- Maximum control over quality, capacity and supply
- Seamless transition from clinical to commercial development

These devastating, rare disorders have limited or no treatment options. Gene therapy targets the genetic cause of disease.

Aromatic L-Amino Acid Decarboxylase (AADC) Deficiency causes profound neurological and developmental failure at a very young age. Most children never hold up their head, sit, stand or speak.[6]

A defect in the DDC gene causes insufficient AADC protein, critical for dopamine production.[6] The body needs dopamine to develop/function normally.[7,8]

Friedreich ataxia (FA) can progressively rob patients of their ability to walk, speak, see and hear.[9]

A defect in the FXN gene causes loss of frataxin protein, critical for cell function.[10,11]

Angelman syndrome (AS) is characterized by profound intellectual and developmental delays.[12]

A missing maternal copy of the UBE3A gene causes insufficient ubiquitin protein ligase E3A, critical for normal development and function of the CNS.[13]

REFERENCES: 1. U.S. Food & Drug Administration website. What is Gene Therapy? How Does it Work? Available at: https://www.fda.gov/ForConsumers/ConsumerUpdates/ucm589197.htm. Last accessed April 2019. 2. EURORDIS website. About Rare Diseases. Available at: https://www.eurordis.org/about-rare-diseases. Last accessed April 2019. 3. Edelstein ML et al. Gene therapy clinical trials worldwide 1989-2004-an overview. J Gene Med. 2004 Jun;6(6):597-602. 4. European Medicines Agency Press Release (2012). European Medicines Agency recommends first gene therapy for approval. Available at: https://www.ema.europa.eu/en/news/european-medicines-agency-recommends-first-gene-therapy-approval. Last accessed April 2019. 5. U.S Food & Drug Administration. News Release (2017). FDA approves novel gene therapy to treat patients with a rare form of inherited vision loss. Available at: https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm589467.htm. Last accessed April 2019. 6. Hwu et al. Natural History of Aromatic L-Amino Acid Decarboxylase Deficiency in Taiwan. JIMD Rep. 2018; 40: 1-6. 7. The Genetic and Rare Diseases Information Center (GARD) website. Available at: https://rarediseases.info.nih.gov/diseases/770/aromatic-l-amino-acid-decarboxylase-deficiency#ref_10801. Last accessed April 2019. 8. U.S National Library of Medicine Genetics Home Reference. Aromactic l-amino acid decarboxylase deficiency. Available at: https://ghr.nlm.nih.gov/condition/aromatic-l-amino-acid-decarboxylase-deficiency#genes. Last accessed April 2019. 9. National Institute of Neurological Disorders and Stroke. Friedreich Ataxia Fact Sheet. Available at: https://www.ninds.nih.gov/Disorders/Patient-Caregiver-Education/Fact-Sheets/Friedreichs-Ataxia-Fact-Sheet. Last accessed April 2019. 10. Koeppen AH. Friedreich's ataxia: Pathology, pathogenesis, and molecular genetics. J Neurol Sci. 2011; 303 (1-2): 1-12. Doi: doi:10.1016/j.jns.2011.01.010. 11. Cook A and Giunti P. Friedreich's ataxia: clinical features, pathogenesis and management. British Medical Bulletin. 2017; 124:19-30. Doi: 10.1093/bmb/ldx034. 12. Wheeler AC, et al. Unmet clinical needs and burden in Angelman syndrome: a review of the literature. Orphanet Journal of Rare Diseases. 2017;12:164. Doi 10.1186/s13023-017-1716-z. 13. U.S National Library of Medicine Genetics Home Reference. UBE3A gene. Available at: https://ghr.nlm.nih.gov/gene/UBE3A. Last accessed April 2019.

Big Efforts for a Small Island

Ever since Hurricane Maria devastated Puerto Rico, it's been hard for most to see past the devastation, an ensuing chaos inflicted upon the Caribbean island, but a small team at PTC defied the odds to provide help to the Duchenne community.

Beyond the abandoned buildings and broken trees that are still visible more than a year after the hurricane, there are families who continue to cope with the storm's aftereffects while caring for boys with Duchenne.

"My husband's family is from Puerto Rico and I was aware of the island's struggles before the hurricane, so it was difficult for me to imagine how things would be after," said Christie Castaneda, Regional Account Manager for New York and Puerto Rico. "The only thing I did feel certain about was PTC's commitment to the Duchenne community. I knew the company would give us whatever we needed to provide physicians and patients the resources they needed."

Puerto Rico always was an under-served community where families lack financial resources and support navigating a complicated insurance process. The hurricane amplified those challenges with the extensive damaged caused to the island's infrastructure, wiping out the few resources that were available to families and physicians before the storm hit in September 2017.

PTC went beyond just providing medicine, one employee worked with the Puerto Rico chapter of the Muscular Dystrophy Association to get medical equipment and other resources donated to the Duchenne community in Puerto Rico, including solar panel chargers for electric wheelchairs. They also provided

medicine and educational support to a San Juan physician who wanted to prescribe EMFLAZA to eight boys but struggled to do so because the island's infrastructure was crippled after the hurricane.

"PTC mobilized its patient engagement, patient services, and sales teams to help physicians and families cope with these unique challenges," said Joe Mansfield, Vice President of Sales, U.S. "We knew we had kids who needed help and the prevailing message we sent to our teams was to do whatever we could to help."

STRIVE
STRATEGIES TO REALIZE INNOVATION, VISION AND EMPOWERMENT

STRIVE for Duchenne Awards

Celebrating five years of helping patient advocacy groups make a positive difference to patients and their communities.

In 2015, we launched the STRIVE grant award program for Duchenne. The program recognizes the vital role that patient advocacy groups play in meeting the needs of their local Duchenne communities by providing funding for some of the best community support projects around the world.

Over the past five years, STRIVE has supported more than 20 programs that have addressed a specific need and made a positive difference to Duchenne communities in 15 countries across **Europe, Australasia, North America, South American and Asia**.

2018 Program Highlights

"Among other achievements for the Duchenne community, the programs funded by STRIVE have improved access to diagnostic testing, supported independent living and personal empowerment, provided education for families and healthcare professionals and psychological support via a range of online platforms."

—Mary Frances Harmon, Senior Vice President, Corporate Relations

Recognizing that boys with Duchenne often miss out on the social life and activities that other children and adolescents take for granted, the *Muscular Dystrophy Association of Slovenia*, planned a 'No Parents Fun Week', giving boys with Duchenne the opportunity to take part in activities and workshops at a residential center near the coast of Slovenia. While the boys enjoyed a week of no-parent fun, their familes experienced a much-needed week of respite.

Depression and isolation can be common among those affected by Duchenne. To help address this, *DMD TURKİYE, Fight Against Duchenne* and *KASDER, Neuromuscular Disorders Association of Turkey* have applied STRIVE funds to provide a free online video conferencing service with a psychologist accessbile on the boys' smartphones.

Because Duchenne is rare, healthcare professionals often have limited understanding of its impact. *Rare Diseases Croatia* has applied funding from their STRIVE award toward their Little Big Signs of Diagnosis project, which uses video content from families affected by Duchenne in educational online training modules for medical students, and hosts screenings of the movies at local colleges.

"Patients and their communities are at the heart of everything we do and I love that STRIVE is encouraging patient communities to think outside-the-box with their solutions and plant seeds of change across the world. We look forward to continuing our quest for innovation in the area of rare diseases, as well as ongoing partnerships with the advocacy community."

—Stuart W. Peltz, Ph.D., Chief Executive Officer

Glossary

AADC: AADC Deficiency 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.

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. It is estimated that there are up to 15,000 people in the U.S. living with AS. 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. There are less than 1,000 cases per year reported in the U.S. and Canada. 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 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. 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, with an estimated 5,000 to 10,000 patients in the U.S. 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.

FD: Familial Dysautonomia (FD) is a rare genetic disorder affecting the sensory and autonomic neurons. It is caused by a splicing altering mutation in the IKBKAP gene resulting in low levels of IKAP protein, which is critical in neuronal development. Decreased expression of IKAP in certain cell types is the molecular basis for the severe, neurodevelopmental disorder.

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. There are an estimated 50,000 patients with hATTR amyloidosis worldwide. 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.

LMS: Leiomyosarcomas (LMS) are malignant tumors of muscle tissue. They are rare tumors with approximately 3,000 new cases in the U.S. There is a high rate of relapse with a median overall survival of 14 months.

Reelin: Reelin is a large protein that helps regulate processes of neuronal migration and positioning in the developing brain by controlling cell-cell interactions. It is important in early brain development and continues to work in the adult brain. It is found not only in the brain, but also in the liver, thyroid gland, adrenal gland, Fallopian tube, breast and in comparatively lower levels across different areas of the body. Reelin has been suggested to be implicated in several brain diseases.

SMA: Spinal Muscular Atrophy (SMA) is a genetic disease caused by mutation or deletion of the SMN1 (survival of motor neuron) gene. It affects one in approximately 10,000 live births and, in its most severe forms, is associated with a high rate of childhood mortality. SMA is characterized by progressive loss of α 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

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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, 2018

or

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

Commission file number: 001-35969

PTC THERAPEUTICS, INC.
(Exact name of registrant as specified in its charter)

Delaware (State or other jurisdiction of incorporation or organization)	**04-3416587** (I.R.S. Employer Identification No.)
100 Corporate Court **South Plainfield, New Jersey** (Address of principal executive offices)	**07080** (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	Name of each exchange on which registered
Common Stock, $0.001 par value	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 if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K (§229.405 of this chapter) is not contained herein, and will not be contained, to the best of registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K. ☑

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 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 29, 2018, the last business day of the registrant's most recently completed second fiscal quarter, was $1,521,120,427. 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 25, 2019, the registrant had 58,401,698 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 2019 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, 2018.

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PTC Therapeutics, Inc.

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 ability to realize the anticipated benefits of our acquisition of Agilis Biotherapeutics, Inc., or Agilis, including the possibility that the expected impact of benefits from the acquisition, including with respect to the business of Agilis and our expectations with respect to the potential achievement of development, regulatory and sales milestones and our contingent payments to the former Agilis equityholders with respect thereto, will not be realized or will not be realized within the expected time period, significant transaction costs, the integration of Agilis's operations and employees into our business, our ability to obtain marketing approval of our gene therapy for the treatment of Aromatic L-Amino Acid Decarboxylase, or AADC, deficiency, or PTC-AADC, and other product candidates we acquired from Agilis, unknown liabilities, the risk of litigation and/or regulatory actions related to the acquisition, and other business effects, including the effects of industry, market, economic, political or regulatory conditions;
- 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 Emflaza™ (deflazacort) for the treatment of Duchenne muscular dystrophy, or DMD, in the United States and for Translarna™ (ataluren) for the treatment of nonsense mutation DMD, or nmDMD, in the European Economic Area, or EEA, and other countries in which we have or may obtain regulatory approval, or in which there exist significant reimbursed early access programs, or EAP programs;
- our ability to maintain our marketing authorization of Translarna for the treatment of nmDMD in the EEA (which is subject to the specific obligation to conduct and submit the results of Study 041 to the EMA and annual review and renewal by the European Commission following reassessment of the benefit-risk balance of the authorization by the European Medicines Agency, or EMA);
- our ability to enroll, fund, and 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;
- the anticipated period of market exclusivity for Emflaza for the treatment of DMD in the United States under the Orphan Drug Act of 1983, or Orphan Drug Act, the Drug Price Competition and Patent Term Restoration Act of 1984, or the Hatch-Waxman Act;
- our ability to complete the United States Food and Drug Administration, or FDA, post-marketing requirements to the marketing authorization of Emflaza;
- our ability to complete any dystrophin study necessary in order 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 New Drug Application, or 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;
- the timing and scope of our continued commercialization of Translarna as a treatment for nmDMD in the EEA or other territories outside of the United States;
- 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;
- our expectations and the potential financial impact and benefits related to our Collaboration and Licensing Agreement with Akcea Therapeutics, Inc., or Akcea, including with respect to the timing of regulatory approval of TegsediTM (inotersen) and WaylivraTM (volanesorsen) in countries in which we are licensed to commercialize them, the potential commercialization of Tegsedi and Waylivra, and our expectations with respect to contingent payments to Akcea based on the potential achievement of certain regulatory milestones and royalty payments by us to Akcea based on our potential achievement of certain net sales thresholds;

- our estimates regarding the potential market opportunity for Translarna, Emflaza, PTC-AADC, Tegsedi, Waylivra, risdiplam or any other product candidate, 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;
- our expectations with respect to future revenue generation from Emflaza and contingent payments to Marathon Pharmaceuticals, LLC (now known as Complete Pharma Holdings, LLC), or Marathon, based on annual net sales;
- the timing and conduct of our ongoing, planned and potential future clinical trials and studies of Translarna for the treatment of nmDMD, aniridia, and Dravet syndrome/CDKL5, each caused by nonsense mutations, and Emflaza for the treatment of limb-girdle 2I, as well as studies in our gene therapy, splicing and oncology programs, including the timing of initiation, enrollment and completion of the trials and the period during which the results of the trials will become available;
- the rate and degree of market acceptance and clinical utility of Translarna, Emflaza, PTC-AADC, Tegsedi, Waylivra and risdiplam;
- 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 timing of, and our ability to obtain additional marketing authorizations for, Translarna, Tegsedi and our other product candidates;
- the ability of Translarna, Emflaza, PTC-AADC, Tegsedi, Waylivra and risdiplam and our other 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 in non-ambulatory patients or otherwise;
- the potential receipt of revenues from future sales of Translarna, Emflaza and other product candidates, including our ability to earn a profit from sales or licenses of Translarna for the treatment of nmDMD in the countries in which we have or may obtain regulatory approval and of Emflaza for the treatment of DMD in the United States;
- the potential impact that enrollment, funding and 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 Translarna and Emflaza 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 Translarna, Emflaza and our other product candidates that are sufficient to meet clinical trial and commercial launch requirements;
- our ability to increase our manufacturing capabilities for our gene therapy platform;
- our ability to satisfy our obligations under the terms of the credit and security agreement with MidCap Financial Trust, or MidCap Financial, as administrative agent and MidCap Financial and certain other financial institutions as lenders thereunder;
- our other regulatory submissions, including with respect to timing and outcome of regulatory review;
- our plans to pursue development of Translarna and Emflaza for additional indications;
- our plans to advance our earlier stage programs and pursue research and development of other product candidates, including our splicing, gene therapy 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 Translarna, Emflaza, PTC-AADC, Tegsedi, Waylivra and risdiplam and any other 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;
- our competitive position; and
- our expectations with respect to the development and regulatory status of our product candidates, including risdiplam, and 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 achievement of milestones in that program.

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 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.

PART I

Item 1. Business

Overview

We are a science-led 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 globally commercialize products is the foundation that drives our continued investment in a robust pipeline of transformative medicines and our mission to provide access to best-in-class treatments for patients who have an unmet medical need.

Our Strategy

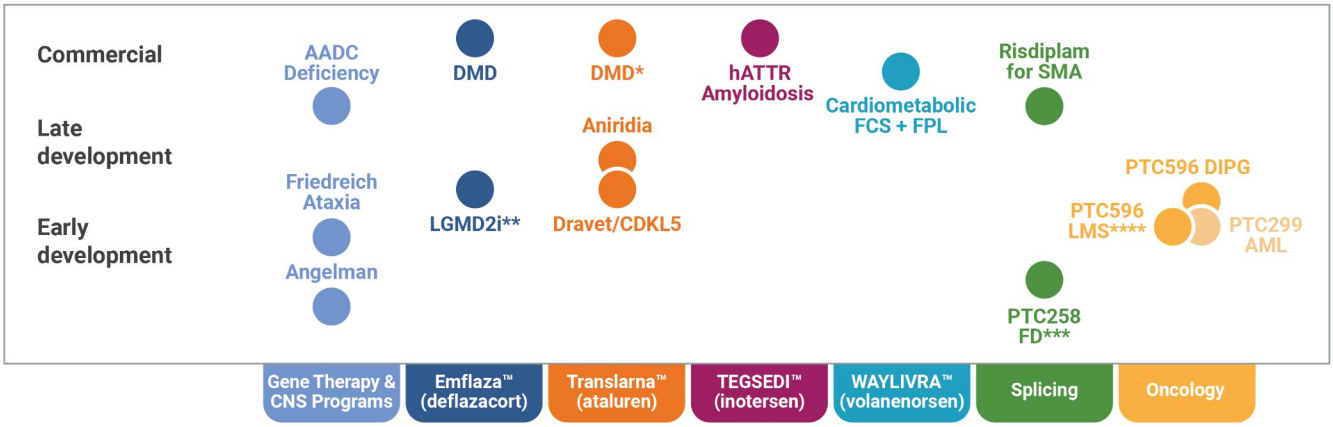
Our strategy is to bring best-in-class therapies with differentiated clinical benefit to patients affected by rare disorders and to leverage our global commercial infrastructure to maximize value for our patients and other stakeholders.

- ***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 received marketing authorization from the European Commission in August 2014 for the treatment of nonsense mutation Duchenne muscular dystrophy, or nmDMD, in ambulatory patients aged five years and older in the 31 member states of the European Economic Area, or EEA. In July 2018, the European Commission renewed our marketing authorization, which is subject to annual renewal and other conditions, and approved a label-extension to our marketing authorization to include patients from two to five years of age. During fiscal year 2018, Translarna achieved net sales of $171.0 million and is currently available for the treatment of nmDMD in over 40 countries. Emflaza is approved in the United States for the treatment of DMD in patients five years and older. During fiscal year 2018, Emflaza achieved net sales of $92.0 million.
- ***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. We are preparing a biologics license application, or BLA, for PTC-AADC for the treatment of AADC deficiency in the United States, which we anticipate submitting to the U.S. Food and Drug Administration, or FDA, in late 2019, with an anticipated commercial launch in the United States in 2020. We are also preparing a marketing authorization application, or MAA, for PTC-AADC for the treatment of AADC deficiency in the European Union, or EU, for submission to the European Medicines Agency, or EMA, which will follow our BLA submission to the FDA.
- ***Akcea Partnership*** **-** 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 our Collaboration and License Agreement with Akcea Therapeutics, Inc., or Akcea. Tegsedi has received marketing authorization in the United States, EU and Canada for the treatment of stage 1 or stage 2 polyneuropathy in adult patients with hereditary transthyretin amyloidosis, or hATTR amyloidosis, and was recently granted priority review by Agência Nacional de Vigilância Sanitária, or ANVISA, the Brazilian health regulatory authority. Waylivra is currently under regulatory review in the EU for the treatment of familial chylomicronemia syndrome, or FCS.
- ***Splicing Platform*** **-** 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. Currently, our collaboration has two pivotal clinical trials ongoing to evaluate the safety and effectiveness of risdiplam (RG7916, RO7034067), the lead compound in the SMA program. Roche is preparing an NDA and a MAA for risdiplam for the treatment of SMA in the United States and the EU, respectively, which Roche anticipates submitting to the FDA and the EMA in the second half of 2019.
- ***Pursuing Value-Creation Opportunities*** **-** In April 2017, we acquired all rights to Emflaza from Marathon Pharmaceuticals, LLC (now known as Complete Pharma Holdings, LLC), or Marathon. In August 2018, we acquired our gene therapy platform for rare monogenic diseases that affect the CNS through our acquisition of Agilis Biotherapeutics, Inc., or Agilis. Also in August 2018, we entered into a Collaboration and License Agreement with Akcea for the commercialization of Tegsedi™ (inotersen), Waylivra™ (volanesorsen) and products containing those compounds in countries in Latin America and the Caribbean. As part of our business strategy, we may engage in further 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.

Our Pipeline

In addition to our commercial products, we have a pipeline of product candidates and discovery programs at various stages of development, including clinical, pre-clinical and research and discovery stages, focused on the development of new treatments

for multiple therapeutic areas, including rare diseases and oncology. The chart below summarizes the status of our more advanced programs as of the date of this report, including those with our strategic partners:



* MA requires annual renewal for nmDMD for Translarna following reassessment by the European Medicines Agency (EMA)
** Limb-girdle 2I
*** Familial dysautonomia
**** Leiomyosarcoma

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 approximately 1 in 40,000 worldwide. While several diagnostic tests for AADC deficiency are available, the condition remains largely misdiagnosed or undiagnosed.

PTC-AADC is an adeno-associated virus, or AAV, gene therapy, which has been assessed in two completed clinical trials, and one trial in which enrollment and dosing is ongoing. 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 where dopamine is made and released, called the putamen. 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 L-Dopa cerebrospinal fluid, or CSF, levels, presence of more than one DDC gene mutation, and presence of clinical

symptoms of AADC deficiency (including developmental delay, hypotonia, dystonia, and oculogyric crisis), and 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 FDOPA 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. A total of 10 patients is planned for recruitment, of which 8 have been enrolled and treated to date. With these 8 patients, we now have 26 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. 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 late 2019, with an anticipated commercial launch in the United States in 2020. 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.

In April 2018, a protocol assistance meeting was held with the Scientific Advice Working Party of the EMA in anticipation of the expected submission of a MAA in the EU and received feedback indicating the clinical and non-clinical data available to date were sufficient to support the submission of an MAA without undertaking additional trials or studies at this time. We are preparing an MAA for the treatment of AADC deficiency with PTC-AADC in the EU, which we plan to submit to the EMA following our BLA submission to the FDA. Based on the FDA's input and feedback from the EMA, we do not deem necessary and do not plan to conduct a Phase 3 trial for PTC-AADC for the treatment of AADC deficiency.

There is no guarantee that we will be able to make the BLA or MAA submissions within our expected timelines or that following such submissions, the FDA or EMA would not have additional comments or requirements with respect to the respective submissions that we would be required to address before obtaining regulatory submission and approval, or that the FDA, the EMA or any other regulatory authority will approve PTC-AADC for treatment of AADC deficiency at all.

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 of

1983, or Orphan Drug Act. We are pursuing patent protection for PTC-AADC, and, in the meantime, 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.

Our gene therapy platform also includes a gene therapy 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. We expect to submit an investigational new drug application, or IND, to the FDA for this program in late 2019. Additionally, the gene therapy platform includes two other gene therapy programs targeting CNS disorders, including Angelman syndrome, a rare, genetic, neurological disorder characterized by severe developmental delays. We expect to submit an IND to the FDA for this program in 2020.

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 and 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. However, there can be no assurances that we will successfully obtain such label extension. In July 2018, the European Commission renewed our marketing authorization, making it effective, unless extended, through August 5, 2019. In February 2019, we submitted a marketing authorization renewal request to the EMA.

The conditional 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, as well as our satisfaction of any specific obligation or other requirement placed upon the marketing authorization, including Study 041, a three-year clinical trial to confirm the efficacy and safety of Translarna.

In January 2016, we submitted the final clinical study report from our Phase 3 clinical trial in nmDMD (referred to as ACT DMD) to the EMA in fulfillment of the initial specific obligation placed on our marketing authorization. The primary efficacy endpoint of ACT DMD was not achieved with statistical significance. We made our submission to the EMA as a type II variation request that sought to have this initial specific obligation to our marketing authorization removed and a full marketing authorization granted. In February 2016, we also submitted a marketing authorization renewal request with the EMA.

The European Commission's renewal of our marketing authorization in January 2017 was based on the totality of the clinical data available from our trials and studies of Translarna for the treatment of nmDMD, including the safety and efficacy results of our Phase 2b and Phase 3 clinical trials, and our commitment to conduct and submit the results of Study 041 to the EMA by the end of the third quarter of 2021. Due to enrollment at a slower pace in certain countries than initially expected, in our February 2019 marketing authorization renewal request, we asked the EMA to extend the timeframe for submission of the results of Study 041 to the EMA to the end of the third quarter of 2022. 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. See "Item 1. Business-Planned and ongoing clinical development of Translarna in nonsense mutation Duchenne muscular dystrophy-Study 041" for further information regarding the specific obligation to the marketing authorization in the EEA. The authorization remains subject to the annual EMA reassessment, as the EMA did not grant our request for full marketing authorization.

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 U.S. 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 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 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 intend to follow the FDA's recommendation and will collect, using newer technologies via procedures and methods that we designed, such dystrophin data in a new study, Study 045, which we initiated in the fourth quarter of 2018. We expect that a potential re-submission of an NDA could occur in 2020. Additionally, should a re-submission of an NDA receive accelerated approval, the Office of New Drugs stated that Study 041, which is currently enrolling, could serve as the confirmatory post-approval trial required in connection with the accelerated approval pathway.

There is substantial risk that Study 045, or any other studies we may use to collect the dystrophin data, will not provide the necessary data to support a marketing approval for Translarna for the treatment of nmDMD in the U.S.

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 and Chile in 2018 and these licenses are currently active. We have filed for marketing authorization with ANVISA, the Brazilian regulatory authority. We expect a regulatory decision on approval in Brazil by the end of 2019. 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 determines not to renew or otherwise modifies or withdraws our marketing authorization in the EEA. 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. We estimate that there are between approximately 10,000 and 15,000 DMD patients in the United States. We are obligated to complete certain post-marketing requirements in connection with the FDA's approval, including pre-clinical and clinical safety studies. In recent interactions with the FDA, we were invited to submit a supplementary NDA, or sNDA, for Emflaza for patients 2 to 5 years of age on the basis that existing data support its safety and efficacy in this population. We recently submitted the sNDA for potential approval in 2019, recently received an approval action date of July 4, 2019, and now expect to launch Emflaza in this younger population before the end of 2019.

Emflaza has a seven-year exclusive marketing period in the United States for the approved indication, commencing on the date of FDA approval, under the provisions of the Orphan Drug Act of 1983, or the Orphan Drug Act, as well as a concurrent five-year exclusive marketing period in the United States for the active moiety in Emflaza under the provisions of the Drug Price Competition and Patent Term Restoration Act of 1984, or the Hatch-Waxman Act. In 2017, the FDA had requested that we conduct a pediatric study of Emflaza, which, upon completion of an agreed-upon study, we expected to be granted a six-month term of pediatric exclusivity, added to the end of the term of any existing regulatory exclusivity, including the seven-year orphan exclusivity period. With the invitation to submit the sNDA, discussed above, this previous request from the FDA that a trial in patients 2 to 5 years of age be performed has been officially withdrawn and the trial will no longer be conducted, and therefore we will no longer receive the six-month term of pediatric exclusivity. See “Item 1. Business-Government Regulation-The new drug and biologic approval process-Hatch-Waxman Act for Drugs” below for further discussion with respect to marketing protection we rely on.

Akcea Partnership

In August 2018 we entered into a Collaboration and License Agreement with Akcea for the commercialization by us of Tegsedi™ (inotersen), Waylivra™ (volanesorsen) and products containing those compounds in countries in Latin America and the Caribbean, or the PTC Territory. See “Item 1. Business-Our Collaboration and Funding Arrangements-Akcea Therapeutics” below for further discussion with respect to our Collaboration and License Agreement with Akcea.

Tegsedi

Tegsedi, a product of Ionis Pharmaceuticals, Inc.’s, an affiliate of Akcea, 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. It has received marketing authorization in the U.S., EU and Canada for the treatment of stage 1 or stage 2 polyneuropathy in adult patients with hATTR amyloidosis. We have filed for marketing authorization with ANVISA, which granted priority review. We expect approval in Brazil by the end of 2019.

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 under regulatory review in the EU for the treatment of familial chylomicronemia syndrome, or FCS. The U.S. and EU regulatory agencies have granted orphan drug designation to Waylivra for the treatment of FCS. In August 2018, Waylivra received a Complete Response Letter from the FDA's Division of Metabolism and Endocrinology Products. In the fourth quarter of 2018, Waylivra received a notice of noncompliance withdrawal letter from Health Canada. Additionally, Waylivra is currently in Phase 3 clinical development for the treatment of people with familial partial lipodystrophy, or FPL. The EMA has granted orphan drug designation to Waylivra for the treatment of patients with FPL.

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.

Neither Tegsedi nor Waylivra is currently approved for marketing in the PTC Territory.

Product development programs

Our pipeline has a number of development programs in the clinical and pre-clinical stages. These include our splicing, gene therapy and oncology programs as well additional studies of our current commercial products to both expand marketing labels and find benefits that these treatments may have in additional indications.

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 messenger RNA, or 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 the results of Study 041 to the EMA by September 2021. Due to enrollment at a slower pace in certain countries than initially expected, in our February 2019 marketing authorization renewal request, we asked the EMA to extend the timeframe for submission of the results of Study 041 to the EMA to the end of the third quarter of 2022. The protocol for Study 041 has been approved by the CHMP.

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

Enrollment. According to the study protocol, Study 041 will enroll 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 will also need 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.

Of the approximately 250 patients planned to be enrolled in Study 041, approximately 160 patients are expected to 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).

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, was initiated in the fourth quarter of 2018, and will have a 40-week study period. We expect the study to be completed in the first quarter of 2020.

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 the five-year 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)%	103 (89.6)%	204 (88.7)%
Adverse events by severity			
Grade 1 (mild)	54 (47.0)%	61 (53.0)%	115 (50.0)%
Grade 2 (moderate)	37 (32.2)%	35 (30.4)%	72 (31.3)%
Grade 3 (severe)	9 (7.8)%	7 (6.1)%	16 (7.0)%
Grade 4 (life-threatening)	—	—	—
Adverse events by relatedness			
Unrelated	47 (40.9)%	44 (38.3)%	91 (39.6)%
Unlikely	30 (26.1)%	20 (17.4)%	50 (21.7)%
Possible	18 (15.7)%	27 (23.5)%	45 (19.6)%
Probable	6 (5.2)%	12 (10.4)%	18 (7.8)%
Discontinuations due to adverse events	1 (0.9)%	1 (0.9)%	2 (0.9)%
Serious adverse events	4 (3.5)%	4 (3.5)%	8 (3.5)%
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).

Translarna™ for additional indications

Over the last seven years, multiple independent investigators have conducted preclinical studies in which Translarna enabled readthrough of the premature stop codons from a large set of nonsense mutations across a diverse group of experimental models exhibiting various genetic disorders. The studies evaluated the ability of Translarna to read through premature stop codons in mRNA in cell-free systems, transfected cell lines, mouse models and patient cells. Based on these studies by independent investigators in addition to our own trials and studies, we expect to continue to pursue additional indications for Translarna, including aniridia caused by nonsense mutation and, via an investigator initiated study, Dravet syndrome/CDKL5 caused by nonsense mutation.

Nonsense mutation aniridia

Aniridia is a genetic disorder due to mutations in the PAX6 gene associated with ocular anatomical defects at birth, progressive loss of eyesight, and other symptoms. We estimate that approximately one-third of all aniridia cases are due to a nonsense mutation.

In a prior study conducted by an independent investigator, Translarna-treated mice with nonsense mutation aniridia showed a significant increase in the PAX6 protein in a nonsense mutation PAX6 gene, but not in mice with a PAX6 gene harboring a splice-site mutation. The investigators in this study found that Translarna not only inhibited disease progression, but also reversed corneal, lens and retinal defects and restored electrical responses of the retina.

The first patient in our clinical study of Translarna in nonsense mutation aniridia, which we refer to as STAR, was dosed in February 2016. STAR is a Phase 2, randomized, double-blinded, placebo-controlled study of Translarna in patients with aniridia caused by a nonsense mutation, followed by an open-label extension study. Patients will receive blinded study drug for 48 weeks followed by open-label Translarna for another 96 weeks. The open label portion of the study was extended from the initially planned 48 weeks to 96 weeks as our knowledge of the disease and endpoint evolved from when the study was originally initiated. Safety and efficacy will be assessed. We have completed enrollment for our aniridia study and anticipate results during 2019.

Nonsense mutation Dravet syndrome/CDKL5

Dravet syndrome and CDKL5 are two different genetically defined disorders of epilepsy. Dravet syndrome, also called severe myoclonic epilepsy of infancy, is a debilitating form of epilepsy caused by mutations in the sodium voltage gated channel a1 subunit gene required for the proper function of brain cells. People with Dravet syndrome experience frequent seizures and developmental delays. CDKL5 is caused by a mutation of the Cyclin-dependent kinase-like 5 (CDKL5) gene leading to a lack of the protein critical in brain development. CDKL5 is characterized by seizures starting early in life and severe developmental impairment.

A clinical study assessing Translarna in nonsense mutation Dravet syndrome/CDKL5 was initiated in the first quarter of 2017. The study is an investigative trial and we do not expect to use it as the basis for a regulatory submission. The study is fully enrolled and we expect it to be completed in the first quarter of 2021, at which point we will reassess the program.

Emflaza for Limb-girdle 2I

Limb-girdle muscular dystrophy type 2I, or LGMD2I, is a form of limb-girdle muscular dystrophy, which refers to a group of conditions that cause weakness and wasting of the muscles in the arms and legs. The proximal muscles (those closest to the body such as the upper arms and thighs) are generally most affected by the condition. In LGMD2I, specifically, signs and symptoms often develop in late childhood (average age 11.5 years) and may include difficulty running and walking. The symptoms gradually worsen over time and affected people generally rely on a wheelchair for mobility approximately 23-26 years after onset. LGMD2I is caused by changes (mutations) in the FKRP gene and is inherited in an autosomal recessive manner. There is currently no cure for LGMD2I and treatment is based on the signs and symptoms present in each person.

We plan on initiating a clinical study assessing Emflaza in limb-girdle 2I in the second quarter of 2019. The study is expected to be a 52 week placebo controlled study and we anticipate results during 2020.

Splicing Platform

Spinal muscular atrophy program

Spinal muscular atrophy, or 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, SMN2, is very similar to SMN1, except that SMN2 contains a T nucleotide at position 6 in exon 7 that results in splicing and production of reduced levels of functional SMN protein. According to the SMA Foundation, SMA is the leading genetic cause of death in infants and toddlers and that one in approximately 11,000 children is born with the disease. We estimate that SMA affects approximately 20,000 to 30,000 children and adults in the United States, Europe and Japan.

Using our splicing technology and in collaboration with the SMA Foundation, 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 mRNA and the levels of SMN protein produced by SMN2. 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 collaboration and licensing agreement with Roche which included a $30 million upfront payment, the potential for up to $460 million in milestone payments and royalties on net sales. Roche is responsible for pursuing clinical development of compounds from the research program under the collaboration and then commercializing any resulting products. We have received $47.5 million in milestone payments from Roche, including a $20 million milestone payment upon the transition into the pivotal second part of the Sunfish study for risdiplam. We also previously received $13.3 million in sponsored research funding for this program from the Spinal Muscular Atrophy Foundation.

One of the compounds in the SMA collaboration that is currently being advanced in development is risdiplam. In October 2016, a two-part clinical study, called Sunfish, initiated in pediatric and adult type 2 and type 3 SMA patients to investigate the safety, tolerability, and efficacy of risdiplam. Both parts of Sunfish are double-blinded, placebo-controlled, and randomized. Part one of the study was a dose-finding study in 51 type 2 and type 3 SMA patients randomized 2:1 risdiplam vs. placebo and treated for 12 weeks with the primary objective of evaluating the safety, pharmacokinetics, and pharmacodynamics of risdiplam in patients. Data from the open label extension of part 1 of the Sunfish trial were presented in October 2018 at the 23rd International Annual Congress of the World Muscle Society, or the World Muscle conference. Risdiplam was well-tolerated at all doses and there have been no drug-related safety findings leading to withdrawal. In Sunfish, the data demonstrated that the previously reported median greater-than-2-fold SMN protein level increase was maintained over 52 weeks of treatment indicating the durability of the pharmacodynamic effect.

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 million milestone payment to us from Roche. Part two of Sunfish completed recruitment in October 2018 with 180 type 2 and type 3 SMA patients enrolled. The patients are randomized 2:1 risdiplam vs. placebo for 12 months followed by 12 months of all study participants receiving risdiplam. Patients enrolled in part 2 of Sunfish have a broad age range (2-24 years; median age 8 years) and broad functional characteristics. The primary endpoint is change from baseline in the total Motor Function Measure 32, or MFM-32, score at Month 12. Both part one and part two of the study will be followed by an open-label extension.

In December 2016, a two-part clinical study, called Firefish, also initiated in infants with type 1 SMA to investigate safety, tolerability, and efficacy of risdiplam. 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 one was to assess the safety profile of risdiplam in infants and determine the dose for part two. Interim clinical data from the Firefish part 1 trial were also presented in October 2018 at the World Muscle conference. The median age of first dose was 6.7 months and babies have received risdiplam for a duration of up to 20.3 months. Risdiplam has been well tolerated at all doses and there have been no drug-related safety findings leading to withdrawal. At day 245 of treatment, over 90% of the babies achieved a greater than 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. The CHOP-INTEND data were further supported by video footage presented by a principal investigator in the trial, who showed a video of an additional type 1 SMA baby sitting unassisted, bringing the total to 4 babies sitting unassisted as shown in patient videos. Natural history indicates that type 1 SMA babies never achieve this milestone. The video also showed type 1 SMA babies from the Firefish trial demonstrating head control and rolling. Moreover, no babies have required a tracheostomy or permanent ventilation since study initiation and no baby has lost the ability to swallow. 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 one of Firefish, part two of Firefish was initiated in March 2018 and completed recruitment in November 2018 with 41 type 1 SMA infants enrolled. The primary objective of part two is to assess the efficacy of risdiplam measured as the proportion of infants 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).

Based on recent feedback from the FDA and national health authorities in Europe that Part 1 of FIREFISH and SUNFISH may be sufficient to file NDA and an MAA, Roche is preparing an NDA and a MAA for risdiplam for the treatment of SMA in the United States and the EU, respectively, which Roche anticipates submitting to the FDA and the EMA in the second half of 2019.

Jewelfish, an open-label study investigating the safety, tolerability, PK, and PK/pharmacodynamic relationship of risdiplam in type 2 and type 3 SMA patients who have been previously treated with one of several experimental SMA therapies, initiated in the first quarter of 2017. Preliminary PD 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, risdiplam was well tolerated, without drug- related adverse events leading to withdrawal from the study.

Familial dysautonomia

Familial dysautonomia, or FD, is a rare genetic neurological disorder that effects the sensory and autonomic nervous systems, causing life-threatening medical complications from birth. It is caused by a splicing-altering mutation in the IKBKAP (ELP1) gene resulting in low levels of IKAP protein. FD occurs primarily in people of Ashkenazi (central or eastern European) Jewish descent, affecting about 1 in 3,700 individuals in Ashkenazi Jewish populations. It is extremely rare in the general population. There are currently no available therapies for FD, only supportive treatments.

Using our splicing technology and in collaboration with the with Massachusetts General Hospital, or MGH, and New York University, we identified the splicing compound PTC258 which is a splicing modifier that restores IKAP levels. We expect to finalize IND-enabling studies and submit an IND for PTC258 in late 2019.

Oncology program

We have two oncology agents in Phase 1 clinical development, PTC299 and PTC596. PTC299 is a small molecule dihydrooratate dehydrogenase (DHODH) inhibitor that inhibits de novo pyrimidine nucleotide synthesis. In the fourth quarter of 2018, we initiated a Phase 1 dose-escalation trial in patients diagnosed with acute myelogenous leukemia, or AML, who have relapsed or are refractory to current treatment options and have no other approved treatment options. We expect to fully enroll this trial by the end of 2019. In addition to assessing PTC299 as a monotherapy in our Phase 1 study, we are also assessing PTC299 in a variety of therapeutic combinations preclinically.

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.

PTC596 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 PTC596 in a Phase 1 trial as a monotherapy for the treatment of ovarian cancer and we are in the process of reformulating PTC596 as a tablet to decrease pill burden and minimize exposure to excipients. PTC596 is now being assessed in clinical trials in combination with standards of care in pediatric patients with diffuse intrinsic pontine glioma, or DIPG, in combination with radiation as first-line therapy, with PTC596 continuing as monotherapy after radiation is completed. 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 and Canada. In the fourth quarter of 2018, we initiated a Phase 1 dose-escalation trial in DIPG patients and expect to fully enroll this trial by the end of 2019.

PTC596 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 PTC596 had synergistic effects in combination with dacarbazine. Of about 3,000 sarcoma patients diagnosed annually in the U.S., approximately 20% have LMS. We expect to initiate a Phase 1 dose escalation study of PTC596 for LMS in the first quarter of 2019.

We received grant funding of $5.4 million for our oncology program from the Wellcome Trust. 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. 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”.

Pre-clinical and other programs

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 RNA and DNA approaches.

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 precursor messenger RNA, or pre-mRNA, molecules are spliced, and how efficiently mRNA molecules are translated to produce a protein. In the majority of human protein-encoding genes, the sequence representing the mature mRNA transcript is not contiguous but rather has an interrupted structure consisting of nucleotide sequences, called introns, that are removed from the final mRNA product and nucleotide sequences, called exons, that are retained in the mature mRNA. The process of intron removal and exon joining is called splicing.

We use our splicing technology to identify molecules that modulate splicing of the pre-mRNA. Pre-mRNA splicing is a multi-step biochemical reaction. Approximately 94% of all human genes encode pre-mRNAs that undergo splicing. In addition, through splicing, one gene can often generate several mRNA products by including or excluding exons that can result in the mRNA being regulated differently or translated into different proteins. Altered regulation of splicing is the direct cause of many human diseases, including many forms of cancer, SMA, Riley-Day syndrome (familial dysautonomia) and myotonic dystrophy.

We have developed a powerful high-throughput drug discovery technology that enables us to identify small molecule modifiers of pre-mRNA splicing. The technology relies on a sensitive quantification of mRNA directly in human cells or tissue samples.

Using this technology, we have successfully identified orally bioavailable small molecules that correct splicing of the Survival of Motor Neuron 2, or SMN2, mRNA, which is implicated in the genetic disorder SMA. Based on this experience, we believe that other small molecule drug candidates can be rapidly identified that correct splicing of pre-mRNA, promote inclusion of specific exons into mRNA 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 in all therapeutic areas.

Nonsense suppression

An mRNA contains multiple regions that have specific functions. Although the protein coding region of mRNA contains the information for the amino acid sequence of the protein product, 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 on the mRNA determine when and how much protein is produced as well as how mRNA is degraded and eliminated from the cell.

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 a full-length protein. We anticipate that this approach will be applicable to a wide variety of therapeutic areas.

In addition to identifying molecules that increase readthrough, we are identifying molecules that can enhance the nonsense suppression effect of Translarna and other readthrough agents 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 eliminate 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 developed competitive advantages and a gene therapy platform which we believe is highly differentiated and provides practical approaches for delivery of gene therapies to the CNS in a range of disease indications. Our platform utilizes commercially-available advanced 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 and keeps the dose levels low. 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 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, and a collaboration and license agreement with Akcea for Tegsedi and Waylivra. We also have received grant funding from Wellcome Trust pursuant to funding agreements under which we have continuing obligations. In addition to these collaboration, license and funding agreements, which are described in more detail below, during 2015 we announced our research collaboration with Massachusetts General Hospital, or MGH, a Partners Healthcare hospital, for the treatment of rare genetic disorders resulting from pre-mRNA splicing defects pursuant to which we have certain licensing, development and commercialization obligations to MGH.

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 million in payments if specified development and regulatory milestones are achieved and up to an aggregate of $325 million in payments if specified sales milestones are achieved. As of December 31, 2018, we have earned $47.5 million of these development and regulatory milestone payments based on the progression of the collaboration from the pre-clinical stage to Phase 2 clinical study in SMA patients. 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.

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, if we outlicense rights to a collaboration product, 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 a specified amount, 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 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 GT-AADC 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, 2018, an aggregate amount of $617,045 in funding payments has been paid to NTU and an additional $197,266 is expected to become due and payable between now and December 31, 2020.

Intellectual property. All intellectual property developed or obtained by NTU relating to the Research shall 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 September 30, 2020, 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. The NTU Licensing Agreement also stipulates milestones in relation to a Phase 3 trial with respect to PTC-AADC for the treatment of AADC deficiency, which such Phase 3 trial we do not deem necessary and do not plan to conduct.

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 a 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.

Akcea

Overview. In August 2018, PTC Therapeutics International Limited, our subsidiary, entered into a Collaboration and License Agreement, or the Akcea Agreement, with 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 Akcea 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 Akcea 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 affiliate, Ionis Pharmaceuticals, Inc., or 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 agreed to pay 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 Akcea Agreement, and $6.0 million to be paid within 30 days after receipt of regulatory approval of Waylivra from the FDA or the EMA, whichever occurs earlier. In addition, Akcea is 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. 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 Akcea 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 Akcea 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 Akcea 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 Akcea 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.

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 and antibacterial programs. 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, which we refer to as our oncology program. 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 PTC596 (for our oncology program), 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 program. 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 program. 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 PTC596, 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.

Additional continuing financial obligations. Our obligation to pay the royalties describe 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).

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 foreign 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, 2019, our patent portfolio included a total of 74 active U.S. patents and 13 pending U.S. patent applications, including original filings, continuations and divisional applications, as well as numerous foreign counterparts to many of these patents and patent applications. We own or exclusively in-license these patents and patent applications with claims directed to composition of matter, pharmaceutical formulation and methods of use of many of our compounds, including ataluren, the active ingredient in the formulated product Translarna™.

The patent rights relating to Translarna™ (ataluren) owned by us consist of 35 issued U.S. patents relating to composition of matter, methods of use, formulation, dosing regimens and methods of manufacture and multiple pending U.S. patent applications relating to composition of matter, 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 Africa countries, certain Asian countries and certain Eurasian countries. We own nine 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. The expiration dates of the granted European patents occur for composition of matter in 2024, for dosing regimen patents in 2026 and 2027, and for the manufacturing process in 2027. 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 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 NDA submission that the drug is under regulatory review 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 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.

Similar provisions are available in Europe and certain other foreign 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 (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. In the future, if and when our product candidates receive approval by the FDA or other non-European foreign 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 presently have no patent rights to protect the approved use of Emflaza, and we rely on non-patent market exclusivity periods under the Orphan Drug Act of 1983, or the Orphan Drug Act, and the Drug Price Competition and the Hatch-Waxman Act to commercialize Emflaza in the United States. See "Item 1. Business-Government Regulation-The new drug and biologic approval process-Hatch-Waxman Act for Drugs" for further information regarding the exclusivity periods that we rely on.

We are pursuing patent protection for PTC-AADC and our other gene therapy product candidates, and, in the meantime, if PTC-AADC is approved, we expect to rely on the non-patent market exclusivity periods under the Orphan Drug Act Biologics Price Competition and Innovation Act of 2009, or 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 rely on.

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, by confidentiality agreements with our employees, consultants,

scientific advisors and contractors. 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, 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 consultants, contractors or collaborators use intellectual property owned by others in their work for us, disputes may arise as to the rights in related or resulting know-how and inventions.

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-license all of the patents and patent applications, with claims directed to composition of matter, formulation and methods of use, for our gene therapy programs, including for the target disease 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 Collaboration, Licensing and Funding Arrangements-National Taiwan University."

Manufacturing

We do not own or operate manufacturing or distribution facilities for the production of clinical or commercial quantities of Translarna, Emflaza or for our other 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 Translarna, Emflaza as well as any other product or product candidate that we may develop, other than small amounts of compounds that we may synthesize ourselves for preclinical testing. We anticipate taking steps to increase our manufacturing capabilities for our gene therapy platform.

The active pharmaceutical ingredients in Translarna, Emflaza and our 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 and the drug substance for our oncology program through another third-party manufacturer.

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, although we are still in the process of finalizing arrangements with one of these manufacturers with respect to commercial product services.

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. We may be unable to conclude agreements for commercial or clinical supply with third-party manufacturers, or may be unable to do so on acceptable terms.

We currently obtain our supplies of Translarna and our other 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. 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 initial term of five years. 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 expect to rely market exclusivity periods available to us under the Orphan Drug Act and Hatch-Waxman 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 presently contract with third parties for the manufacturing of program materials for our gene therapy product candidates. The use of contracted manufacturing and reliance on collaboration partners is relatively cost efficient. Although we rely on contract manufacturers, we have personnel with manufacturing and quality experience to oversee our contract manufacturers. Although we anticipate taking steps to increase our manufacturing capabilities for our gene therapy platform, we currently rely on third-party manufacturers to be capable of providing sufficient quantities of our program materials to meet anticipated clinical trial and commercial scale demands.

Translarna and Emflaza are manufactured in reliable and reproducible synthetic processes. Our raw materials are not scarce and are readily available. 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. No shortages or delays of raw materials were encountered in 2018, and none are currently expected in 2019. 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.

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 foreign regulatory authorities. We depend on our third-party suppliers and manufacturers for continued compliance with cGMP requirements and applicable foreign standards.

We currently have a contract with a pharmacy and hospital distributor in the European Union that distributes Translarna for clinical programs and 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 a specialty pharmacy to sell and distribute Emflaza to patients. The specialty pharmacy provides us with third-party call center services to provide patient support and financial services, prescription intake and distribution, reimbursement adjudication, and ongoing compliance support.

Commercial Matters

Sales and marketing team

Our product revenue has 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. In addition to the United States and multiple European countries, we have employees in Latin America and Canada. As of December 31, 2018, our commercial team was comprised of approximately 110 employees, including support personnel and members of our commercial team who work with physicians, patient advocacy groups and other stakeholders who are involved in the treatment of patients suffering from the diseases for which we seek to develop treatments.

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 Translarna. We continue to evaluate new territories to determine in which geographies we might, if approved, choose to commercialize Translarna 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 2018, our product revenue was 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 a single, exclusive specialty pharmacy to sell and distribute Emflaza to patients. The specialty pharmacy receives prescription orders for Emflaza directly from physicians and ships 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 2018, three 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 15, "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. We have never had a request for a product return 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.

Market Access Considerations

Translarna for the treatment of nmDMD is currently available on a commercial basis in Austria, Czech Republic, Denmark, Hungary, Israel, Italy, Latvia, Norway, Portugal, Romania, Slovakia, Slovenia, Sweden and the United Kingdom (including England, Scotland, Northern Ireland, and Wales). Commercial drug is also currently available in Germany, subject to the matters discussed below. We consider Translarna to be commercially available when a reference price for the drug is established in the applicable country and 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 Argentina, Brazil, Canada, Colombia, Cyprus, Ecuador, France, Greece, Hong Kong, Kuwait, Lebanon, Russia, Saudi Arabia, Singapore, Spain, Switzerland, Turkey and United Arab Emirates. 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 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. See "Item 1. Business-Marketing authorization matters for Translarna in nonsense mutation Duchenne muscular dystrophy-European Economic Area" 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 Translarna, Emflaza 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 complete. As a result, our commercial launch 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 that can be realized 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.

We delisted Translarna from the German pharmacy ordering system, effective April 1, 2016, based on unsustainable pricing established by the arbitration board in Germany. However, patients and healthcare professionals in Germany have generally been able to access Translarna through a reimbursed importation pathway possible under German law. There can be no assurance that all such patients will continue to be successful in obtaining reimbursed access to Translarna.

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 pharmacy we utilize provides patient services program to support product access and, when eligible, out-of-pocket assistance.

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.

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 Translarna, Emflaza, PTC-AADC, Tegsedi, Waylivra, risdiplam and our other 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 Translarna, Emflaza and our other 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 recently received approval in the United States for a treatment addressing the underlying cause of disease for different mutations in the DMD gene. Other biopharmaceutical companies are developing treatments addressing the underlying cause of disease for different mutations in the DMD gene (Sarepta, Daiichi Sankyo, Nippon Shinyaku, and Solid Biosciences).
- ***Translarna for Other Indications.*** Diacomit is marketed in the European Union by Laboratoires Biocodex for the treatment of Dravet syndrome. In the United States, both GW Pharmaceuticals and Zogenix have approved products for the treatment of Dravet syndrome. Aniridia therapeutic interventions, such as artificial iris implantation, are being developed by HumanOptics AG.
- ***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.
- ***Gene therapy product candidates.*** 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. While there is currently no treatment options

available for FA, Voyager Therapeutics is also working on pre-clinical studies for a potential gene therapy solution. 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.

- ***Risdiplam.*** Risdiplam also faces competition. For example, in December 2016, the FDA approved nusinersen, a drug developed by Ionis Pharmaceuticals, Inc. and marketed by Biogen, to treat SMA. AveXis, Inc., (acquired by Novartis in 2018) is also evaluating a gene therapy product candidate for the treatment of SMA. Other companies are also pursuing product candidates for the treatment of SMA, including Trophos (also in collaboration with Roche), Kowa, Novartis Pharmaceuticals Corporation, and Cytokinetics.
- ***Waylivra.*** If approved, Waylivra could face competition from drugs like metreleptin. Metreleptin, produced by Novelion Therapeutics, Inc., is currently approved for use in generalized lipodystrophy patients.
- ***Tegsedi.*** Tegsedi could face competition from drugs like patisiran and ALN-TTRsc02 in development by Alnylam, tafamidis commercialized in some countries in LATAM by Pfizer and tolcapone in development by SOM Biotech.

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 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 foreign 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, 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, until recently, the National Institutes of Health, or the NIH, through its Recombinant DNA Advisory Committee, or RAC, also reviewed certain proposed gene therapy trials pursuant to the NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules, or NIH Guidelines,; however, the NIH recently proposed to change this practice so that the RAC will no longer review individual human gene transfer protocols. Certain aspects of the NIH Guidelines, such as review of studies by Institutional Biosafety Committees, or IBCs remain in effect. The NIH has stated that it will finalize this change after taking public comments. 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.

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 Biologics License Application, or 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 biologics 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 with 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 gene therapy studies, 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. Gene therapy research must also be conducted in accordance with the 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 current good manufacturing practices, or 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 the 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. 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 gene therapy studies, an IBC at the local level must 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 National Institutes of Health, or 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 requests. 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 represent the first human clinical trial 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 approval may be based upon a single adequate and well-controlled clinical trial plus 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.

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.

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 stability studies must be conducted to demonstrate that the biologic product candidate does not undergo unacceptable deterioration over its shelf life.

If a drug or biologic product's approved indication is dependent on the measurement or detection of specified biomarkers, the therapeutic approval may require the contemporaneous approval or clearance of an *in vitro* companion diagnostic device. An *in vitro* companion diagnostic device provides information that is essential for the safe and effective use of a corresponding therapeutic product. The use of an *in vitro* companion diagnostic device with a therapeutic product is stipulated in the instructions for use in the labeling of both the diagnostic device and the corresponding therapeutic product. The FDA has explained in guidance *in vitro* diagnostic companion diagnostic devices may be used for a number of purposes, including identifying appropriate subpopulations for treatment. According to the guidance, *in vitro* companion diagnostic devices may require the submission and approval of a preauthorization application before they are marketed. Some *in vitro* companion diagnostic devices, however, could potentially be cleared through a 510(k) premarket notification submission. The guidance states that the FDA generally will not approve a drug or biologic that is dependent upon the use of an *in vitro* 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 product without an approved or cleared *in vitro* companion diagnostic device when the drug or 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 product are so pronounced as to outweigh the risks from the lack of an approved or cleared *in vitro* companion diagnostic device. Under these circumstances, the FDA expects that a diagnostic would be subsequently approved or cleared through an appropriate device submission, and that the therapeutic product labeling would be revised to stipulate the use of the 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 Duchenne Muscular Dystrophy and related dystrophinopathies, the FDA has stated that for drugs and biologics in which efficacy or safety may be related to the patient's specific dystrophin mutation or to another type of finding related to a biomarker for which a suitable diagnostic device is not available, a sponsor should contemporaneously develop a companion diagnostic device. 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 or 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.

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 Prescription Drug User Fee Act, or PDUFA, the FDA has set the review goal of completing its review of 90% of all applications for new molecular entities within ten 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. 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 new 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 current good manufacturing practice, or cGMP, compliance is satisfactory. The FDA may also take into account results of inspections performed by certain counterpart foreign regulatory agencies in assessing compliance with GCP or cGMP. The FDA has entered into international agreements with foreign agencies, including the EMA, in order to facilitate this type of information sharing. 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 various guidance documents regarding 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 assessment of gene therapies; 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 follow up to observe delayed adverse effects in subjects who have been exposed to investigational gene therapies when the risk of such effects is high. Further, long-term follow up may be required for gene therapies to assess delayed adverse events. The NIH and the FDA have a publicly accessible database, the Genetic Modification Clinical Research Information System, which includes information on gene therapy trials and serves as an electronic tool to facilitate the reporting and analysis of adverse events on these trials.

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.

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 health care 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 new 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 of 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 foreign manufacturing establishments must register and provide additional information to the FDA upon their initial participation in the manufacturing process for a commercial product.

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.

We rely, and expect to continue to rely, on third parties for the production of clinical and commercial quantities of our product and product candidates. 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.

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 and nonsense mutation aniridia, for PTC-AADC for the treatment of AADC deficiency, for risdiplam for the treatment of SMA, for PTC-FD for the treatment of Friedreich ataxia and PTC-AS for the treatment of Angelman syndrome. 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 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.

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, 2020, and approved no later than September 30, 2022, 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, 2022, 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.

Upon submission of an ANDA or 505(b)(2) NDA, an applicant must certify to the FDA that (1) no patient 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. 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 of 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 of 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.

In addition to the above, the Hatch Waxman Act established certain periods of regulatory exclusivity. 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 and the Hatch-Waxman Act to commercialize Emflaza in the United States.

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 references the previously approved drug. 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

We are currently pursuing patent protection for GT-AADC for the treatment of AADC deficiency, and, in the meantime, we expect to rely on the twelve-year BPCIA regulatory exclusivity to commercialize PTC-AADC in the United States, if it is approved.

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. As of January 1, 2019, the FDA has approved sixteen biosimilar products for use in the United States. No interchangeable biosimilars have been approved. The FDA has issued a number of guidance documents outlining an approach to review and approval of biosimilars.

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.

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.

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 foreign 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 conditional 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 European Union, or (2) a life threatening, seriously debilitating or serious and chronic condition in the European Union and that without incentives it is unlikely that sales of the drug in the European Union 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 European Union 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 the possibility to apply for a centralized EU marketing authorization, as well as 10 years of EU market exclusivity following a marketing authorization. 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 and 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.

Overview of application process. To obtain regulatory approval of a drug under the European Union'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. 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 European Union 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.

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.

Additional requirements and considerations. Prior to obtaining a marketing authorization in the European Union, 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 European Union, independently generated data submitted as part of a full marketing authorization application dossier are protected by regulatory data protection ('data exclusivity') for a period of eight years from the granting of a marketing authorization for a 'reference product'. This means that for a period of eight years, competent authorities may not accept marketing authorization applications that rely on the independently generated data in the marketing authorization dossier of the reference product. 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 the 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 and market 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.

Off-label promotion of medicinal products is prohibited in the European Union. The applicable laws at European Union level and in the individual European Union 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 European Union could be penalized by administrative measures, fines and imprisonment. These laws may further limit or restrict our promotional activities with health care professionals. In addition, legislation adopted at the European Union level and by individual European Union 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.

The EMA is responsible for coordinating inspections to verify compliance with the principles of good clinical practice, or GCP, good manufacturing practice, or GMP, good laboratory practice, or GLP, and good pharmacovigilance practice, or GVP. These inspections are also intended to verify compliance with other aspects of the supervision of authorized medicinal products in use in the European Union. 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 European Union and the European Economic Area. 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.

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 European Union, 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 new 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 foreign governments, and the prices of pharmaceuticals have been a focus of this effort. Foreign 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, restrictions on reimbursement and requirements for substitution of generic products for branded prescription drugs.

In some countries, particularly the countries of the European Union, 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. 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 health care programs similarly obligate us to report drug pricing information that is used as the basis for their reimbursement of pharmacies and other health care providers. Payment for a manufacturer's drugs by these programs is conditioned on submission of this pricing information. Some government health care 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 cap price increases. 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 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 for the manufacturer's drugs.

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 Patient Protection and Affordable Care Act of 2010, as amended by the Health Care and Education Reconciliation Act of 2010, referred to together as 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, and repeal efforts may occur again, and there are ongoing legal challenges to the Affordable Care Actwhich may contribute to the uncertainty of the ongoing implementation and impact of the Affordable Care Act and also underscores the potential for additional reform going forward. Certain provisions of enacted or proposed legislative changes may negatively impact coverage and reimbursement of 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, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for drugs. For example, the Centers for Medicare and Medicaid Services, or CMS, recently reduced the payment rate for certain hospitals purchasing outpatient drugs at the 340B program discounted price, 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 Affordable Care Act, or ACA. Similarly, 340B program guidance regulations on civil monetary penalties for statutory violations, which had been was finalized in early 2017, recently went into effect. In October 2018, CMS issued an advance notice of proposed rulemaking paving the way for a proposed rule in 2019 that would significantly

reduce the price of drugs paid by Medicare Part B by basing reimbursement on the average prices among other industrialized countries, and in January 2019, CMS proposed eliminating the Anti-Kickback Act safe harbor for rebates typically provided to PBMs and health plans that are included in their cost effectiveness determinations. 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 foreign 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-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 European Union 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 have appealed the General Court's decision to the Court of Justice of the European Union and the EMA has confirmed that it will not release the documents while the matter is still subject to the appeal process. However, there can be no assurance that we will be successful in the appeal and we may not ultimately succeed in preventing disclosure of the data in our marketing authorization for Translarna for the treatment of nmDMD. 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, once the Clinical Trials Regulation 536/2014 is fully in place, 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, 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 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. 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 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's product from reimbursement under government programs, debarment, 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, as well as for making a false statement to avoid, decrease or conceal an obligation to pay money to the federal government. Claims may be pursued by whistleblowers through qui tam actions, even if the government declines to intervene. Intent to deceive is not necessary to establish civil liability, which may be predicated on 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 health care companies. These investigations have involved, for example, allegations of 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. Violations of the Anti-Kickback Statute may also be grounds for civil False Claims Act actions. Potential liability under the federal False Claims Act includes treble damages and significant per claim penalties, currently set at $10,957 to $21,916 (as adjusted for inflation) per false claim. 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 government contracting 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 included a provision requiring certain providers and suppliers of items and services to Federal Health Care Programs to report and return overpayments within sixty days after they are "identified" (the "Overpayment Statute"). In 2014 and 2016, the Centers for Medicare and Medicaid Services, or CMS, released regulatory guidance (in the form of a final rule) 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, 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 to report to CMS information related to payments and other transfers of value made to covered recipients, such as physicians and teaching hospitals, as well as physician ownership and investment interests. Payments made to physicians and certain research institutions for clinical trials are included within the ambit of this law. Pharmaceutical manufacturers are required annually to report and disclose payments and ownership and investment interests held by physicians and their immediate family members during the preceding calendar year. 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 all payments, transfers of value or ownership or investment interests not 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, 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 to, 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 or payment for health care benefits, knowingly and willfully embezzling or stealing from a health care benefit program, willfully obstructing a criminal investigation of a health care 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 ACA 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, the Health Information Technology for Economic and Clinical Health Act of 2009, or HITECH, and similar state laws, also impose obligations on certain entities with respect to safeguarding the privacy, security and transmission of certain individually identifiable health information, known as protected health information. Among other things, HITECH and implementing regulations makes 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. HITECH 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 attorney's fees and costs associated with pursuing federal civil actions. Civil and criminal penalties include up to $50,000 per violation plus a criminal fine of up to $250,000 and ten years in prison. In addition, other federal and state laws 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,

Any continuing efforts by the Trump Administration and the U.S. Congress 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.

Employees

As of December 31, 2018, we had 517 employees, of whom 511 were employed on a full-time basis, and 48 consultants and contractors, of whom 47 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.

Our Corporate Information

We were incorporated under the laws of the State of Delaware on March 31, 1998, under the name PTC Therapeutics, Inc. 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 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. 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 late 2019, with an anticipated commercial launch in the United States in 2020. 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 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. We are preparing an MAA for PTC-AADC for the treatment of AADC deficiency in the European Union, which we expect to submit to the EMA following our BLA submission to the FDA. There is no guarantee that we will be able to make our BLA or MAA submissions within our expected timelines or that upon our making the submissions, the FDA 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, such as PTC-AADC and our other gene therapy product candidates, is technically complex and necessitates substantial expertise and capital investment. Production difficulties caused by unforeseen events 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 with third parties for the manufacturing of program materials for our gene therapy product candidates. The use of contracted manufacturing and reliance on collaboration partners is relatively cost-efficient. Although we rely on contract manufacturers, we have personnel with manufacturing and quality experience to oversee our contract manufacturers.

Although we anticipate taking steps to increase our manufacturing capabilities for our gene therapy platform, we currently rely on third-party manufacturers to be capable of providing sufficient quantities of our program materials to meet anticipated clinical trial scale demands. To meet our projected needs for commercial manufacturing, the third party from whom we currently obtain our clinical supply of PTC-AADC may need to increase its 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. 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 foreign 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 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.

Our 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.

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. 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 health care 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, 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 and cell 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 and the FDA has approved several cell-based gene therapy treatments to date, the FDA has only approved one vector-based gene therapy product to date. In addition, there are only two gene therapy products for genetic diseases approved to date in the European Union**.** 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 and cell therapy products are still evolving and may continue to change in the future. For example, in 2018, the FDA issued a number of new guidance documents on human gene therapy development. The FDA will likely continue to issue new guidance and replace existing guidance. Similarly, the U.S. National Institutes of Health, which also has authority over research involving gene therapy products, issued a proposed rule in October 2018, seeking to streamline the oversight of such protocols and reduce duplicative reporting requirements that are already captured within existing regulatory frameworks. 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 and cell 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 and cell therapy products are complex, the manufacture of such products and product candidates is more difficult and costly. We may not be able to have such products reliably manufactured 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. Delays as a result of lengthier regulatory approval process and further restrictions on development 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 follow up 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 monitoring and sample testing. 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 potential gene therapy product candidates and adversely affect our ability to conduct our business or obtain regulatory approvals for PTC-AADC or our other potential 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 product. 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. Moreover, reimbursement agencies in the European Union 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 UK 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.

Our gene therapy product candidates are regulated by the FDA as biologics 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.

In the European Union, another company could gain approval for a competing product based on a MAA with a complete independent data package of 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 foreign 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

We depend heavily on the success of Translarna, which we are developing for nmDMD and other indications, and Emflaza, for DMD. If we are unable to execute our commercial strategy for Translarna for the treatment of nmDMD in the EEA or for Emflaza for the treatment of DMD in the United States, fail to receive regulatory approval for Translarna for the treatment of nmDMD in the United States and other territories, fail to obtain renewal of, or satisfy the conditions of our marketing authorization for Translarna for the treatment of nmDMD in the EEA, or fail to maintain our marketing authorization or market exclusivity for Emflaza in the United States, 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 in the development of Translarna for nmDMD and in the acquisition of Emflaza for DMD. Our ability to generate product revenues will depend heavily on the successful development and commercialization of Translarna and our successful integration of Emflaza into our business and commercialization of Emflaza for DMD in the United States. Prior to our commercialization of Emflaza in the United States, we had no history of commercializing pharmaceuticals in the United States.

As we presently have no patent rights to protect the approved use of Emflaza, we rely on the concurrently running market exclusivity periods currently available to us under the Hatch-Waxman Act and the Orphan Drug Act to commercialize Emflaza for DMD in the United States. Further, we are obligated to complete certain FDA post-marketing requirements in connection with our marketing authorization of Emflaza. Failure to maintain these market exclusivity periods, complete the FDA post-marketing requirements, 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 are currently pursuing further clinical development efforts for Translarna for the treatment of nmDMD, nonsense mutation aniridia, and nonsense mutation CDKL5/Dravet syndrome. 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 Translarna for any given indication based on the merits of the clinical efficacy evidence available for such indication. However, because we are developing Translarna for the treatment of multiple indications associated with genetic disorders that arise as a result of a nonsense mutation, there is a risk that negative results in a clinical trial evaluating the efficacy of Translarna for one indication, such as the negative results of our ACT CF trial for nonsense mutation cystic fibrosis, or nmCF, which we announced in 2017, could adversely affect the perception of the efficacy of Translarna 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 Translarna for any indication, including in connection with 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. We have submitted the safety results of ACT CF to regulators with any applicable safety updates and submissions, including the EMA. While the safety profile of Translarna in the ACT CF study was consistent with previous studies and no new safety signals were identified, there can be no assurance that the EMA or other regulators will agree with our interpretation of the safety data from the trial.

If we do not successfully renew and maintain our marketing authorization and commercialize Translarna in the EEA, receive regulatory approval in the United States for Translarna for the treatment of nmDMD and subsequently successfully commercialize Translarna in the United States, or receive regulatory approval in other territories, including in Brazil, our ability to generate additional revenue will be jeopardized and, consequently, our business will be materially harmed. Likewise, if we do not successfully commercialize or maintain our marketing authorization for Emflaza for the treatment of DMD in the United States, our ability to generate additional revenue will be jeopardized and, consequently, our business will be materially harmed.

The success of Emflaza and Translarna 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 and scope 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;
- 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;
- a continued acceptable safety profile of the drug;
- the costs, timing and outcome of post-marketing studies and trials for Emflaza and Translarna, including, with respect to Translarna, Study 041;
- obtaining and maintaining patent and trade secret protection and regulatory exclusivity, including with respect to Emflaza, whether we are able to maintain market exclusivity periods under the Hatch-Waxman Act and 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;
- the successful advancement of Translarna in additional indications, in particular, nonsense mutation aniridia and nonsense mutation Dravet syndrome/CDKL5;
- the successful advancement of Emflaza in additional indications, in particular, limb-girdle 2I;
- 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;
- our ability to successfully prepare and advance regulatory submissions for marketing authorizations for Translarna 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 Translarna 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 Translarna or Emflaza, either of which would have a material adverse effect on our business, results of operations and financial condition.

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 conditional 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 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 it is probable that we will enroll patients in territories where Translarna has already become available on a reimbursed basis, which could negatively impact growth in our product sales. We may enroll patients in countries with a different standard of care for nmDMD patients or at clinical trial sites that are inexperienced with clinical trials in general, or specifically with nmDMD trials. 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.

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. We are launching the first therapy specifically aimed at nmDMD patients. 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. Although we intend 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 authorization in the EEA for Translarna for the treatment of nmDMD in ambulatory patients aged two years and older and we also may need to receive 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. Due to enrollment at a slower pace in certain countries than initially expected, in our February 2019 marketing authorization renewal request, we asked the EMA to extend the timeframe for submission of the results of Study 041 to the EMA to the end of the third quarter of 2022. There is no guarantee that the EMA will grant the extension of the date by which we are required to submit the results of Study 041. The marketing authorization was last renewed in July 2018 and is effective, unless extended, through August 5, 2019. Enrolling Study 041 may further reduce the number of patients available for reimbursed treatment.

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.

If there are delays in obtaining regulatory approval in the United States, we will not be able to commercialize 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 intend to follow the FDA's recommendation and will collect, using newer technologies via procedures and methods that we designed, such dystrophin data in a new study, Study 045, which we initiated in the fourth quarter of 2018. We expect that a potential re-submission of an NDA could occur in 2020. Additionally, should a re-submission of an NDA receive accelerated approval, the Office of New Drugs stated that Study 041, which is currently enrolling, could serve as the confirmatory post-approval trial required in connection with the accelerated approval framework.

While we have discussed the procedures and methods for Study 045 with the FDA, the procedures and methods have never previously been utilized in DMD studies. In addition to us providing data showing positive results, the FDA will need to accept the methods utilized in the study. There is a substantial risk that Study 045, or any other studies we may use to collect the dystrophin data, will not provide the necessary data to support a marketing approval for Translarna for the treatment of nmDMD in the U.S. or that the FDA will not accept the methods used to collect the data. Even if we are successful in resolving some or all of the matters raised by the FDA in its denial of our appeal of the Complete Response Letter, 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.

Even if we do ultimately receive approval for Translarna in the United States, if such approval is via the accelerated approval pathway, there is a risk that the FDA would not view our completed studies as satisfying the requirement for post-approval confirmatory studies of the product's clinical benefit. In such an instance, we would potentially need to invest substantial time, effort, and funds into the conduct of such a post-approval study. Moreover, 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. 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.

If clinical trials of Translarna 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 Translarna or any other product candidate.

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.

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 Translarna or any other product candidate 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 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 Translarna for other indications, or 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 our marketing authorization request for Translarna in Brazil is unsuccessful, we may lose our ability to sell Translarna in Brazil.

All of our sales of Translarna in Brazil to date have been to patients who have had access to Translarna via judicial authorization, which has allowed the Brazilian authorities to purchase Translarna even though Translarna is not approved by the Agência Nacional de Vigilância Sanitária, or ANVISA. In the fourth quarter of 2018, we filed for marketing authorization with ANVISA for Translarna. Should ANVISA reject our marketing authorization request, patients may lose their access via judicial authorization, as the courts may take into account ANVISA's rejection. Our inability to sell Translarna in Brazil would have a material adverse effect on our business, financial condition and results of operations.

If Tegsedi or Waylivra fail to obtain or maintain regulatory approval, we will not be able to commercialize them in the PTC Territory.

Tegsedi has only received marketing authorization from the FDA, EMA and Health Canada, and Waylivra has not yet received regulatory approval from the EMA or any other regulatory agency. We have submitted a marketing authorization request for Tegsedi to ANVISA and it was granted priority review. Should Tegsedi or Waylivra not receive marketing authorization in the territories in which we have obtained the rights to commercialize such product candidates, or should Tegsedi lose its marketing authorizations that it currently has, we would not be able to commercialize Tegsedi or Waylivra, as applicable, successfully, and we would fail to realize the anticipated benefit of our licensing rights to Tegsedi and Waylivra or those benefits may take longer to realize than expected, any of which could have a material adverse effect on our business.

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;

- 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;
- 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 foreign 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 foreign 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 foreign regulatory authorities may fail to approve or subsequently find fault with the manufacturing processes or our contract manufacturer's manufacturing facility for clinical and future commercial supplies;
- the data collected from clinical trials of our product candidates may not be sufficient to the satisfaction of the FDA or comparable foreign regulatory authorities to support the submission of a marketing application, or other comparable submission in foreign 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 Translarna, Emflaza, risdiplam or our product candidates and allow our competitors to bring products to market before we do, or impair our ability to successfully commercialize Translarna, Emflaza, risdiplam 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 our last 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 Translarna, Emflaza and our 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, including, nmCF, nmMPS I, nonsense mutation aniridia, and nonsense mutation Dravet syndrome/CDKL5. 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 have discontinued our clinical development of Translarna for nmCF.

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.

We are faced with similar challenges in connection with the design of our studies of Translarna in nonsense mutation aniridia, and nonsense mutation Dravet syndrome/CDKL5 and of Emflaza in limb-girdle 2I, and such similar challenges existed in our study of nmMPS I, which study we stopped in 2017, because there is also limited historical clinical trial experience for the development of drugs to treat the underlying cause of these disorders.

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 Study 041, our Phase 2 studies of Translarna in nonsense mutation Dravet syndrome/CDKL5, or our studies of Emflaza in limb-girdle 2I if we are unable to locate and enroll a sufficient number of eligible patients to participate in these trials. The studies under our SMA collaboration for risdiplam face similar risks.

Each of the indications we are currently pursuing for Translarna, Emflaza, risdiplam and our product candidates are characterized by relatively small patient populations, which could result in slow enrollment of clinical trial participants. The feasibility of patient enrollment was a critical factor discussed with the EMA in connection with the specific obligation to conduct Study 041, in particular due to factors that increase the challenges of enrollment, such as the small nmDMD patient population, the patient

eligibility criteria for the mITT for Study 041, and the fact that Translarna is available to patients in the EEA and other limited territories pursuant to commercial and EAP programs.

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.

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;
- 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.

Enrollment delays in our clinical trials may result in increased development costs for our product candidates. Our inability to enroll a sufficient number of patients in Study 041, our Phase 2 studies of Translarna in nonsense mutation Dravet syndrome/CDKL5, or our studies of Emflaza in limb-girdle 2I 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. As the conduct of Study 041 is a specific obligation to our marketing authorization in the EEA for Translarna for the treatment of nmDMD, any such delay or inability to enroll sufficient patients could have a material adverse effect on our ability to maintain our authorization in the EEA and, failure to maintain such authorization would have a material adverse effect on our business, results of operations and financial performance.

For example, we amended the study design for our proof-of-concept study for Translarna for the treatment of nmMPS I to include patients currently on enzyme replacement therapy, which contributed to delays in site initiation and patient accrual. Despite the protocol amendment, we continued to encounter difficulties identifying qualified patients for this study and stopped the study due to the lack of patients.

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 are obligated to perform certain FDA post-marketing requirements in connection with our marketing authorization of Emflaza in the United States, including pre-clinical and clinical safety studies. 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 authorization for Emflaza 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 health care 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. For example, Yescarta, which is a cell-based gene therapy approved by FDA in 2017 for adult patients with certain types of large B-cell lymphoma who have not responded to or who have relapsed after at least two other kinds of treatment, is subject to a substantial REMS program. The Yescarta REMS includes requirements for dispensing hospital and clinic certification, training, adverse event reporting, documentation, and audits and monitoring conducted by the sponsor, among other conditions. Similarly, also in 2017, the FDA approved Kymriah, a cell-based gene therapy for the treatment of patients up to 25 years of age with B-cell precursor ALL that is refractory or in second or later relapse. This indication was expanded in 2018 to include adult patients with relapsed or refractory (r/r) large B-cell lymphoma after two or more lines of systemic therapy including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, high grade B-cell lymphoma and DLBCL arising from follicular lymphoma. Like Yescarta, Kymriah was approved with a REMS that includes requirements for hospital and clinic certification, training, adverse event reporting, documentation, and audits and monitoring conducted by the sponsor, among other conditions. The Yescarta and Kymriah sponsors are responsible for implementing the REMS. REMS, such as these, can be expensive and burdensome to implement, and burdensome for hospitals, clinics, and health care providers to comply with. Accordingly, should any of our product candidates be subject to a REMS, it may materially harm our business.

Translarna for the treatment of nmDMD, Emflaza for the treatment of DMD, 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 for Translarna for the treatment of nmDMD is maintained, or we are successful in obtaining marketing authorization for Translarna for other indications or territories or marketing authorization for any of our other product candidates, 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 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, such as the results from our ACT CF trial for nmCF, 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 European Union, 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 Translarna for the treatment of nmDMD, Emflaza for the treatment of DMD, or any of our other product candidates that receive marketing authorization.

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 replace services being performed pursuant to a transition services agreement with Marathon before the termination of such agreement;
- 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 Translarna, Emflaza 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 Translarna is available on a reimbursed basis under an EAP program.

All of our sales of Translarna for the treatment of nmDMD currently occur in territories outside of the United States, which subjects us to additional business risks that could adversely affect our revenue and results of operations.

All of our revenue from sales of Translarna to date has been generated from countries other than the United States. We have operations in multiple European countries and other territories, including Latin America. 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:

- 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 health care policies of foreign 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 foreign 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, we face risks arising out of the potential uncertainty caused by the June 2016 vote in the United Kingdom in favor of exiting the European Union, commonly referred to as Brexit. In March 2017, the UK government initiated the exit process under Article 50 of the Treaty of the European Union, commencing a period of up to two years for the UK and the other EU member states to negotiate the terms of the withdrawal. Uncertainty over the terms of the UK's withdrawal from the EU could adversely affect European or worldwide political, regulatory, economic or market conditions and could contribute to instability in global political institutions, regulatory agencies and financial markets. Currency exchange rates in the pound sterling and the euro with respect to each other and the U.S. dollar have already been adversely affected by Brexit and, in the event that such foreign exchange volatility were to continue, it could cause volatility in our quarterly financial results. In addition, if the United Kingdom were to significantly alter its regulations affecting the pharmaceutical industry, we could face significant new regulatory costs and challenges.

In addition, some countries in which Translarna for the treatment of nmDMD is not approved allow patients access to Translarna through other legal mechanisms. For example, all of our sales in Brazil to date have been to patients who have had access to Translarna via judicial authorization, which has allowed the Brazilian authorities to purchase Translarna even though Translarna is not approved by ANVISA. Should the current political and legal framework which allows access to non-ANVISA approved drugs in Brazil change, and Translarna does not receive approval by ANVISA, patients currently being prescribed Translarna may have temporary interruptions in treatment in the future or may not have access to Translarna at all.

Additionally, some of the countries in which Translarna for the treatment of nmDMD is 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.

In addition, 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. Other factors may also contribute to fluctuations in quarterly net product sales including Translarna'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.

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.

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 recently received approval in the United States for a treatment addressing the underlying cause of disease for different mutations in the DMD gene. Other biopharmaceutical companies are developing treatments for the underlying cause of disease for different mutations in the DMD gene (Sarepta, Daiichi Sankyo, Eloxx, Nippon Shinyaku and Solid Biosciences).

Diacomit is marketed in the European Union by Laboratoires Biocodex for the treatment of Dravet syndrome. GW Pharmaceuticals and Zogenix are marketing products for the treatment of Dravet syndrome in the United States. Aniridia therapeutic interventions, such as artificial iris implantation, are being developed by HumanOptics AG. Our SMA collaboration with Roche and the SMA Foundation also faces competition. For example, in December 2016, the FDA approved nusinersen, a drug developed by Ionis Pharmaceuticals, Inc. and marketed by Biogen, to treat SMA. AveXis, Inc. is also evaluating a gene therapy product candidate for the treatment of SMA. Other companies are also pursuing product candidates for the treatment of SMA, including Trophos (also in collaboration with Roche), Kowa, Novartis Pharmaceuticals Corporation, and Cytokinetics.

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.

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. While there is currently no treatment options available for FA, Voyager Therapeutics is also working on pre-clinical studies for a potential gene therapy solution. 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 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 metreleptin. Metreleptin, produced by Novelion Therapeutics, Inc., is currently approved for use in generalized lipodystrophy patients. Additionally, Tegsedi could face competition from drugs like patisiran and ALN-TTRsc02 in development by Alnylam, tafamidis commercialized in some countries in LATAM by Pfizer and tolcapone in development by SOM Biotech. 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.

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.

Even if we are able to commercialize Translarna for the treatment of nmDMD on a broad scale, commercialize Emflaza for the treatment of DMD in the United States, or commercialize any other product candidate for which we may receive marketing authorization, Translarna, Emflaza and any other product or product candidate 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, including Emflaza and Translarna, 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 foreign 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 Translarna, Emflaza or any other product candidate that receives 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 health care organizations and other third-party payors and organizations. Government authorities and other third-party payors, such as private health insurers and managed health care 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 Translarna, Emflaza or any other product 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 that presently restrict 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 health care 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 health care programs 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 the manufacturer enter into a Federal Supply Schedule (FSS) agreement with the Secretary for Veterans Affairs to extend discounted pricing to the Veterans Health Administration.

Similarly, in order for a covered outpatient drug to receive federal reimbursement under the Medicare Part B and Medicaid programs or to be sold directly to U.S. government agencies, 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. Further, CMS is proposing to relax Part D coverage requirements to give plans more leverage in negotiating their formularies.

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. There are legal challenges to the Affordable Care Act pending and the Trump Administration and the U.S. Congress may continue to seek to modify, repeal, or otherwise invalidate all, or certain provisions 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.

In the European Union, 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 European Union, 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. 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, 2018, we had an accumulated deficit of $938.9 million. We have historically financed our operations primarily through the issuance and sale of our common stock in public offerings, the private placements of our preferred stock, collaborations, bank 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 and 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 in May 2017, we began to recognize revenue generated from net sales of Emflaza for the treatment of DMD in the United States. 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 both Translarna and Emflaza. We expect to continue to generate operating losses through 2019 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 quarter to quarter.

On April 20, 2017, we acquired all rights to Emflaza. Upfront consideration for the acquisition was comprised of $75 million in cash, funded through cash on hand, and 6,683,598 shares of our common stock. In addition, we expect to incur significant costs in connection with liabilities we assumed as part of the acquisition, including the obligation to complete certain post-marketing requirements in connection with the Emflaza marketing authorization.

On August 23, 2018, we completed our acquisition of Agilis. Upfront consideration was 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 are required to pay $40.0 million of the development milestone payments no later than the second anniversary of the closing of the acquisition, regardless of whether the applicable milestones have been achieved.

Our current ability to generate revenue from sales of Translarna is dependent upon our ability to maintain our marketing authorization in the EEA of Translarna for the treatment of nmDMD in ambulatory 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. In addition, it is likely that we will enroll patients in Study 041 in countries where Translarna for the treatment of nmDMD is currently available on a reimbursed basis, which could negatively impact growth in our net product sales. 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 the results of Study 041 by September 2021, 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 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, 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, "*If there are delays in obtaining regulatory approval in the United States, we will not be able to commercialize 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 a new clinical trial 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 Study 041 and Study 045 and our open label extension trials of Translarna for the treatment of nmDMD as well as our studies for nonsense mutation aniridia and nonsense mutation Dravet syndrome/CDKL5 and our FDA post-marketing requirements with respect to Emflaza in the United States and our studies for limb-girdle 2I. We also expect to incur ongoing research and development expenses for our other product candidates, including our gene therapy, splicing and oncology programs. In addition, we may incur substantial costs in connection with our efforts to advance our regulatory submissions. 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 and we may also seek marketing authorization for Translarna for other indications. In late 2019, we plan to submit a request for marketing authorization for PTC-AADC with the FDA followed by a submission for marketing authorization to the EMA and we recently submitted a request for marketing authorization for Tegsedi with ANVISA. 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 Convertible Notes, cash interest payments are payable on a semi-annual basis in arrears, which will require total funding of $4.5 million annually. Additionally, under the terms of our credit and security agreement with MidCap Financial Trust, cash interest payments are payable monthly in arrears.

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

- seek to integrate Agilis's operations and employees into our business and seek to satisfy contractual and regulatory obligations we assumed in connection with the Agilis acquisition;
- seek to satisfy contractual and regulatory obligations in conjunction with the Akcea Agreement, including the potential commercialization of Tegsedi and Waylivra in Latin America and the Caribbean, or the PTC Territory;
- execute our strategy for Emflaza in the United States, including commercialization efforts;
- satisfy contractual and regulatory obligations that we assumed through the Emflaza acquisition;
- 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 for Translarna for the treatment of nmDMD or to obtain further marketing authorizations for Translarna for the treatment of nmDMD or other indications;
- initiate or continue the research and development of Translarna and Emflaza for additional indications and of our other product candidates, including for our gene therapy, splicing and oncology programs;
- 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 Emflaza for the treatment of DMD in the United States;
- negotiating, securing, and maintaining adequate pricing, coverage and reimbursement terms, on a timely basis, with third-party payors for Emflaza for the treatment of DMD in the United States and for Translarna for the treatment of nmDMD in the EEA and other territories outside of the United States;
- maintaining orphan exclusivity for Emflaza and successfully completing all FDA post-marketing requirements with respect to Emflaza;
- 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 submission by us and, ultimately, may support approval of Translarna for nmDMD in the United States;
- expanding the territories in which we are approved to market Translarna for the treatment of nmDMD;
- minimizing the enrollment impact of Study 041 on commercialization efforts for Translarna for nmDMD;
- commercializing and marketing Tegsedi and Waylivra in the PTC Territory;
- developing Translarna and Emflaza for the treatment of additional indications, including nonsense mutation aniridia, nonsense mutation Dravet syndrome/CDKL5 and limb-girdle 2I and successfully advancing our other programs and collaborations, including our gene therapy, splicing and oncology programs;
- establishing a global commercial infrastructure, including the sales, marketing and distribution capabilities to effectively market and sell Translarna for the treatment of nmDMD in the EEA and other parts of the world;
- implementing marketing and distribution relationships with third parties in territories where we do not pursue direct commercialization;
- launching commercial sales of Translarna for the treatment of nmDMD in accordance with our estimated timeline;
- identifying patients eligible for treatment with our products and product candidates;
- obtaining approval to market Translarna and Emflaza for the treatment of other indications;
- expanding the approved product label of Translarna for the treatment of nmDMD;
- 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
- contracting for the manufacture and distribution of commercial quantities of Translarna, Emflaza and other 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 the net proceeds from our term loan facility with MidCap Financial, our Convertible Note offering, public offerings of common stock, marketable securities and research funding that we expect to receive under our collaborations, 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 Emflaza for the treatment of DMD in the United States;
- our ability to negotiate, secure and maintain adequate pricing, coverage and reimbursement terms, on a timely basis, with third-party payors for Emflaza for the treatment of DMD in the United States and for Translarna for the treatment of nmDMD in the EEA and other territories outside of the United States;
- our ability to maintain orphan exclusivity for, and successfully complete all FDA post-marketing requirements with respect to, Emflaza;
- 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 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 submission by us and, ultimately, may support approval of Translarna for nmDMD in the United States;
- our ability to commercialize and market Tegsedi and Waylivra in the PTC Territory;
- the progress and results of our open label extension clinical trials of Translarna for the treatment of nmDMD as well as our studies for nonsense mutation aniridia and nonsense mutation Dravet syndrome/CDKL5 and activities under our gene therapy and oncology programs;
- the scope, costs and timing of our commercialization activities, including product sales, marketing, legal, regulatory, distribution and manufacturing, for both Emflaza for the treatment of DMD and Translarna for the treatment of nmDMD, for Tegsedi, for Waylivra 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 Translarna;
- the costs, timing and outcome of regulatory review of our other product candidates, including those in our gene therapy and oncology programs, and Translarna in other territories or for indications other than nmDMD;
- our ability to satisfy our obligations under the terms of the Credit Agreement with MidCap Financial;
- 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 Translarna and Emflaza for additional indications and for our other product candidates, including those in our gene therapy and oncology programs;
- revenue received from commercial sales of Translarna, Emflaza, Tegsedi, Waylivra, or any of our other 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 acquisition of Emflaza, our acquisition of Agilis, 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 commercial success, including Translarna for the treatment of nmDMD and Emflaza for the treatment of DMD.

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. We are continuing to engage in significant commercialization efforts for this product. In order to continue sales and our commercial launch of Translarna, we must maintain our marketing authorization 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. Although we have begun to commercialize and market Emflaza in the United States, to date, we have not generated significant revenue from Emflaza. 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.

Other commercial revenue, if any, would be derived from product acquisitions or, if none, from sales of products that we are not planning to have commercially available for several years, if at all. If our marketing authorization for Translarna 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 for the treatment of nmDMD, whether pursuant to a commercial or an EAP program and throughout all territories. Likewise, if we fail to maintain our marketing authorization for Emflaza in the United States or lose the non-patent market exclusivity for Emflaza, we will be unable to commercialize and generate revenue from sales of that product.

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.

Our indebtedness resulting from our credit and security agreement with MidCap Financial Trust could adversely affect our financial condition or restrict our future operations.

On May 5, 2017, we entered into a credit and security agreement with Midcap Financial Trust, a Delaware statutory trust, or MidCap Financial, as administrative agent and MidCap Financial and other certain institutions as lenders thereto, or the Credit Agreement, that provides for a senior secured term loan facility of $60 million, of which $40 million was drawn by us on May 5, 2017. Our ability to draw on the remaining $20 million under the senior secured term loan facility expired on December 31, 2018. The maturity date of the Credit Agreement is May 1, 2021, unless terminated earlier.

Borrowings under the Credit Agreement bear interest at a rate per annum equal to LIBOR (with a LIBOR floor rate of 1.00%) plus 6.15%. The Credit Agreement requires us to not have less than $100 million of net revenue for the prior twelve months to be measured on the last day of each fiscal quarter beginning on December 31, 2017.

Additionally, subject to customary exceptions and exclusions, all obligations under the Credit Agreement are secured pursuant to the terms of the Credit Agreement, a Pledge Agreement between us, certain of our subsidiaries, and Midcap Financial, or the Pledge Agreement, and an Intellectual Property and Security Agreement between us and Midcap Financial, or the IP Security Agreement, each dated May 5, 2017. Under the Credit Agreement, the Pledge Agreement, and the IP Security Agreement, we provided to Midcap Financial and the other lenders (i) a perfected, first-priority security interest in all of our personal property, (ii) a perfected, first-priority security interest in all of our intellectual property (except that this security interest will not be perfected in intellectual property located outside the United States unless our cash position falls below a pre-specified threshold), and (iii) a perfected, first-priority pledge of 65% of the equity ownership interests directly held by us in our wholly owned subsidiary, PTC Therapeutics Holdings (Bermuda) Corp. Limited.

A failure to comply with the conditions of our Credit Agreement could result in an event of default. An event of default under the Credit Agreement includes, among other things, a failure to pay any amount due under the Credit Agreement as well as the occurrence of events that could reasonably be expected to result in a material adverse effect, including if we were to fail to maintain our marketing authorization for Translarna for the treatment of nmDMD in the EEA or if the FDA were to withdraw any of our products from the market, including Emflaza for the treatment of DMD in the United States.

In the event of an acceleration of amounts due under our Credit Agreement as a result of an event of default, we may not have sufficient funds or may be unable to arrange for additional financing to repay the term loans or to make any accelerated payments,

and the lenders could seek to enforce security interests in the collateral securing the term loans, which would have a material adverse effect on our business, financial condition and results of operations.

In addition, our indebtedness under the Credit Agreement could have significant adverse consequences, including, among other things:

- requiring us to dedicate a substantial portion of cash and cash equivalents and marketable securities to the payment of interest on, and principal of, the term loans, which will reduce the amounts available to fund working capital, capital expenditures, product development efforts and other general corporate purposes;
- obligating us to negative covenants restricting our activities, including limitations on dispositions, mergers or acquisitions, encumbering our intellectual property, incurring indebtedness or liens, paying dividends, making investments and engaging in certain other business transactions;
- limiting our flexibility in planning for, or reacting to, changes in our business and our industry;
- placing us at a competitive disadvantage compared to our competitors who have less debt or competitors with comparable debt at more favorable interest rates; and
- limiting our ability to borrow additional amounts for working capital, capital expenditures, research and development efforts, acquisitions, debt service requirements, execution of our business strategy and other purposes.

Any of these factors could materially and adversely affect our business, financial condition and results of operations.

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 Agilis and Emflaza and our collaboration and license agreement with Akcea. 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; and marketing, distribution or licensing 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 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, 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 of the Code are extremely complex provisions with respect to which there are many uncertainties, and we have not requested a ruling from the IRS to confirm our analysis of the ownership change limitations related to the NOLs generated by us. Therefore, we have not established whether the IRS would agree with our analysis regarding the application of Section 382 and 383 of the Code. Our public offerings of common stock in April 2018 and January 2019 (including the shares issued in February 2019 upon exercise by the underwriter of its option to purchase additional shares) and the common shares issued to Agilis as a result of being acquired by us in August 2018 may put us closer to another ownership change for purposes of Section 382. We continue to fully evaluate the impact of a Section 382 limitation on the use of our NOLs and other tax attributes.

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 addition, under the 2017 Tax Cuts and Jobs Act (the 2017 Tax Act) enacted on December 22, 2017, the deductibility of federal net operating losses incurred in 2018 and in future years generally is limited to 80% of taxable income for each taxable year, although such losses may be carried forward indefinitely. Therefore, we cannot predict with certainty when, or whether the Company will generate sufficient taxable income to use all of our NOLs.

Changes in our effective income tax rates and the 2017 Tax Act 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 foreign jurisdictions. Taxes will be incurred as income is earned among 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 U.S. Internal

Revenue Service 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.

In October 2015, the OECD published "final reports" and launched a global dialogue among member and non-member countries on measures to limit harmful tax competition. These measures are largely directed at counteracting the effects of preferential tax regimes in countries around the world. The measures have, among other things, resulted in the development of a multilateral instrument, or MLI, to incorporate and facilitate changes to tax treaties. In June 2017, a number of countries signed the MLI. In addition, in January 2016, the EU Commission announced an Anti-Tax Avoidance Package containing measures to regulate certain elements of tax planning further and to boost tax transparency for consideration by the European Parliament and Council. In July 2016, the Economic and Financial Affairs Council adopted a Council Directive forming part of the EU Anti-Tax Avoidance Package and building upon the OECD BEPS recommendations. EU Member States are required to implement the directive into their domestic laws by December 31, 2018 (or December 31, 2019 in the case of provisions on exit taxation). Further changes, including to the directive, have been proposed as part of an EU corporate tax reform package published in October 2016.

Changes arising from any proposals introduced in connections with the possible new OECD and EU measures could have material adverse consequences on our effective tax rate, the amount of tax we pay and on our financial position and results of operations.

Additionally, in the United States, the 2017 Tax Act was enacted on December 22, 2017, making significant changes to the U.S. corporate income tax system. These changes include a federal statutory rate reduction from 35% to 21%, the elimination or reduction of certain domestic deductions and credits and limitations on the deductibility of interest expense and executive compensation. The 2017 Tax Act also transitions international taxation from a worldwide system to a modified territorial system and includes base erosion prevention measures on non-U.S. earnings, which has the effect of subjecting certain earnings of our foreign subsidiaries to U.S. taxation as global intangible low-taxed income (GILTI). These changes became effective in January 2018. The U.S. Department of Treasury has broad authority to issue regulations and interpretative guidance that may significantly impact how we will apply the law. The effect of the 2017 Tax Act will differ across the states. Many states have enacted new legislation in response to the federal tax reform law. As a result of the reduction in the U.S. corporate income tax rate, we revalued our ending net deferred tax assets as of December 31, 2017. In the fourth quarter of 2018, we completed our analysis to determine the effect of the Tax Act and recorded no further adjustments.

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 the results of Study 041 by September 2021, 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 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, 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. 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 the results of Study 041 by September 2021 to the EMA. Due to enrollment at a slower pace in certain countries than initially expected, in our February 2019 marketing authorization renewal request, we asked the EMA to extend the timeframe for submission of the results of Study 041 to the EMA to the end of the third quarter of 2022. 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 it is probable that we will enroll patients in territories where Translarna has already become available on a reimbursed basis. We may enroll patients in countries with a different standard of care for nmDMD patients or at clinical trial sites that are inexperienced with clinical trials in general, or specifically with nmDMD trials. 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.

Translarna, Emflaza, and our 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 recently submitted marketing authorization requests for Translarna and Tegsedi. Failure to obtain or renew marketing authorization for Translarna, Tegsedi or any product candidate, or maintain our marketing authorization for Emflaza in the United States will prevent us from commercializing such product or product candidate.

As noted in the foregoing risk factors, we may not receive necessary approvals from the FDA, the EMA, ANVISA or other regulators to further commercialize Translarna for nmDMD, to commercialize Translarna or Emflaza for any other indication, to commercialize Tegsedi 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.

We have not proven our ability to successfully obtain marketing authorizations to sell our product or product candidates, other than with respect to the marketing authorization granted by the European Commission in August 2014 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 and satisfaction of any conditions that may be imposed by the EMA, including the specific obligation to conduct and report the results of Study 041 and our marketing authorizations in Chile, Israel and South Korea (which are largely contingent upon continued EMA approval). 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, including in Brazil where we have submitted a marketing authorization request to ANVISA. 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. Regulatory authorities may determine that Translarna or any of our other 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. Additionally, we are obligated to complete certain post-marketing requirements in connection with the FDA's approval of Emflaza, including pre-clinical and clinical safety studies.

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 European Union 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 PTC-AADC and for Translarna for the treatment of nmDMD, Becker muscular dystrophy (in the EU), and nonsense mutation aniridia. The FDA has also granted an orphan drug designation to risdiplam, PTC-FA and PTC-AS. 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 European Union and in the United States, may be important to a product candidate's future success.

In the EU, if a product with an orphan drug designation 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. The EU exclusivity period can be reduced to six years 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. However, in the European Union, generic medicinal products that rely on the independently generated data submitted as part of a full marketing authorization application dossier of an authorized medicinal product, a "reference product", may not be placed on the market for 10 years from the granting of the initial marketing authorization for the reference product.

In the European Union, 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.

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.

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 Hatch-Waxman Act and the Orphan Drug Act to commercialize Emflaza for the approved indication in the United States and failure to maintain either exclusivity period would have a material adverse effect on our ability to commercialize Emflaza, 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 of 1983, or the Orphan Drug Act, and the Drug Price Competition and Patent Term Restoration Act of 1984, or the Hatch-Waxman 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 has a seven-year exclusive marketing period in the United States for the approved orphan indication, which commenced on February 9, 2017 (the date of FDA approval), under the Orphan Drug Act as well as a concurrent five-year exclusive marketing period in the United States for the active ingredient in Emflaza under the provisions of the Hatch-Waxman Act. The FDA awarded an orphan drug designation to Emflaza for the treatment of patients with DMD and later approved Emflaza 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.

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.

Under the Hatch-Waxman Act, a five-year period of exclusivity is granted to NDAs for products, such as Emflaza, containing active moieties never previously approved by the FDA either alone or in combination with another drug substance. The active moiety is the molecule or ion, excluding certain appended portions and other noncovalent derivatives, responsible for the physiological or pharmacological action of the drug substance. During the five-year exclusivity period, third parties may not submit certain types of applications to the FDA, except that such applications may be submitted after four years if they contain a certification of patent invalidity or non-infringement with respect to any patents of the exclusivity holder covering the drug product that are listed in FDA's list of Approved Drug Products with Therapeutic Equivalence Evaluations, commonly referred to as the Orange Book. The two types of applications prevented by Hatch-Waxman exclusivity are 505(b)(2) applications and abbreviated new drug applications, or ANDAs. A 505(b)(2) application allows the FDA to rely for approval of an NDA on data not developed by or for the applicant such as published literature or the FDA's finding of safety and effectiveness of a previously approved drug, and for which the applicant has not obtained a right of reference or use. An ANDA is an application that contains information to show that the proposed product is identical in active ingredient, dosage form, strength, route of administration, labeling, and conditions of use, among other things to a previously approved application (known as 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 do not generally contain clinical studies as required in full NDAs but are required to contain information establishing bioequivalence to the reference listed drug, allowing the FDA to use this bioequivalence information to rely on the prior finding of safety and efficacy for the reference listed drug and may face competition from 505(b)(2) and ANDA products sooner than anticipated.

Exclusivity under the Hatch-Waxman Act does not prevent the submission, filing and approval of a full NDA containing full reports of investigations of safety and effectiveness either owned by the applicant or to which the applicant has obtained a right of reference. Moreover, Hatch-Waxman Act exclusivity does not prevent physicians from prescribing and third-party payors from reimbursing products off-label for the same use as any of our products. It is also possible that we may not receive any anticipated periods of regulatory exclusivity for our product candidates that are not yet approved. As a result, it is possible that we will not realize the full period of market exclusivity under the Hatch-Waxman Act.

Further, each of the Orphan Drug Act and the Hatch-Waxman 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 Translarna for the treatment of nmDMD in the EEA and Emflaza for the treatment of DMD in the United States, 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, Translarna, Emflaza, our 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. We are 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, and there is no guarantee that the post-marketing trial and studies will not result in changes to Emflaza's labeling or that they will support the continued approval of Emflaza in the United States. Commencement of the post-marketing trial and studies is pending feedback from the FDA. 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 foregoing 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 the results of Study 041 by September 2021, 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 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, 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 current good manufacturing practice, or 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 for Translarna for the treatment of nmDMD and for Emflaza for the treatment of DMD described above. 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 Federal Food, Drug, and Cosmetic Act relating to the promotion of prescription drugs may lead to civil and criminal penalties, investigations alleging violations of federal and state health care 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 misconduct,

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 conditional 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 complete. 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 five-year 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 to be reviewed again at the end of the five-year period, 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 European Union 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 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 also showed increased interest in pharmaceutical companies' product and patient assistance programs, including reimbursement and co-pay support services, and 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 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.

- Laws and regulations related to the privacy, security and transmission of individually identifiable health information, including the U.S. Health Insurance Portability and Accountability Act of 1996, or HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act of 2009, or HITECH, and similar state laws. For example, HIPAA, as amended by HITECH, along with its implementing regulations, which impose obligations, including mandatory contractual terms, with respect to safeguarding the privacy, security and transmission of individually identifiable health information, and may impose criminal and civil liability for violations of these obligations. In addition, international data protection laws including the European General Data Protection Regulation, and supplementary member state legislation may apply to some or all of the clinical or other protected data obtained, transmitted, or stored outside of the United States. Furthermore, 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 health care benefits, knowingly and willfully embezzling or stealing from a health care benefit program, willfully obstructing a criminal investigation of a health care 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 ACA 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 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.

- Laws and regulations regulating off-label promotion of medicinal products, which is prohibited in the European Union. The applicable laws at European Union 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 European Union 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 health care professionals.

- Laws and regulations in the United States, including the Federal Food, Drug and Cosmetic Act 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 physicians, 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 payments and other transfers of value made to or at the request of covered recipients, such as physicians and teaching hospitals, as well as physician 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 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 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 European Union. 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 foreign 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 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 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 foreign 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 Prescription Drug, Improvement, and Modernization Act of 2003, or 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, the current Presidential Administration and U.S. Congress have expressed a desire to modify, repeal or otherwise invalidate all, or certain provisions of, the Affordable Care Act, and there are pending lawsuits challenging the Affordable Care Act, which has contributed to the uncertainty of the ongoing implementation and impact of the Affordable Care Act and also underscores the potential for additional reform going forward. 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. For example, CMS recently reduced the payment rate for certain hospitals purchasing outpatient drugs at the 340B program discounted price, 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. Similarly, 340B program guidance regulations on civil monetary penalties for statutory violations, which was finalized in early 2017, recently went into effect. In October 2018, CMS issued an advance notice of proposed rulemaking paving the way for a proposed rule in 2019 that would significantly reduce the price of drugs paid by Medicare Part B by basing reimbursement on the average prices among other industrialized countries, and in January 2019, CMS proposed eliminating the Anti-Kickback Act safe harbor for rebates typically provided to PBMs and health plans that are included in their cost effectiveness determinations.

We anticipate that the U.S. Congress, 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 on mandatory discounts under certain government sponsored programs;
- controls on healthcare providers;
- challenges to the pricing of drugs or limits on prohibitions on reimbursement or specific products through other means;
- reform of drug importation laws;
- expansion of use of managed care systems in which the healthcare providers contract to provide comprehensive healthcare for a fixed cost per person; and
- prohibition on 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. 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.

In the European Union, 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 European Union 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 European Union, 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, and restrict sales and promotional activities for pharmaceutical products. 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 foreign 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 fail to realize the anticipated benefits of our acquisition of Agilis Biotherapeutics, Inc., or Agilis, those benefits may take longer to realize than expected, and we may encounter significant integration difficulties.

On August 23, 2018, we completed the acquisition of Agilis pursuant to an agreement and plan of merger, dated July 19, 2018, or the Merger Agreement.

Our ability to realize the anticipated benefits of our acquisition of Agilis will depend, to a large extent, on our ability to integrate Agilis's operations and employees into our business and realize anticipated growth opportunities and synergies. Prior to our acquisition of Agilis, we had no substantial experience developing or manufacturing large molecules including gene therapy. The development and manufacture of these product candidates will be more complex and is subject to additional and/or different regulatory requirements as compared to the small molecule products that we have historically developed and/or commercialized. Accordingly, we may ultimately not be successful in developing and manufacturing the gene therapy product candidates.

We will be required to devote significant management attention and resources to integrating Agilis's operations and employees into our business and any product candidates acquired from Agilis into our development and commercialization efforts and business strategy. The process may be disruptive to our business and the expected benefits may not be achieved within the anticipated time frame, or at all. The failure to meet the challenges involved and to realize the anticipated benefits of the transaction could cause an interruption of, or a loss of momentum in, our development and commercialization efforts and could adversely affect our business, financial condition and results of operations.

Our ability to realize the anticipated benefits of the transaction is expected to entail numerous material potential difficulties, including, among others:

- the diversion of management attention to integration matters;
- difficulties in achieving anticipated business opportunities and growth prospects from our acquisition of Agilis;
- challenges related to public and market perception of our acquisition of Agilis and gene therapy and increased regulatory scrutiny of gene therapy;
- difficulties in managing the expanded operations of a larger and more complex company following our acquisition of Agilis;
- difficulties in assimilating employees and in attracting and retaining key personnel; and
- potential unknown liabilities, adverse consequences, unforeseen increased expenses or other unanticipated problems associated with the transaction.

Many of these factors are outside of our control, and any one of them could result in increased costs, decreased expected revenues and further diversion of management time and energy, which could materially impact our business, financial condition and results of operations.

All of these factors could decrease or delay the expected accretive effect of the transaction and negatively impact our stock price. As a result, it cannot be assured that our acquisition of Agilis will result in the full realization of the benefits anticipated from the transaction within the anticipated timeframes or at all.

Upfront consideration for our acquisition of Agilis was comprised of $49.2 million in cash and 3,500,907 shares of our common stock. In addition, pursuant to the Merger Agreement, Agilis equityholders will be entitled to receive contingent payments from us 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 of Friedreich ataxia and Angelman Syndrome products during specified terms, ranging from 2-6%. Under the Merger Agreement, we are required to pay $40.0 million of the development milestone payments no later than August 23, 2020, regardless of whether the applicable milestones have been achieved. There is no guarantee that we will be able to make these milestone payments through cash on hand and expected cash flows and we may be required to raise additional capital in order to fund these payments.

Following completion of the acquisition, we became responsible for Agilis's liabilities and obligations, including with respect to certain agreements, financial, regulatory and compliance matters, in addition to the expenses we expect to incur based on our current commercial, regulatory, research and development plans for PTC-AADC and the other assets acquired from Agilis. These expenses and obligations will result in additional cost and investment by us and, if we have underestimated the amount of these costs and investments or if we fail to satisfy any such obligations, we may not realize the anticipated benefits of the transaction. Further, it is possible that there may be undisclosed, contingent or other liabilities or problems that may arise in the future, the existence and/or magnitude of which we were previously unaware. Any such liabilities or problems could have an adverse effect on our business, financial condition or results of operations.

The issuance of our common stock to complete this transaction was dilutive to our existing stockholders and because we have limited financial resources, by investing in this transaction, we may forego or delay pursuit of other opportunities that may have proven to have greater commercial potential.

We may expend our limited 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.

Because we have limited financial and managerial resources, 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 are required to pay $40.0 million of the development milestone payments no later than the second anniversary of the closing of the acquisition, regardless of whether the applicable milestones have been achieved. We may never realize the anticipated benefits of the acquisition of Agilis and by investing our limited resources in this product, we may be required to forgo or delay other opportunities.

In addition, we initiated separate Phase 2 clinical trials of Translarna for the treatment of hemophilia in 2009 and the metabolic disorder methylmalomic acidemia in 2010, but then suspended these clinical trials to focus on the development of Translarna for nmDMD and nmCF when we found variability in the assays used in these trials and preliminary data from these trials did not indicate definitive evidence of activity. We also initiated a Phase 2 clinical trial of Translarna for treatment of mucopolysaccharidosis type I caused by nonsense mutation in 2015, but in the third quarter of 2017 we stopped enrollment and began to wind down this study due to difficulties identifying qualified patients. In March 2017, we discontinued our clinical development of Translarna for nmCF based on the negative outcome of a Phase 3 clinical trial. 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.

Until our recent acquisition of a gene therapy platform, historically, we have based our research and development efforts on small-molecule drugs that target post-transcriptional control processes. 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 only been granted marketing authorization in the EEA to treat nmDMD under a restricted label that is subject to the specific obligation to conduct Study 041 as well as annual renewal and reassessment requirements and 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 authorization for nmDMD in the EEA 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 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.

We do not own or operate manufacturing or distribution facilities for the production or distribution of clinical or commercial supplies of our products or product candidates. We have limited personnel with experience in drug manufacturing and lack the resources and the capabilities to manufacture any of our products or product candidates on a clinical or commercial scale. We currently rely on third parties for supply of the active pharmaceutical ingredients used in Translarna, Emflaza and all of our product candidates. We outsource all manufacturing, packaging, labeling and distribution of our products and product candidates to third parties, including our commercial supply of Translarna and Emflaza. We anticipate taking steps to increase our manufacturing capabilities for our gene therapy platform, although we currently rely on third-party manufacturers to be capable of providing sufficient quantities of our program materials to meet anticipated clinical trial and commercial scale demands.

We do not directly control the manufacturing of our products and product candidates, and we are completely dependent on, our contract manufacturers for compliance with current good manufacturing practice, or cGMP, or good distribution practice, or GDP,

or similar regulatory requirements outside the European Union and the United States for manufacture of both active drug substances and finished drug products. Should 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 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 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 foreign regulatory agencies, they will not be able to secure and/or maintain regulatory approval for their 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, third-party manufacturers or distributors may not be able to comply with current good manufacturing practice, or cGMP, or good distribution practice, or GDP, or similar regulatory requirements outside the European Union 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 Translarna, Emflaza or our 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 foreign regulatory agency do not approve these 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. 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 and the drug substance for our oncology program through another third-party manufacturer. 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, although we are still in the process of finalizing arrangements with one of these manufacturers with respect to commercial product services.

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 a contract with a pharmacy and hospital distributor in the European Union that distributes Translarna for clinical programs and 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 intend to engage additional distributors if and when, if ever, we become authorized to make Translarna available for purchase in such additional geographies.

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. 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 initial term of five years. 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 expect to rely upon market exclusivity periods available to us under the Orphan Drug Act and Hatch-Waxman 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 a specialty pharmacy to sell and distribute Emflaza to patients. The specialty pharmacy provides 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.

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 Translarna or Emflaza 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 Emflaza, or serious adverse events and/or product complaints regarding Emflaza;
- 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 Translarna or Emflaza and any of our product candidates, including human error, natural disasters, labor disputes, acts of terrorism or war, equipment malfunctions, contamination, or raw material shortages.

Our products and our 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 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 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 or Emflaza 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 Translarna, Emflaza or our 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.

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, manufacturers may experience shortages in raw materials and components, not be able to scale up their manufacturing capacities to support more advanced clinical trials or product commercialization, may not be able to qualify or validate their 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 and 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 Good Clinical Practices, or 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 foreign 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 European Union. Failure to comply with the applicable regulatory requirements, including with respect to clinical trials conducted outside the European Union 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 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.

We currently depend, and expect to continue to depend, on collaborations with third parties for the development and commercialization of some of our product candidates. If those collaborations are not successful, we may not be able to capitalize on the market potential of these 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. 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 successful development of a 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 continues clinical development of risdiplam or pursues clinical development of any other compounds identified under the collaborations.

Collaborations involving our 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 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.

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, 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, foreign 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. 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 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 Translarna, Emflaza and any other product that we may market or commercialize, 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 or products 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;
- 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.

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 Translarna and Emflaza, 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.

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 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 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 is new, we might face a shortage of skilled individuals with substantial gene therapy experience. As a result, competition for skilled personnel, including in gene therapy research and vector 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 regulatory and, if approved, commercial plans for PTC-AADC, Tegsedi and Waylivra 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 our acquisition of Agilis. 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 the integration of Agilis. 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 foreign 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 before it is too late to obtain patent protection. 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 foreign 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 (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 European Union 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 European Union 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 European Union 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 European Union 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 have appealed the General Court's decision to the Court of Justice of the European Union and the EMA has confirmed that it will not release the documents while the matter is still subject to the appeal process. However, there can be no assurance that we will be successful in the appeal and we may not ultimately succeed in preventing disclosure of the data in our marketing authorization for Translarna for the treatment of nmDMD.

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 Translarna, Emflaza, PTC-AADC, Tegsedi. Waylivra or risdiplam. Thus, we do not know with certainty whether Translarna, Emflaza, PTC-AADC, Tegsedi, Waylivra, risdiplam or any of our other 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 product 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 (deflazacort) 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.

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, and attempt to assert such patents against us.

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 Translarna and Emflaza, 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 Translarna or Emflaza 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 foreign 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, including Translarna and Emflaza, 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 our product candidates, including Translarna and Emflaza, 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, 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 potential 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 potential gene therapy product candidates. In particular, we have in-licensed certain intellectual property rights and know-how from the National Taiwan University, or 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 potential 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. In addition, absent an amendment or additional agreement, we may not have the right to use intellectual property in-licensed for one of our programs for use in another program.

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 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. 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.

In addition, 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 indenture, to make interest payments on the Convertible Notes when due under the indenture or to pay any cash payable on future conversions of the Convertible Notes as required by the indenture would constitute a default under the indenture. An event of default under the 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, even if holders of the Convertible Notes do not elect to convert their Convertible Notes, we could be required under applicable accounting rules to reclassify all or a portion of the outstanding principal of the Convertible Notes as a current rather than long-term liability, 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:

- our ability to realize the anticipated benefits of our acquisition of Agilis, including our ability to obtain marketing approval for PTC-AADC;
- any developments related to our ability or inability to execute our strategy for Emflaza for the treatment of DMD in the United States, in particular with respect to our commercialization efforts;
- 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 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;
- our ability to commercialize Tegsedi and Waylivra in the PTC Territory;
- 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 Translarna and 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;
- our ability to advance the commercialization of Translarna for the treatment of nmDMD;
- the success of competitive products or technologies;
- the development and regulatory status of risdiplam and our SMA program with Roche and the SMA Foundation;
- results of clinical trials of product candidates of our competitors;
- regulatory or legal developments in the United States and other countries;
- developments or disputes concerning patent applications, issued patents or other proprietary rights;
- the recruitment or departure of key personnel;
- 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;

- 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, the Dodd-Frank Act, the listing requirements of The Nasdaq Global Select Market 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 of the Sarbanes-Oxley Act of 2002, 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 of the Sarbanes-Oxley Act in a timely manner each year, we could be subject to sanctions or investigations by the Securities and Exchange Commission, the Nasdaq Stock Market 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. In addition, 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.

Sales of a substantial number of shares of our common stock in the public market by our existing stockholders 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 or, with respect to certain option grants, will be 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.

In connection with our acquisition of Agilis, we issued to the Agilis equityholders 3,500,907 shares of our common stock. Following the acquisition, we registered these shares under the Securities Act, and such registration was terminated following the six-month anniversary of the acquisition pursuant to the Agilis Merger Agreement. Any shares that have not yet been sold are currently restricted as a result of securities laws. Following expiration of applicable holding periods, the shares will be able to 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.

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 2022, with one three-year renewal option to renew the lease after 2022. 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 2022. We also lease office space in 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, including as a result of patients seeking to participate in our clinical trials or otherwise gain access to our product candidates. 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 25, 2019, there were 84 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

Inducement stock option awards

Pursuant to the Nasdaq inducement grant exception, during the quarter ended December 31, 2018, we issued options to purchase an aggregate of 237,150 shares of common stock to certain new hire employees at a weighted-average exercise price of $35.51 per share. The shares underlying these option awards have been registered on a Form S-8 registration statement.

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. Selected Financial Data

The following table sets forth certain financial data with respect to our business. The selected consolidated financial data is derived from, and should be read in conjunction with, our Consolidated Financial Statements and related Notes and Item 7, "Management's Discussion and Analysis of Financial Condition and Results of Operations", and other information contained elsewhere in this Annual Report on Form 10-K.

	Year ended December 31,				
	2018	2017	2016	2015	2014
	(In thousands, except per share data)				
Statement of Operations Data:					
Revenues:					
Net product revenue	$ 263,005	$ 174,066	$ 81,447	$ 33,696	$ 717
Collaboration and grant revenue	1,729	20,326	1,258	3,070	24,528
Total revenues	264,734	194,392	82,705	36,766	25,245
Operating expenses:					
Cost of product sales, excluding amortization of acquired intangible asset	12,670	4,577	—	—	—
Amortization of acquired intangible asset	22,877	15,380	—	—	—
Research and development	171,984	117,456	117,633	121,816	79,838
Selling, general and administrative	153,548	121,271	97,130	82,080	44,820
Change in the fair value of deferred and contingent consideration	19,340	—	—	—	—
Total operating expenses	380,419	258,684	214,763	203,896	124,658
Loss from operations	(115,685)	(64,292)	(132,058)	(167,130)	(99,413)
Interest (expense) income, net	(12,554)	(12,094)	(8,276)	(2,367)	1,180
Other income (expense), net	129	(1,279)	(1,207)	(465)	(213)
Loss before income tax benefit (expense)	(128,110)	(77,665)	(141,541)	(169,962)	(98,446)
Income tax benefit (expense)	29	(1,335)	(569)	(485)	4,693
Net loss attributable to common stockholders	$ (128,081)	$ (79,000)	$ (142,110)	$ (170,447)	$ (93,753)
Net loss attributable to common stockholders per share:					
Basic	$ (2.75)	$ (2.02)	$ (4.17)	$ (5.07)	$ (2.97)
Diluted	$ (2.75)	$ (2.02)	$ (4.17)	$ (5.07)	$ (2.97)
Weighted-average shares outstanding:					
Basic	46,576,313	39,183,073	34,044,584	33,626,248	31,565,310
Diluted	46,576,313	39,183,073	34,044,584	33,626,248	31,565,310

	As of December 31,				
	2018	2017	2016	2015	2014
			(In thousands)		
Balance Sheet Data:					
Cash, cash equivalents, and marketable securities	$ 227,586	$ 191,246	$ 231,666	$ 338,925	$ 315,241
Working Capital	154,061	167,015	211,662	310,563	291,096
Total assets*	1,119,222	391,653	269,345	365,281	333,219
Total debt*	153,014	144,971	98,216	91,848	—
Accumulated deficit	(938,923)	(814,108)	(735,108)	(592,998)	(422,551)
Total stockholders' equity	350,727	156,437	119,583	226,001	298,467

* Reclassified debt issuance costs of $2.8 million related to the Convertible Notes as of December 31, 2015 from Total Assets and Long-term debt in connection with the adoption of ASU 2015-03.

Item 7. Management's Discussion and Analysis of Financial Condition and Results of Operations.

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-led 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 commercialize products is the foundation that drives our continued investment in a robust pipeline of transformative medicines and our mission to provide access to best-in-class treatments for patients who have an unmet medical need. Our strategy is to bring best-in-class therapies with differentiated clinical benefit to patients affected by rare disorders and to leverage our global commercial infrastructure to maximize value for our patients and other stakeholders.

We have two products, Translarna™ (ataluren) and Emflaza™ (deflazacort), for the treatment of Duchenne muscular dystrophy, or DMD, a rare, life threatening disorder. Translarna received marketing authorization from the European Commission in August 2014 for the treatment of nonsense mutation Duchenne muscular dystrophy, or nmDMD, in ambulatory patients aged five years and older in the 31 member states of the European Economic Area, or EEA. 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. During the year ended December 31, 2018, we recognized $171.0 million in sales of Translarna. Translarna is currently available for the treatment of nmDMD in over 40 countries on a commercial basis or through a reimbursed early access program, or EAP program. 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 five years and older. During the year ended December 31, 2018, Emflaza achieved net sales of $92.0 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 July 2018, the European Commission renewed our marketing authorization, making it effective, unless extended, through August 5, 2019. In February 2019, 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 a18-month, placebo-controlled trial, followed by an 18-month open-label extension, which we refer to together as Study 041. The final report on the trial and open-label extension is to be submitted by us to the EMA by the end of the third quarter of 2021. Due to enrollment at a slower pace in certain countries than initially expected, in our February 2019 marketing authorization renewal request, we asked the EMA to extend the timeframe for submission of the results of Study 041 to the EMA to the end of the third quarter of 2022.

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 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 intend to follow the FDA's recommendation and will collect, using newer technologies via procedures and methods that we designed, such dystrophin data in a new study, Study 045, which we initiated in the fourth quarter of 2018. We expect that a potential re-submission of an NDA could occur in 2020. Additionally, should a re-submission of an NDA receive accelerated approval, the Office of New

Drugs stated that Study 041, which is currently enrolling, could serve as the confirmatory post-approval trial required in connection with the accelerated approval framework.

There is substantial risk that Study 045, or any other studies we may use to collect the dystrophin data, will not provide the necessary data to support a marketing approval for Translarna for the treatment of nmDMD in the U.S.

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, or AADC deficiency, a rare CNS disorder arising from reductions in the enzyme AADC that result from mutations in the dopa decarboxylase gene. We are preparing a biologics license application, or BLA, for PTC-AADC for the treatment of AADC deficiency in the United States, which we anticipate submitting to the U.S. Food and Drug Administration, or FDA, in late 2019, with an anticipated commercial launch in the United States in 2020. We are also preparing a marketing authorization application, or MAA, for PTC-AADC for the treatment of AADC deficiency in the European Union, or EU, for submission to the European Medicines Agency, or EMA, which will follow our BLA submission to the FDA.

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 our Collaboration and License Agreement with Akcea Therapeutics, Inc., or Akcea. Tegsedi has received marketing authorization in the United States, EU and Canada for the treatment of stage 1 or stage 2 polyneuropathy in adult patients with hereditary transthyretin amyloidosis, or hATTR amyloidosis, and was recently granted priority review by ANVISA, the Brazilian health regulatory authority. Waylivra is currently under regulatory review in the EU for the treatment of familial chylomicronemia syndrome, or FCS.

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. Currently, our collaboration has two pivotal clinical trials ongoing to evaluate the safety and effectiveness of risdiplam (RG7916, RO7034067), the lead compound in the SMA program. Roche is preparing an NDA and a MAA for risdiplam for the treatment of SMA in the United States and the EU, respectively, which Roche anticipates submitting to the FDA and the EMA in the second half of 2019.

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, including rare diseases and oncology.

Overview—Funding

The success of Translarna, Emflaza and any other product candidates we may develop, depends largely on obtaining and maintaining reimbursement from governments and third-party insurers. During 2018, our revenues were generated from sales of Translarna for the treatment of nmDMD in territories where we are permitted to distribute Translarna under our EAP programs and in countries in the EEA where we were able to obtain acceptable commercial pricing and reimbursement terms, and from sales of Emflaza for the treatment of DMD in the United States.

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*."

On April 20, 2017, we completed our acquisition of all rights to Emflaza, or the Transaction, for total upfront consideration comprised of $75.0 million in cash, funded through cash on hand, and 6,683,598 shares of our common stock, which was determined by dividing $65.0 million by the volume weighted average price per share of our common stock on the Nasdaq Stock Market for the 15 trading-day period ending on the third trading day immediately preceding the closing.

On May 5, 2017, we entered into a credit and security agreement, or the Credit Agreement, with MidCap Financial Trust, or MidCap Financial, as administrative agent and MidCap Financial and other certain institutions as lenders thereto, that provides for a senior secured term loan facility of $60 million, of which $40 million was drawn by us on May 5, 2017. Our ability to draw on the remaining $20.0 million under the senior secured term loan facility expired on December 31, 2018. The maturity date of the Credit Agreement is May 1, 2021, unless terminated earlier.

In April 2018, we closed an underwritten public offering of our common stock pursuant to a registration statement on Form S-3. We issued and sold an aggregate of 4,600,000 shares of common stock under the registration statement at a public offering price of $27.04 per share, including 600,000 shares issued upon exercise by the underwriters of their option to purchase

additional shares. We received net proceeds of approximately $117.9 million after deducting underwriting discounts and commissions and other offering expenses payable by us.

On August 23, 2018, we completed our acquisition of Agilis for total upfront consideration comprised of $49.2 million in cash and 3,500,907 shares of our common stock, which was determined by dividing $150.0 million by the volume-weighted average price per share of our common stock on the Nasdaq Global Select Market for the 10 consecutive trading-day period ending on the second trading-day immediately preceding the closing.

In January 2019, we closed an underwritten public offering of our common stock pursuant to a registration statement on Form S-3. We issued and sold an aggregate of 7,563,725 shares of common stock under the registration statement 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 $224.1 million after deducting underwriting discounts and commissions and other offering expenses payable by us.

To date, we have financed our operations primarily through our offering of 3.00% convertible senior notes due August 15, 2022, or the Convertible Notes offering, our public offerings of common stock in February 2014, in October 2014, in April 2018, and in January 2019, our initial public offering of common stock in June 2013, private placements of our preferred stock, collaborations, bank debt and convertible debt financings, the Credit Agreement and grants 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.

As of December 31, 2018, we had an accumulated deficit of $938.9 million. We had a net loss of $128.1 million and $79.0 million for the fiscal years ended December 31, 2018 and 2017, 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 and administrative and employee-based expenses. In addition to the foregoing, we expect to continue to incur significant costs in connection with Study 041 and Study 045 and our open label extension trials of Translarna for the treatment of nmDMD as well as our studies for nonsense mutation aniridia and nonsense mutation Dravet syndrome/CDKL5 and our FDA post-marketing requirements with respect to Emflaza in the United States and studies for limb-girdle 2I. We also expect to incur ongoing research and development expenses for our other product candidates, including our gene therapy. splicing and oncology programs. In addition, we may incur substantial costs in connection with our efforts to advance our regulatory submissions. 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 and we may also seek marketing authorization for Translarna for other indications. In late 2019, we plan to submit a request for marketing authorization for PTC-AADC with the FDA, followed by a request for marketing authorization for PTC-AADC with the EMA and we recently submitted a request for marketing authorization for Tegsedi with ANVISA. 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 Convertible Notes, cash interest payments are payable on a semi-annual basis in arrears, which require total funding of $4.5 million annually. Additionally, under the terms of our Credit Agreement cash interest payments are payable monthly in arrears. Furthermore, as a result of our initial public offering in June 2013, we have incurred and expect to continue to incur additional costs associated with operating as a public company including significant legal, accounting, investor relations and other expenses. See also, "*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*" under Part II, Item 1A. Risk Factors - Risks Related to Our Common Stock.

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 solely 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 a license and collaboration agreement, or licensing agreement, with Roche and the SMA Foundation pursuant to which we are collaborating with Roche and the SMA Foundation to further develop and commercialize compounds identified under our spinal muscular atrophy program with the SMA Foundation. The research component of this agreement terminated effective December 31, 2014. The licensing agreement included a $30 million upfront payment made in 2011 which was recognized on a deferred basis over the research term, and the potential for up to $460 million in milestone payments and royalties on net sales.

In August 2013, we announced the selection of a development candidate, RG7800. The achievement of this milestone triggered a $10.0 million payment to us from Roche, which we recorded as collaboration revenue for the year ended December 31, 2013.

In January 2014, we initiated a Phase 1 clinical program for RG7800, which triggered a $7.5 million milestone payment to us from Roche which we recorded as collaboration revenue for the year ended December 31, 2014.

In November 2014, we announced that our joint development program in Spinal Muscular Atrophy (SMA) with Roche and the SMA Foundation (SMAF) has started a Phase 2 study for RG7800 in adult and pediatric patients. The achievement of this milestone triggered a $10 million payment to us from Roche which we recorded as collaboration revenue for the year ended December 31, 2014.

In October 2017, we announced that the joint development program in SMA with Roche and SMAF had transitioned into the pivotal second part of its study evaluating the efficacy and safety of RG7916 in pediatric and adult Type 2/3 SMA patients. The achievement of this milestone triggered a $20.0 million payment to us from Roche which we recorded as collaboration revenue at time of achievement.

Grant revenue. From time to time, we receive grant funding from various institutions and governmental bodies. The grants are typically for early discovery research, and generally such grant programs last from two to five years.

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, 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 studies of Translarna in nonsense mutation aniridia and nonsense mutation Dravet syndrome/CDKL5, our studies of Emflaza in limb-girdle 2I, activities under our gene therapy, splicing and oncology programs, and performance of our FDA post-marketing requirements with respect to Emflaza in the United States. 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, 2018, 2017, and 2016.

	Year ended December 31,		
	2018	2017	2016
	(in thousands)		
Translarna (nmDMD, nmCF, nmMPS I, aniridia and Dravet)	$ 80,859	$ 75,954	$ 84,566
Gene therapy	6,534	—	—
Oncology	16,438	4,481	7,532
Next generation nonsense readthrough	6,735	5,609	6,428
Emflaza	16,461	7,053	—
Akcea	11,957	—	—
Other research and preclinical	33,000	24,359	19,107
Total research and development	$ 171,984	$ 117,456	$ 117,633

We discontinued our clinical studies for nonsense mutation cystic fibrosis (nmCF) and nonsense mutation mucopolysaccharidosis type I (nmMPS I) in 2017 and we expect the research and development costs for those programs to continue to decline as we complete the wind down of those programs.

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 product 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 Translarna or any other product candidate could mean a significant change in the costs and timing associated with the development of that product candidate. 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 Translarna or any other 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.

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, 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 Emflaza in the United States, and our continued efforts to commercialize Translarna for the treatment of nmDMD in territories outside the United States, including increased payroll, expanded infrastructure, commercial operations, increased consulting, legal, accounting and investor relations expenses.

Interest expense, net

Interest expense, net consists of interest income earned on investments and interest expense from the Convertible Notes outstanding and interest expense from the Credit Agreement.

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.

Revenue recognition

In May 2014, the Financial Accounting Standards Board ("FASB") issued Accounting Standards Update ("ASU") No. 2014-9, "Revenue from Contracts with Customers (Topic 606)". ASU No. 2014-9 eliminated transaction- and industry-specific revenue recognition guidance under FASB Accounting Standards Codification ("ASC") Subtopic 605-15, Revenue Recognition-Products (Topic 605) and replaced it with a principle-based approach for determining revenue recognition. ASC Topic 606 requires entities to recognize revenue to depict the transfer of promised goods or services to customers in an amount that reflects the consideration to which the entity expects to be entitled in exchange for those goods or services. On January 1, 2018, the Company adopted ASC Topic 606 using the modified retrospective approach, a practical expedient permitted under Topic 606, and applied this approach only to contracts that were not completed as of January 1, 2018. The Company calculated a one-time transition adjustment of $3.3 million, which was recorded on January 1, 2018 to the opening balance of accumulated deficit, related to the product sales of Emflaza. The ASC 606 transition adjustment recorded for Emflaza resulted in sales being recognized earlier than under Topic 605, as the deferred revenue recognition model (sell-through) is not allowed under Topic 606. The one-time adjustment consisted of $3.9 million in deferred revenue offset by $0.6 million of variable consideration. The information presented for the periods prior to January 1, 2018 has not been adjusted and is reported under Topic 605.

Periods prior to January 1, 2018

We recognize revenue when amounts are realized or realizable and earned. Revenue is considered realizable and earned when the following criteria are met: (1) persuasive evidence of an arrangement exists; (2) delivery has occurred or services have been rendered; (3) the price is fixed or determinable; and (4) collection of the amounts due are reasonably assured.

Net Product Sales

Prior to the second quarter of 2017, our net product sales have consisted primarily of sales of Translarna for the treatment of nmDMD in territories outside of the U.S. We recognize revenue from product sales when there is persuasive evidence that an arrangement exists, title to product and associated risk of loss has passed to the customer, the price is fixed or determinable, collectability is reasonably assured and we have no further performance obligations in accordance with Financial Accounting Standards Board, or FASB, Accounting Standards Codification, or ASC, Subtopic 605-15, Revenue Recognition—Products.

We have recorded revenue on sales where Translarna is available either on a commercial basis or through a reimbursed EAP program. Orders for Translarna are generally received from hospital and retail pharmacies and 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. For the years ended December 31, 2017 and 2016 we recognized Translarna sales of $145.2 million, and $81.4 million, respectively.

In May 2017, we began the commercialization of Emflaza in the U.S. We recorded product revenue related to the sales of Emflaza in the U.S. in accordance with ASC 605-15, when persuasive evidence of an arrangement exists, delivery has occurred and title of the product and associated risk of loss has passed to the customer, the price is fixed or determinable and collection from the customer has been reasonably assured. Due to the early stage of the product launch, we determined that we were not able to reliably make certain estimates, including returns, necessary to recognize product revenue upon shipment to distributors. As a result, we recorded net product revenue for Emflaza using a deferred revenue recognition model (sell-through). Under the deferred revenue model, we did not recognize revenue until Emflaza was shipped to the specialty pharmacy. During the fourth quarter of 2017, we evaluated and determined that we had sufficient volume of historical activity and visibility into the distribution channel to reasonably make all estimates required under ASC 605 to recognize revenue upon shipment to its specialty pharmacy. The change from the sell-through model to recognizing revenue upon shipment to specialty pharmacies during the fourth quarter of 2017 was immaterial to the financial statements. For the year ended December 31, 2017, we recognized Emflaza sales of $28.8 million.

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. Allowances for government and other third-party rebates and discounts are established or estimated at the time of delivery. These allowances are adjusted to reflect known changes in factors and may impact such allowances in the quarter those changes are known.

We expect that net product sales of Translarna for the treatment of nmDMD will fluctuate quarter-over-quarter. 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. In addition, net product sales may fluctuate quarter-over-quarter as a result of government actions, economic pressures and political unrest. Net product sales may be significantly impacted by multiple factors, including, among other things, decisions by regulatory authorities, in particular the FDA and the EMA with respect to our submissions for 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.

Collaboration and Grant Revenue

The terms of collaboration agreements typically include payments of one or more of the following: nonrefundable, upfront license fees; milestone payments; research funding; and royalties on future product sales. If applicable, we generate service revenue through collaboration and grant agreements that provide for fees for research and development services or additional payments upon achievement of specified events.

We evaluate all contingent consideration earned, such as a milestone payment, using the criteria as provided by the FASB guidance on the milestone method of revenue recognition. At the inception of a collaboration arrangement, we evaluate if milestone payments are substantive. The criteria requires that (1) we determine if the milestone is commensurate with either its performance to achieve the milestone or the enhancement of value resulting from our activities to achieve the milestone; (2) the milestone be related to past performance; and (3) the milestone be reasonable relative to all deliverable and payment terms of the collaboration arrangement. If these criteria are met then the contingent milestones can be considered as substantive milestones and will be recognized as revenue in the period that the milestone is achieved. We recognize royalties as earned in accordance with the terms of various research and collaboration agreements. If not substantive, the contingent consideration is allocated to the existing units of accounting based on relative selling price and recognized following the same basis previously established for the associated unit of accounting.

We recognize reimbursements for research and development costs under collaboration agreements as revenue as the services are performed. We record these reimbursements as revenue and not as a reduction of research and development expenses as we have the risks and rewards as the principal in the research and development activities.

Our principal obligation under our grant agreements is to conduct the internal or external research in the specific field funded by the grant. We determine, through the grant's normal research process, which research and development projects to pursue. We recognize grant revenues as the research activities are performed. If the grant includes an upfront payment, we defer the amount and recognize it as revenue as the expenditures are incurred.

Periods commencing January 1, 2018

Our net product revenue 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.

Net Product Revenue

We recognize revenue when performance obligations with customers have been satisfied. Our performance obligations are to provide Translarna or Emflaza 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 either Translarna or Emflaza, 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 either product sales of Translarna or Emflaza. 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. For the year ended December 31, 2018, we recognized Translarna sales of $171.0 million and Emflaza sales of $92.0 million.

We record product sales net of any variable consideration, which includes discounts, allowances, rebates 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. Historically, returns of Translarna and Emflaza were immaterial to our financial statements. 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.

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.

Upon adoption of ASC Topic 606 on January 1, 2018, we have elected the following practical expedients:

- Portfolio Approach - We applied the Portfolio Approach to contract reviews within identified revenue streams that have similar characteristics and we believe this approach would not differ materially than if applying ASC Topic 606 to each individual contract.
- Significant Financing Component - We expect the period between when an we transfer a promised good or service to a customer and when the customer pays for the good or service to be one year or less.
- Immaterial Performance Obligations - We disregard promises deemed to be immaterial in the context of the contract.
- Shipping and Handling Activities - We consider 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 Revenue

The terms of these agreements typically include payments to us of one or more of the following: nonrefundable, upfront license fees; milestone payments; research funding and royalties on future product sales. In addition, we generate 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, we need to first evaluate if the arrangement meets the criteria in 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, we assess the promises in the arrangement to identify distinct performance obligations.

For licenses of intellectual property, we assess, 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. We determine if the bundled performance obligation is satisfied over time or at a point in time. If we conclude that the nonrefundable, upfront license fees will be recognized over time, we assess the appropriate method of measuring proportional performance.

For milestone payments, we assess, 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, we 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 our control. If it is probable that a significant revenue reversal will not occur, we will estimate the milestone payments using the most likely amount method. We will re-assess the development and sales-based milestones each reporting period to determine the probability of achievement.

We recognize revenue for reimbursements of research and development costs under collaboration agreements as the services are performed. We record these reimbursements as revenue and not as a reduction of research and development expenses as we have the risks and rewards as the principal in the research and development activities.

Inventories and Cost of Product Revenues

In January 2017, the European Commission granted an annual renewal of our marketing authorization for Translarna for the treatment of nmDMD. Until this renewal, we had considered the authorization to be subject to risk and did not capitalize productions costs in inventory as it was not probable that such costs would be recovered. With the renewal, we now consider recovery of the costs to be probable and began capitalizing production costs in inventory, effective January 1, 2017. Since January 1, 2017, production costs are expensed as cost of product sales when the related products are sold. The costs for a portion of the inventory available for sale were expensed as research and development costs prior to the January 1, 2017 annual renewal of the Translarna marketing authorization and as such the cost of products sold and related gross margins prior to January 1, 2017 are not directly comparable to the cost of products sold and gross margin after January 1, 2017.

In April 2017, we completed the Transaction (see Note 3). Emflaza, both in tablet and suspension form, received approval from the FDA on February 9, 2017 as a treatment for DMD in patients five years of age and older. We began the commercialization

of Emflaza in the United States shortly after the Transaction was completed. We utilize third parties for the commercial distribution of Emflaza, including a third-party logistics company to warehouse Emflaza as well as a specialty pharmacy to sell and distribute Emflaza to patients. All of our manufacturing needs for Emflaza are fulfilled pursuant to exclusive supply agreements assumed by us upon close of the Transaction. Production costs will be expensed as cost of product sales when the related products are sold.

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. We capitalize inventory costs associated with products following regulatory approval when future commercialization is considered probable and the future economic benefit is expected to be realized. Translarna and Emflaza product 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.

We periodically review inventory for excess amounts or obsolescence and write down obsolete or otherwise unmarketable inventory to its estimated net realizable value. We recorded a $1.8 million inventory write down for the twelve month period ended December 31, 2018 primarily related to inventory labeling changes. No write down was recorded for the twelve month period ended December 31, 2017. Additionally, though our products are subject to strict quality control and monitoring which is performed throughout the manufacturing processes, certain batches or units of product may not meet quality specifications resulting in a charge to cost of product sales.

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 and royalty payments associated with net product sales.

Accrued expenses

As part of the process of preparing our financial statements, we are required to estimate accrued expenses. This process involves communicating with our applicable personnel to identify services that have been performed on our behalf and estimating the level of service performed and the associated cost incurred for the service when we have not yet been invoiced or otherwise notified of actual cost. The majority of our service providers invoice us monthly in arrears for services performed. We make estimates of our accrued expenses as of each balance sheet date in our financial statements based on facts and circumstances known to us. Examples of estimated accrued expenses include:

- fees paid to contract research organizations in connection with preclinical and toxicology studies and clinical trials;
- fees paid to investigative sites in connection with clinical trials;
- fees paid to contract manufacturers in connection with the production of clinical trial materials; and
- professional service fees.

Share-based compensation

We expect to grant additional stock options that will result in additional share-based compensation expense. We measure the cost of employee services received in exchange for an award of equity instruments based on the grant date fair value of the award. 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, we estimate the likelihood of satisfaction of the performance condition and recognize compensation expense when achievement of the performance condition is deemed probable using an accelerated attribution model.

In 2018, we issued a total of 3,181,623 stock options to various employees. Of those, 1,352,800 were non-statutory stock option inducement grants made pursuant to the Nasdaq inducement grant exception as a material component of our new hires' employment compensation. All other stock option grants were made under our 2013 Long Term Incentive Plan.

The fair values of grants made in the year ended December 31, 2018, 2017 and 2016 were contemporaneously estimated on the date of grant using the following assumptions:

	2018	2017	2016
Risk-free interest rate	2.25% - 3.10%	1.84% - 2.45%	1.30% - 2.24%
Expected volatility	64% - 90%	76% - 81%	67% - 78%
Expected term	5.03 - 10.00 years	5.04 - 10.00 years	5.05 - 10.00 years

We assumed no expected dividends for all grants. The weighted average grant date fair value of options granted during the years ended December 31, 2018, 2017 and 2016 was $17.48, $8.45, and $17.31 per share, respectively.

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. We calculate expected volatility based on a historical volatility analysis of peers that were similar to us with respect to industry, stage of life cycle, size, and financial leverage and will continue to do so until the historical volatility of our common stock is sufficient to measure expected volatility for future option grants. We use 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. 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 ASU 2016-0, we made a policy election to continue our methodology for estimating our forfeiture rate.

Restricted Stock Awards—Restricted stock awards are granted subject to certain restrictions, including service conditions. The grant-date fair value of restricted stock awards, which has been determined based upon the market value of our common stock on the grant date, is expensed over the vesting period.

Restricted Stock Units—Restricted stock units are granted subject to certain restrictions, including in some cases service or time conditions (restricted stock). The grant-date fair value of restricted stock units, which has been determined based upon the market value of the Company's shares on the grant date, is expensed over the vesting period.

The following table summarizes information on our restricted stock awards and units:

	Restricted Stock Awards and Units	
	Number of Shares	Weighted Average Grant Date Fair Value
Unvested at December 31, 2017	393,011	$ 15.64
Granted	354,691	$ 19.09
Vested	(114,295)	$ 16.36
Forfeited	(61,928)	$ 17.24
Unvested at December 31, 2018	571,479	$ 17.61

Stock Appreciation Rights—Stock appreciation rights (SARs) entitle the holder to receive, upon exercise, an amount of our common stock or cash (or a combination thereof) determined by reference to appreciation, from and after the date of grant, in the fair market value of a share of our common stock over the measurement price based on the exercise date.

In May 2016, a total of 897,290 SARs were granted to non-executive employees (the 2016 SARs). The 2016 SARs will vest annually in equal installments over four years and will be settled in cash on each vest date, requiring us to remeasure the SARs at each reporting period until vesting occurs. For the period ending December 31, 2018, we recorded $4.1 million in compensation expense related to the 2016 SARs.

Employee Stock Purchase Plan—In June 2016, we established an Employee Stock Purchase Plan (ESPP or the Plan) for certain eligible employees. The Plan is administered by our Board of Directors or a committee appointed by the Board. The total number of shares available for purchase under the Plan is one million shares of our common stock. Employees may participate over a six-month period through payroll withholdings and may purchase, at the end of the six-month period, our common stock at a purchase price of at least 85% of the closing price of a share of our common stock on the first business day of the offering period or the closing price of a share of our common stock on the last business day of the offering period, whichever is lower. No participant will be granted a right to purchase our common stock under the Plan if such participant would own more than 5% of the total combined voting power of our or any subsidiary of ours after such purchase. For the period ending December 31, 2018, we recorded $1.0 million in compensation expense related to the ESPP.

We 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:

(in thousands)	Year ended December 31, 2018	2017	2016
Research and development	$ 16,096	$ 15,456	$ 16,812
Selling, general and administrative	17,156	15,103	18,197
Total	$ 33,252	$ 30,559	$ 35,009

As of December 31, 2018, 2017 and 2016 there was approximately $62.6 million, $38.2 million and $60.8 million, respectively, of total unrecognized compensation cost related to unvested share-based compensation arrangements granted under the Company's 2013 Long Term Incentive Plan and prior equity awards plans or made pursuant to the Nasdaq inducement grant exception for new hires. This cost is expected to be recognized as share-based compensation expense over the weighted average remaining service period of approximately 2.96 years.

Warrant liability

Warrants to purchase our common stock with nonstandard antidilution provisions, regardless of the probability or likelihood that may conditionally obligate the issuer to ultimately transfer assets, are classified as liabilities and are recorded at their estimated fair value at each reporting period. Any change in fair value of these warrants is recorded as gain (loss) on warrant valuation each reporting period in Other income (expense) on our statement of operations.

Convertible notes offering

In August 2015, we issued, at par value, $150.0 million aggregate principal amount of 3.0% convertible senior notes due 2022, which we refer to as the Convertible Notes. The Convertible Notes bear cash interest at a rate of 3.0% per year, payable semi-annually on February 15 and August 15 of each year, beginning on February 15, 2016. The Convertible Notes will mature on August 15, 2022, unless earlier repurchased or converted. The net proceeds to us from the offering were $145.4 million after deducting the initial purchasers' discounts and commissions and the offering expenses payable by us.

The Convertible Notes are governed by an indenture (the Convertible Notes Indenture) with U.S Bank National Association as trustee (the Convertible Notes Trustee).

Holders may convert their 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: (1) during any calendar quarter commencing on or after September 30, 2015 (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 (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 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 February 15, 2022, until the close of business on the business day immediately preceding the maturity date, holders may convert their Convertible Notes at any time, regardless of the foregoing circumstances. Upon conversion, we will pay cash up to the aggregate principal amount of the Convertible Notes to be converted and deliver shares of its common stock in respect of the remainder, if any, of its conversion obligation in excess of the aggregate principal amount of Convertible Notes being converted.

The conversion rate for the Convertible Notes was initially, and remains, 17.7487 shares of our common stock per $1,000 principal amount of the 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 Convertible Notes prior to August 20, 2018. As of August 20, 2018, we may redeem for cash all or any portion of the Convertible Notes, at our option, on or after August 20, 2018 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 Convertible Notes to be redeemed, plus accrued and unpaid interest to, but excluding, the redemption date. No sinking fund is provided for the Convertible Notes, which means that we are not required to redeem or retire the Convertible Notes periodically. There have been no redemptions to date.

If we undergo a "fundamental change" (as defined in the Indenture governing the Convertible Notes Indenture), subject to certain conditions, holders of the Convertible Notes may require us to repurchase for cash all or part of their Convertible Notes

at a repurchase price equal to 100% of the principal amount of the Convertible Notes to be repurchased, plus accrued and unpaid interest to, but excluding, the fundamental change repurchase date.

The Convertible Notes Indenture contains customary events of default with respect to the Convertible Notes, including that upon certain events of default (including our failure to make any payment of principal or interest on the Convertible Notes when due and payable) occurring and continuing, the Convertible Notes Trustee by notice to us, or the holders of at least 25% in principal amount of the outstanding Convertible Notes by notice to us and the Convertible Notes Trustee, may, and the Convertible Notes Trustee at the request of such holders (subject to the provisions of the Convertible Notes Indenture) shall, declare 100% of the principal of and accrued and unpaid interest, if any, on all the 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 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.

Credit facility

On May 5, 2017, we entered into the Credit Agreement, with MidCap Financial as administrative agent and MidCap Financial and other certain institutions as lenders that provides for a senior secured term loan facility of $60.0 million, of which $40.0 million was drawn by us on May 5, 2017. Our ability to draw on the remaining $20.0 million under the senior secured term loan facility expired on December 31, 2018.

Borrowings under the Credit Agreement bear interest at a rate per annum equal to LIBOR (with a LIBOR floor rate of 1.00%) plus 6.15%. We are obligated to make interest only payments (payable monthly in arrears) through April 30, 2019. Commencing on May 1, 2019 and continuing for the remaining twenty-four months of the facility, we will be required to make monthly interest payments and monthly principal payments. The principal payments are to be made based on straight-line amortization of the principal over the twenty-four month period. The maturity date of the Credit Agreement is May 1, 2021, unless terminated earlier.

Income taxes

As part of the process of preparing our financial statements, we are required to estimate our income taxes in each of the jurisdictions in which we operate. This process involves estimating our actual current tax expense together with assessing temporary differences resulting from differing treatments of items for tax and accounting purposes. These differences result in deferred tax assets and liabilities. At December 31, 2018 and 2017, we recorded a valuation allowance against our net deferred tax assets of approximately $180.5 million and $177.6 million, respectively. The change in the valuation allowance during the years ended December 31, 2018 and 2017 was approximately $2.8 million and $5.4 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, 2018, we have approximately $296.0 million, $202.4 million, and $5.9 million of federal, state, and foreign net operating loss carryforwards, respectively. As a result of the adoption of ASU 2016-09, we no longer exclude 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, we acquired in-process research and development, or 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, 2018, research and development credit carryforwards for federal and state purposes are approximately $15.2 million and $6.6 million, respectively. In addition, the Orphan Drug Credit Carryover available as of December 31, 2018 is approximately $74.0 million. As a result of U.S. tax reform legislation, federal net operating losses, or NOLs, generated in 2018 carryforward indefinitely, however, we have federal net operating losses that pre-date U.S. tax reform legislation which begin to expire in 2021 and federal credit carryforwards that begin to expire in 2019. State net operating loss carryforwards begin to expire in 2030, and the state credit carryforwards began to expire in 2016. 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. We have undergone an ownership change and have 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 our NOL carryforwards are limited and we 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 NOLs 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. In summary, there are $296.0 million

of net operating losses available, out of which $231.5 million are limited by IRC Section 382. At December 31, 2018, there is $194.5 million available for immediate use and an additional $5.7 million will free up in 2019.

Business combinations and asset acquisitions

We evaluate 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 we have 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, we account for the transaction under the acquisition method of accounting as indicated in ASC 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, we recognize 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, we recognize and measure 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 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 obligations, other than changes due to payments, are recognized as a gain or loss on fair value remeasurement of contingent consideration in the consolidated statements of operations.

If determined to be an asset acquisition, we account for the transaction under ASC 805-50, which requires the acquiring entity in an asset acquisition to recognize assets (net assets) 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 shall be measured based on the fair value of the consideration given) or the fair value of the assets (net assets) acquired, 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.

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 acquired in business combinations are capitalized. Several methods may be used to determine the estimated fair value of the IPR&D acquired in a business combination. 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. 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. IPR&D intangible assets that are determined to have had a drop in their fair value are adjusted downward and an impairment is recognized in the statement of operations. These assets are tested at least annually or sooner when a triggering event occurs that could indicate a potential impairment.

Goodwill

Goodwill represents the amount of consideration paid in excess of the fair value of net assets acquired as a result of our business acquisitions accounted for using the acquisition method of accounting. Goodwill is not amortized and is subject to impairment testing on an annual basis or when a triggering event occurs that may indicate the carrying value of the goodwill is impaired.

Year ended December 31, 2018 compared to year ended December 31, 2017

The following table summarizes revenues and selected expense and other income data for the year ended December 31, 2018 and 2017:

(in thousands)	Year ended December 31, 2018	2017	Change 2018 vs. 2017
Net product revenue	$ 263,005	$ 174,066	$ 88,939
Collaboration and grant revenue	1,729	20,326	$ (18,597)
Cost of product sales, excluding amortization of acquired intangible asset	12,670	4,577	$ 8,093
Amortization of acquired intangible asset	22,877	15,380	$ 7,497
Research and development expense	171,984	117,456	$ 54,528
Selling, general and administrative expense	153,548	121,271	$ 32,277
Change in the fair value of deferred and contingent consideration	19,340	—	$ 19,340
Interest expense, net	(12,554)	(12,094)	$ (460)
Other income (expense), net	129	(1,279)	$ 1,408
Income tax benefit (expense)	29	(1,335)	$ 1,364

Net product revenue. Net product revenue was $263.0 million for the year ended December 31, 2018, an increase of $88.9 million, or 51%, from net product revenue of $174.1 million for the year ended December 31, 2017. The increase in net product revenue was primarily due to the increase in net product sales of $25.8 million in existing markets where Translarna is available as well as continued geographic expansion into new territories, in addition to an increase in $63.2 million in net product sales of Emflaza, which launched domestically in May 2017.

Collaboration and grant revenue. Collaboration and grant revenue was $1.7 million for the year ended December 31, 2018, a decrease of $18.6 million, or 91%, from collaboration and grant revenue of $20.3 million for the year ended December 31, 2017. The decrease in collaboration and grant revenue was primarily due to the $20.0 million milestone achieved during the fourth quarter of 2017 from Roche. In October 2017, we announced that Sunfish, a two-part clinical trial in pediatric and adult type 2 and type 3 spinal muscular atrophy initiated in the fourth quarter of 2016, had transitioned into the pivotal second part of its study which triggered the milestone payment.

Cost of product sales, excluding amortization of acquired intangible asset. Cost of product sales, excluding amortization of acquired intangible asset, was $12.7 million for the year end December 31, 2018, an increase of $8.1 million, or 177%, from $4.6 million for the year ended December 31, 2017. Cost of product sales consist primarily of royalty payments associated with Emflaza and Translarna net product sales, excluding Marathon contingent payments, and costs associated with Emflaza and Translarna product sold during the period. For Translarna sold in 2017, the majority of related manufacturing costs incurred had previously been expensed prior to January 1, 2017 as research and development expenses.

Amortization of acquired intangible asset. Amortization of acquired intangible asset was $22.9 million for the year ended December 31, 2018, an increase of $7.5 million, or 49%, from $15.4 million for the year ended December 31, 2017, which is related to the acquisition of all rights to Emflaza, acquired in May 2017 and 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.

Research and development expense. Research and development expense was $172.0 million for the year ended December 31, 2018, an increase of $54.5 million, or 46%, compared to $117.5 million for the year ended December 31, 2017. The increase reflects costs associated with advancing the gene therapy platform and increased investment in research programs as well as advancement of the clinical pipeline.

Selling, general and administrative expense. Selling, general and administrative expense was $153.5 million for the year ended December 31, 2018, an increase of $32.3 million, or 27%, from $121.3 million for the year ended December 31, 2017. The increase was primarily due to continued investment in commercial activities for Emflaza and Translarna.

Change in the fair value of deferred and contingent consideration. Change in the fair value of deferred and contingent consideration was $19.3 million for the year ended December 31, 2018. The change is related to the fair valuation of the potential future consideration to be paid to former Agilis' equity holders as a result of the Merger, 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.

Interest expense, net. Net interest expense was $12.6 million for the year ended December 31, 2018, an increase of $0.5 million, or 4% from net interest expense of $12.1 million for the year ended December 31, 2017. The increase in interest expense was primarily due to current year interest expense recorded from the Convertible Notes and the Credit Agreement partially offset by interest income from investments.

Other income (expense), net. Other income, net was $0.1 million for the year ended December 31, 2018, an increase of $1.4 million, or 110%, from other (expense), net of $1.3 million for the year ended December 31, 2017. The increase in other income (expense), net resulted primarily from exchange rate changes in the current period.

Income tax benefit (expense). Income tax benefit was $0.03 million for the year ended December 31, 2018, a change of $1.4 million, or 102%, from income tax expense of $1.3 million for the year ended December 31, 2017. We 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. We are paying minimum income taxes in the United States because of incurred losses in the various state jurisdictions. The current year foreign tax benefit is primarily driven by the Akcea upfront licensing fee.

Year ended December 31, 2017 compared to year ended December 31, 2016

The following table summarizes revenues and selected expense and other income data for the years ended December 31, 2017 and 2016:

(in thousands)	Year ended December 31, 2017	2016	Change 2017 vs. 2016
Net product revenue	$ 174,066	$ 81,447	$ 92,619
Collaboration and grant revenue	20,326	1,258	$ 19,068
Cost of product sales, excluding amortization of acquired intangible asset	4,577	—	$ 4,577
Amortization of acquired intangible asset	15,380	—	$ 15,380
Research and development expense	117,456	117,633	$ (177)
Selling, general and administrative expense	121,271	97,130	$ 24,141
Interest expense, net	(12,094)	(8,276)	$ (3,818)
Other expense, net	(1,279)	(1,207)	$ (72)
Income tax expense	(1,335)	(569)	$ (766)

Net product revenue. Net product revenue was $174.1 million for the year ended December 31, 2017, an increase of $92.6 million, or 114%, from net product revenue of $81.4 million for the year ended December 31, 2016. The increase in net product revenue was primarily due to the increase in net product sales of $63.8 million in existing markets where Translarna is available as well as continued geographic expansion into new territories, in addition to net product sales of $28.8 million from the domestic commercial launch of Emflaza in May 2017.

Collaboration and grant revenue. Collaboration and grant revenue was $20.3 million for the year ended December 31, 2017, an increase of $19.1 million, or 1,516%, from collaboration and grant revenue of $1.3 million for the year ended December 31, 2016. The increase in collaboration and grant revenue was primarily due to the $20.0 million milestone achieved during the fourth quarter of 2017 from Roche. In October 2017, we announced that Sunfish, a two-part clinical trial in pediatric and adult type 2 and type 3 spinal muscular atrophy initiated in the fourth quarter of 2016, had transitioned into the pivotal second part of its study which triggered the milestone payment.

Cost of product sales, excluding amortization of acquired intangible asset. Cost of product sales, excluding amortization of acquired intangible asset, was $4.6 million for the year end December 31, 2017. Cost of product sales consist primarily of royalty payments associated with Emflaza and Translarna net product sales and costs associated with Emflaza and Translarna product sold during the period. For Translarna sold in 2017, the majority of related manufacturing costs incurred had previously been expensed prior to January 1, 2017 as research and development expenses.

Amortization of acquired intangible asset. Amortization of acquired intangible asset was $15.4 million for the year ended December 31, 2017 related to the acquisition of all rights to Emflaza. 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.

Research and development expense. Research and development expense was $117.5 million for the year ended December 31, 2017, relatively flat compared to $117.6 million for the year ended December 31, 2016. The slight decrease resulted primarily from the completion of our Phase 3 Translarna trials at the end of 2016, partially offset by increased clinical activities and regulatory spend.

Selling, general and administrative expense. Selling, general and administrative expense was $121.3 million for the year ended December 31, 2017, an increase of $24.1 million or 25% from $97.1 million for the year ended December 31, 2016. The increase resulted primarily from higher personnel costs of $10.8 million due to additional headcount and higher professional services fees of $13.8 million due to the Emflaza product launch and continued commercial support, as well as continued growth of Translarna marketing activities.

Interest expense, net. Interest expense, net was $12.1 million for the year ended December 31, 2017, an increase of $3.8 million, or 46%, from interest expense, net of $8.3 million for the year ended December 31, 2016. The increase in interest expense was primarily due to current year interest expense recorded from the Convertible Notes and the Credit Agreement partially offset by interest income from investments.

Other expense, net. Other expense, net was $1.3 million for the year ended December 31, 2017, an increase of $0.1 million, or 6%, from other expense, net of $1.2 million for the year ended December 31, 2016. The increase in other expense, net resulted primarily from exchange rate changes in the current period.

Income tax expense. Income tax expense was $1.3 million for the year ended December 31, 2017, an increase of $0.8 million, or 135%, from income tax expense of $0.6 million for the year ended December 31, 2016. We 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. We are paying minimum income taxes in the United States because of incurred losses in the various state 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 Translarna for nmDMD and Emflaza for the treatment of DMD 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 authorization 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.

On August 23, 2018, we completed our acquisition of Agilis for total upfront consideration comprised of $49.2 million in cash and 3,500,907 shares of our common stock, which was determined by dividing $150.0 million by the volume-weighted average price per share of our common stock on the Nasdaq Global Select Market for the 10 consecutive trading-day period ending on the second trading-day immediately preceding the closing. 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. Under the Merger Agreement, we are required to pay $40.0 million of the development milestone payments no later than the second anniversary of the closing of the Merger, regardless of whether the applicable milestones have been achieved.

We have historically financed our operations primarily through the issuance and sale of our common stock in public offerings, the private placements of our preferred stock, collaborations, bank debt, convertible debt financings, the Credit Agreement 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 several years. The net losses we incur may fluctuate significantly from quarter to quarter.

In February 2014, we closed a public offering of 5,163,265 shares of common stock at a public offering price of $24.50 per share, including 673,469 shares pursuant to the exercise by the underwriters of an overallotment option. We received net proceeds from the public offering of approximately $118.4 million after deducting underwriting discounts and commissions and other offering expenses payable by us.

In October 2014, we closed a public offering of 3,450,000 shares of common stock at a public offering price of $36.25 per share, including 450,000 shares pursuant to the exercise by the underwriters of their option to purchase additional shares. We received net proceeds from the public offering of approximately $117.6 million after deducting underwriting discounts and commissions and other offering expenses payable by us.

In August 2015, we closed a private offering of $150 million in aggregate principal amount of 3.00% convertible senior notes due 2022, or the Convertible Notes, including the exercise by the initial purchasers of an option to purchase an additional $25 million in aggregate principal amount of the Convertible Notes. The Convertible Notes bear cash interest payable on February 15 and August 15 of each year, beginning on February 15, 2016. The 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.

On May 5, 2017, we entered into the Credit Agreement with MidCap Financial, which provides for a senior secured term loan facility of $60 million, of which $40 million was drawn by us on May 5, 2017. Our ability to draw on the remaining $20.0 million under the senior secured term loan facility expired on December 31, 2018. The maturity date of the Credit Agreement is May 1, 2021, unless terminated earlier. The facility is structured to require only monthly interest payments for the initial two years with principal amortization beginning in years three and four. The facility bears interest at a rate per annum equal to LIBOR (with a LIBOR floor rate of 1.00%) plus 6.15%, as well as additional upfront and administrative fees and expenses.

In April 2018, we closed an underwritten public offering of our common stock pursuant to a registration statement on Form S-3. We issued and sold an aggregate of 4,600,000 shares of common stock under the registration statement at a public offering price of $27.04 per share, including 600,000 shares issued upon exercise by the underwriters of their option to purchase additional shares. We received net proceeds of approximately $117.9 million after deducting underwriting discounts and commissions and other offering expenses payable by us.

In January 2019, we closed an underwritten public offering of our common stock pursuant to a registration statement on Form S-3. We issued and sold an aggregate of 7,563,725 shares of common stock under the registration statement 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 $224.1 million after deducting underwriting discounts and commissions and other offering expenses payable by us.

Cash flows

As of December 31, 2018, we had cash and cash equivalents and marketable securities of $227.6 million.

The following table provides information regarding our cash flows and our capital expenditures for the periods indicated.

	Years ended December 31,		
(in thousands)	**2018**	**2017**	**2016**
Cash (used in) provided by:			
Operating activities	(27,641)	(10,063)	(103,566)
Investing activities	(42,613)	13,117	104,481
Financing activities	131,571	44,218	968

Net cash used in operating activities was $27.6 million, $10.1 million, and $103.6 million for the years ended December 31, 2018, 2017 and 2016, respectively. The cash used in operating activities primarily related to supporting clinical development, including the manufacture of drug product, commercial launch activities for Emflaza and Translarna, and costs associated with the expansion of our international infrastructure for the years ended December 31, 2018, 2017, and 2016.

Net cash used in investing activities was $42.6 million for the year ended December 31, 2018. The cash used in investing activities was primarily related to the business acquisition of Agilis, purchases of fixed assets, and the acquisition of product rights related to Emflaza, partially offset by net sales and redemptions of marketable securities. Net cash provided by investing activities was $13.1 million and $104.5 million for the years ended December 31, 2017 and 2016. The cash provided by investing activities

was primarily related to net sales and redemptions of marketable securities, partially offset by the cash used in the acquisition of Emflaza for the 2017 period.

Net cash provided by financing activities in 2018 is primarily attributable to net proceeds received from our public stock offering, the exercise of options, and issuance of stock under the ESPP. Net cash provided by financing activities in 2017 was primarily attributable to borrowings under the Credit Agreement and the exercise of options and issuance of stock under the ESPP. Net cash provided by financing activities in 2016 was due to proceeds from the exercise of stock options.

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 Study 041 and Study 045 and our open label extension trials of Translarna for the treatment of nmDMD as well as our studies for nonsense mutation aniridia and nonsense mutation Dravet syndrome/CDKL5 and our FDA post-marketing requirements with respect to Emflaza in the United States and our studies for limb-girdle 2I. We also expect to incur ongoing research and development expenses for our other product candidates, including our gene therapy, splicing and oncology programs. In addition, we may incur substantial costs in connection with our efforts to advance our regulatory submissions. 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 and we may also seek marketing authorization for Translarna for other indications. In late 2019, we plan to submit a request for marketing authorization for PTC-AADC with the FDA, followed by a request for marketing authorization for PTC-AADC with the EMA and we recently submitted a request for marketing authorization for Tegsedi with ANVISA. 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 integrate Agilis's operations and employees into our business and seek to satisfy contractual and regulatory obligations we assumed in connection with the Agilis acquisition;
- seek to satisfy contractual and regulatory obligations in conjunction with the Akcea Agreement, including the potential commercialization of Tegsedi and Waylivra in the PTC Territory;
- execute our strategy for Emflaza in the United States, including commercialization and integration efforts;
- satisfy contractual and regulatory obligations that we assumed through the Emflaza acquisition;
- 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 for Translarna for the treatment of nmDMD or to obtain further marketing authorizations for Translarna for the treatment of nmDMD or other indications;
- initiate or continue the research and development of Translarna and Emflaza for additional indications and of our other product candidates;
- 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 the net proceeds from our term loan facility with MidCap Financial, our offering of the Convertible Notes, public offerings of common stock, marketable securities and research funding that we expect to receive under our collaborations, 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 Emflaza for the treatment of DMD in the United States;

- our ability to negotiate, secure and maintain adequate pricing, coverage and reimbursement terms, on a timely basis, with third-party payors for Emflaza for the treatment of DMD in the United States and for Translarna for the treatment of nmDMD in the EEA and other territories outside of the United States;
- our ability to maintain orphan exclusivity for, and successfully complete all FDA post-marketing requirements with respect to, Emflaza;
- 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 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 submission by us and, ultimately, may support approval of Translarna for nmDMD in the United States;
- our ability to commercialize and market Tegsedi and Waylivra in the PTC Territory;
- the progress and results of our open label extension clinical trials of Translarna for the treatment of nmDMD as well as our studies for nonsense mutation aniridia and nonsense mutation Dravet syndrome/CDKL5 and activities under our gene therapy and oncology programs;
- the scope, costs and timing of our commercialization activities, including product sales, marketing, legal, regulatory, distribution and manufacturing, for both Emflaza for the treatment of DMD and Translarna for the treatment of nmDMD, for Tegsedi, for Waylivra 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 Translarna;
- the costs, timing and outcome of regulatory review of our other product candidates, including those in our gene therapy and oncology programs, and Translarna in other territories or for indications other than nmDMD;
- our ability to satisfy our obligations under the terms of the Credit Agreement with MidCap Financial;
- 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 Translarna and Emflaza for additional indications and for our other product candidates, including those in our gene therapy and oncology programs;
- revenue received from commercial sales of Translarna, Emflaza, Tegsedi, Waylivra, or any of our other 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 acquisition of Emflaza, our acquisition of Agilis, 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 Convertible Notes, cash interest payments are payable on a semi-annual basis in arrears, which will require total funding of $4.5 million annually. Furthermore, as a result of our initial public offering in June 2013, we have incurred and expect to continue to incur additional costs associated with operating as a public company. These costs include significant legal, accounting, investor relations and other expenses that we did not incur as a private company.

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 or debt 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.

Contractual obligations

The following table summarizes our significant contractual obligations and commercial commitments as of December 31, 2018.

(in thousands)	Total	Less than 1 year	1 - 3 years	3 - 5 years	More than 5 years
Operating lease obligations (1)	$ 13,928	3,216	5,309	3,965	1,438
Long-term debt obligations, including interest (2)	$ 168,000	4,500	9,000	154,500	—
Minimum royalty (3)	$ 8,588	1,718	3,435	3,435	—
Credit agreement, including interest (4)	$ 43,986	14,283	29,703	—	—
Deferred Consideration payable (5)	$ 40,000	20,000	20,000	—	—
Total contractual obligations	$ 274,502	$ 43,717	$ 67,447	$ 161,900	$ 1,438

(1) We lease office space for our principal office in South Plainfield, New Jersey under three non-cancelable operating leases with terms that extend through May 2022, August 2024 and October 2024. In addition, we lease office space in various countries for our international employees and operations.

(2) Our long-term debt obligations reflect our obligations under the Convertible Notes to pay interest on the $150.0 million aggregate principal amount of the Convertible Notes and to make principal payments on the Convertible Notes at maturity or upon conversion.

(3) Under an Exclusive License and Supply Agreement ("the Faes Agreement") with Faes Farma, S.A. ("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 amounts above reflect the minimum required payment based on the euro to U.S. dollar exchange rate as of December 31, 2018.

(4) Under the terms of the Credit Agreement, we are required to make interest only payments through April 30, 2019. Commencing on May 1, 2019 and continuing for the remaining twenty-four months of the facility, we will be required to make monthly interest payments and monthly principal payments. The principal payments are to be made based on straight-line amortization of the principal over the twenty-four month period.

(5) Pursuant to the Merger Agreement with Agilis, we are required to pay $40.0 million of development milestone payments, or deferred consideration payments, no later than the second anniversary of the closing of the Merger, regardless of whether the applicable milestones have been achieved. The payment schedule above reflects our expected timing of when the payments will be made as of December 31, 2018. The fair value of the deferred consideration payments at the December 31, 2018 was estimated to be $37.7 million.

The preceding table excludes contingent contractual payments that we may become obligated to make. 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 and antibacterial programs. As we have discontinued development under our antibacterial program, we no longer expect that milestone and royalty payments from us to Wellcome Trust will apply under that agreement, resulting in a change to the total amount of development and regulatory milestone payments we may become obligated to pay for this program. Under our oncology program funding agreement, 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. 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 program 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.

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, 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 a specified amount.

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.

Off-Balance Sheet Arrangements

We did not have during the periods presented, and we do not currently have, any off-balance sheet arrangements, as defined under Securities and Exchange Commission rules.

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, 2018. At December 31, 2018, we held $227.6 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 foreign operations, we face exposure to movements in foreign currency exchange rates, including the British Pound, Euro and Swiss Franc against the U.S. dollar. The current exposures arise primarily from cash, accounts receivable, intercompany receivables and payables, 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, 2018, we recognized foreign currency transaction losses, net of $1.0 million. 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, 2018 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 million of 3.00% convertible senior notes due August 15, 2022, or the Convertible Notes. We do not have economic interest rate exposure on the Convertible Notes as they have a fixed annual interest rate of 3.00%. However, the fair value of the Convertible Notes is exposed to interest rate risk. We do not carry the 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 Convertible Notes will increase as interest rates fall and decrease as interest rates rise. The 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 $146.6 million as of December 31, 2018.

In May 2017, we entered into the Credit Agreement with MidCap Financial, which provides for a senior secured term loan facility of $60.0 million, of which $40.0 million was drawn by us for the year ended December 31, 2018. The maturity date of the Credit Agreement is May 1, 2021, unless terminated earlier. The facility bears interest at a rate per annum equal to LIBOR (with a LIBOR floor rate of 1.00%) plus 6.15%. Borrowings under the term loan facility are at variable rates of interest and expose us to interest rate risk. As such, our net income is sensitive to movements in interest rates. If interest rates increase, our debt obligations on the variable rate indebtedness would increase even though the amount borrowed remained the same, and our net income would decrease. Such increases in interest rates could have a material adverse effect on our cash flow and financial condition. We do not hold any derivative instruments and do not engage in any hedging activities to mitigate interest rate risk. Based on our outstanding borrowings under the Credit Agreement at December 31, 2018, a one-percentage change in interest rates would have affected interest expense on the debt by an immaterial amount on an annualized basis.

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, 2018 and 2017, 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, 2018, 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, 2018 and 2017, and the consolidated results of its operations and its cash flows for each of the three years in the period ended December 31, 2018, 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, 2018, 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 March 1, 2019 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.

/s/ Ernst & Young LLP

We have served as the Company's auditor since 2010.

Iselin, New Jersey

March 1, 2019

PTC Therapeutics, Inc.

Consolidated Balance Sheets

In thousands, except shares

	December 31,	
	2018	2017
Assets		
Current assets:		
Cash and cash equivalents	$ 169,498	$ 111,792
Marketable securities	58,088	79,454
Trade receivables, net	67,907	40,394
Inventory	16,117	10,754
Prepaid expenses and other current assets	9,247	6,669
Total current assets	320,857	249,063
Fixed assets, net	12,694	8,376
Intangible assets, net	701,031	132,993
Goodwill	82,341	—
Deposits and other assets	2,299	1,221
Total assets	$ 1,119,222	$ 391,653
Liabilities and stockholders' equity		
Current liabilities:		
Accounts payable and accrued expenses	128,199	76,446
Current portion of long-term debt	11,667	—
Deferred revenue	3,716	3,937
Other current liabilities	3,814	1,665
Deferred consideration payable- current	19,400	—
Total current liabilities	166,796	82,048
Deferred revenue - long-term	9,722	7,954
Long-term debt	141,347	144,971
Contingent consideration payable	310,240	—
Deferred consideration payable- long-term	18,300	—
Deferred tax liability	122,032	—
Other long-term liabilities	58	243
Total liabilities	768,495	235,216
Stockholders' equity:		
Common stock, $0.001 par value. Authorized 125,000,000 shares; issued and outstanding 50,606,147 shares at December 31, 2018. Authorized 125,000,000 shares; issued and outstanding 41,612,395 shares at December 31, 2017.	51	42
Additional paid-in capital	1,288,137	966,534
Accumulated other comprehensive income	1,462	3,969
Accumulated deficit	(938,923)	(814,108)
Total stockholders' equity	350,727	156,437
Total liabilities and stockholders' equity	$ 1,119,222	$ 391,653

See accompanying consolidated notes.

PTC Therapeutics, Inc.

Consolidated Statements of Operations

In thousands

	Year ended December 31,		
	2018	**2017**	**2016**
Revenues:			
Net product revenue	$ 263,005	$ 174,066	$ 81,447
Collaboration and grant revenue	1,729	20,326	1,258
Total revenues	264,734	194,392	82,705
Operating expenses:			
Cost of product sales, excluding amortization of acquired intangible asset	12,670	4,577	—
Amortization of acquired intangible asset	22,877	15,380	—
Research and development	171,984	117,456	117,633
Selling, general and administrative	153,548	121,271	97,130
Change in the fair value of deferred and contingent consideration	19,340	—	—
Total operating expenses	380,419	258,684	214,763
Loss from operations	(115,685)	(64,292)	(132,058)
Interest expense, net	(12,554)	(12,094)	(8,276)
Other income (expense), net	129	(1,279)	(1,207)
Loss before income tax expense	(128,110)	(77,665)	(141,541)
Income tax benefit (expense)	29	(1,335)	(569)
Net loss attributable to common stockholders	$ (128,081)	$ (79,000)	$ (142,110)
Weighted-average shares outstanding:			
Basic and diluted (in shares)	46,576,313	39,183,073	34,044,584
Net loss per share—basic and diluted (in dollars per share)	$ (2.75)	$ (2.02)	$ (4.17)

See accompanying consolidated notes.

PTC Therapeutics, Inc.

Consolidated Statements of Comprehensive Loss

In thousands

	Year ended December 31,		
	2018	2017	2016
Net loss	$ (128,081)	$ (79,000)	$ (142,110)
Other comprehensive loss:			
Unrealized gain on marketable securities, net of tax	9	225	386
Foreign currency translation (loss) gain	(2,516)	5,229	(671)
Comprehensive loss	$ (130,588)	$ (73,546)	$ (142,395)

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 (loss) income	Accumulated deficit	Total stockholders' equity
	Shares	Amount				
Balance, December 31, 2015	33,916,559	$ 34	$ 820,165	$ (1,200)	$ (592,998)	$ 226,001
Exercise of options	89,216	—	968	—	—	968
Restricted stock vesting and issuance	163,635	—	—	—	—	—
Share-based compensation expense	—	—	35,009	—	—	35,009
Net loss	—	—	—	—	(142,110)	(142,110)
Comprehensive loss	—	—	—	(285)	—	(285)
Balance, December 31, 2016	34,169,410	$ 34	$ 856,142	$ (1,485)	$ (735,108)	$ 119,583
Issuance of common stock related to acquisition	6,683,598	7	75,184	—	—	75,191
Exercise of options	202,085	—	2,182	—	—	2,182
Restricted stock vesting and issuance	287,531	1	—	—	—	1
Issuance of common stock in connection with an employee stock purchase plan	269,771	—	2,467	—	—	2,467
Share-based compensation expense	—	—	30,559	—	—	30,559
Net loss	—	—	—	—	(79,000)	(79,000)
Comprehensive loss	—	—	—	5,454	—	5,454
Balance, December 31, 2017	41,612,395	$ 42	$ 966,534	$ 3,969	$ (814,108)	$ 156,437
Adjustment to accumulated deficit	—	—	—	—	3,266	3,266
Issuance of common stock related to equity offering	4,600,000	5	117,911	—	—	117,916
Issuance of common stock related to acquisition	3,500,907	3	155,857	—	—	155,860
Exercise of options	633,973	1	10,867	—	—	10,868
Restricted stock vesting and issuance	119,691	—	—	—	—	—
Issuance of common stock in connection with an employee stock purchase plan	139,181	—	2,787	—	—	2,787
Share-based compensation expense	—	—	33,252	—	—	33,252
Receivable from investor	—	—	929	—	—	929
Net loss	—	—	—	—	(128,081)	(128,081)
Comprehensive loss	—	—	—	(2,507)	—	(2,507)
Balance, December 31, 2018	50,606,147	$ 51	$ 1,288,137	$ 1,462	$ (938,923)	$ 350,727

See accompanying consolidated notes.

PTC Therapeutics, Inc.
Consolidated Statements of Cash Flows
In thousands

	Year ended December 31,		
	2018	**2017**	**2016**
Cash flows from operating activities			
Net loss	$ (128,081)	$ (79,000)	$ (142,110)
Adjustments to reconcile net loss to net cash used in operating activities:			
Depreciation and amortization	26,087	17,682	3,290
Change in valuation of warrant liability	—	—	(47)
Change in valuation of deferred and contingent consideration	19,340	—	—
Amortization of (discounts) premiums on investments, net	(433)	535	1,885
Amortization of debt issuance costs	524	433	302
Share-based compensation expense	33,252	30,559	35,009
Non-cash interest expense	7,518	6,755	6,065
Disposal of asset	2	5	—
Benefit for deferred income taxes	—	199	(199)
Unrealized foreign currency transaction (gains) losses, net	(59)	(459)	1,202
Changes in operating assets and liabilities:			
Inventory, net	(5,823)	(6,454)	—
Prepaid expenses and other current assets	(1,609)	(1,784)	1,171
Trade receivables, net	(29,589)	(12,203)	(14,842)
Deposits and other assets	(1,093)	(544)	(278)
Accounts payable and accrued expenses	43,877	24,011	4,259
Other liabilities	1,932	733	(799)
Deferred revenue	6,514	9,469	1,526
Net cash used in operating activities	(27,641)	(10,063)	(103,566)
Cash flows from investing activities			
Purchases of fixed assets	(7,097)	(3,101)	(1,776)
Purchases of marketable securities	(68,614)	(81,368)	(85,377)
Sale & redemption of marketable securities	90,423	174,749	191,634
Acquisition of product rights	(8,433)	(77,163)	—
Business acquisition, net of cash acquired	(48,892)	—	—
Net cash (used in) provided by investing activities	(42,613)	13,117	104,481
Cash flows from financing activities			
Proceeds from exercise of options	10,868	2,182	968
Proceeds from shares issued under employee stock purchase plan	2,787	2,468	—
Debt issuance costs related to secured term loan	—	(432)	—
Net proceeds from public offering	117,916	—	—
Proceeds from issuance of secured term loan	—	40,000	—
Net cash provided by financing activities	131,571	44,218	968
Effect of exchange rate changes on cash	(3,611)	6,199	(1,584)
Net increase in cash and cash equivalents	57,706	53,471	299
Cash and cash equivalents, beginning of period	111,792	58,321	58,022
Cash and cash equivalents, end of period	$ 169,498	$ 111,792	$ 58,321
Supplemental disclosure of cash information			
Cash paid for interest	$ 7,773	$ 6,271	$ 4,513
Cash paid for income taxes	$ 1,583	$ 1,101	$ 943
Supplemental disclosures of non-cash information related to investing and financing activities			
Change in unrealized gain on marketable securities, net of tax	$ 9	$ 225	$ 386
Acquisition of product rights and licenses	$ (5,981)	$ —	$ —

See accompanying consolidated notes.

PTC Therapeutics, Inc.

Notes to consolidated financial statements

December 31, 2018

(In thousands except share and per share amount)

1. The Company

PTC Therapeutics, Inc. (the "Company" or "PTC") is a science-led global biopharmaceutical company focused on the discovery, development and commercialization of clinically-differentiated medicines that provide benefits to patients with rare disorders. The Company's ability to globally commercialize products is the foundation that drives its continued investment in a robust pipeline of transformative medicines and its mission to provide access to best-in-class treatments for patients who have an unmet medical need. The Company's strategy is to bring best-in-class therapies with differentiated clinical benefit to patients affected by rare disorders and to leverage its global commercial infrastructure to maximize value for its patients and other stakeholders.

The Company has two products, Translarna™ (ataluren) and Emflaza™ (deflazacort), for the treatment of Duchenne muscular dystrophy, or DMD, a rare, life threatening disorder. Translarna received marketing authorization from the European Commission in August 2014 for the treatment of nonsense mutation Duchenne muscular dystrophy, or nmDMD, in ambulatory patients aged 5 years and over in the 31 member states of the European Economic Area, or EEA, subject to annual renewal and other conditions. In July 2018, the European Commission approved a label-extension request to the marketing authorization for Translarna in the EEA to include patients from two to up to five years of age. Emflaza is approved in the United States for the treatment of DMD in patients five years and older.

The Company has a pipeline of gene therapy product candidates, including PTC-AADC for the treatment of Aromatic L-Amino Acid Decarboxylase, or AADC, deficiency, or AADC deficiency. The Company is preparing a biologics license application, or BLA, for PTC-AADC for the treatment of AADC deficiency in the United States, which it anticipates submitting to the U.S. Food and Drug Administration, or FDA, in late 2019, with an anticipated commercial launch in the United States in 2020. The Company is also preparing a marketing authorization application, or MAA, for PTC-AADC for the treatment of AADC deficiency in the European Union, or EU, for submission to the European Medicines Agency, or EMA, which will follow its BLA submission to the FDA.

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. Tegsedi has received marketing authorization in the U.S., EU and Canada for the treatment of stage 1 or stage 2 polyneuropathy in adult patients with hATTR amyloidosis. The Company filed for marketing authorization with ANVISA, the Brazilian regulatory authority, which granted priority review. It expects approval in Brazil by the end of 2019. Waylivra is currently under regulatory review in EU for the treatment of familial chylomicronemia syndrome, or FCS.

The Company also has a spinal muscular atrophy ("SMA") collaboration with F. Hoffman-La Roche Ltd and Hoffman-La Roche Inc., which it refers to collectively as Roche, and the Spinal Muscular Atrophy Foundation, or SMA Foundation. Currently, its collaboration has two pivotal clinical trials ongoing to evaluate the safety and effectiveness of risdiplam (RG7916, RO7034067), the lead compound in the SMA program. Roche is preparing an NDA and a MAA for risdiplam for the treatment of SMA in the United States and the EU, respectively, which Roche anticipates submitting to the FDA and the EMA in the second half of 2019. 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, including rare diseases and oncology.

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. 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 final report on the trial and open-label extension is to be submitted by the Company to the EMA by the end of the third quarter of 2021. Due to enrollment at a slower pace in certain countries than initially expected, in its February 2019 marketing authorization renewal request, the Company asked the EMA to extend the timeframe for submission of the results of Study 041 to the EMA to the end of the third quarter of 2022. The Company refers to the trial and open-label extension together as Study 041.

The marketing authorization in the EEA was last renewed in July 2018 and is effective, unless extended, through August 5, 2019. The renewal was based on the Company's commitment to conduct Study 041 and the totality of the clinical data available

1. The Company (Continued)

from its trials and studies of Translarna for the treatment of nmDMD, including the safety and efficacy results of the Phase 2b and Phase 3 clinical trials. The primary efficacy endpoint was not achieved in either trial within the pre-specified level of statistical significance.

In June 2014, the Company initiated reimbursed early access programs, or EAP programs, for Translarna for nmDMD patients in selected territories in the EEA and recorded its first sales of Translarna in the third quarter of 2014 pursuant to an EAP program. In December 2014, the Company recorded its first commercial sales in Germany. As of December 31, 2018, Translarna was available in over 40 countries on a commercial basis or pursuant to the EAP program. The Company expects to expand its commercial activities across the EEA pursuant to the marketing authorization granted by the EMA throughout 2019 and future years, subject to continued renewal of its marketing authorization following annual EMA reassessments and successful completion of pricing and reimbursement negotiations. Concurrently, the Company plans to continue to pursue EAP programs in select countries where those mechanisms exist, both within the EEA and in other countries that will reference the marketing authorization in the EEA.

Translarna is an investigational new drug in the United States. During the first quarter of 2017, the Company filed a New Drug Application, or NDA, over protest with the United States Food and Drug Administration, (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 intends to follow the FDA's recommendation and will collect, using newer technologies via procedures and methods that the Company designed, such dystrophin data in a new study, Study 045, which the Company initiated in the fourth quarter of 2018. The Company expects that a potential re-submission of an NDA could occur in 2020. Additionally, should a re-submission of an NDA receive accelerated approval, the Office of New Drugs stated that Study 041, which is currently enrolling, could serve as the confirmatory post-approval trial required in connection with the accelerated approval framework.

On April 20, 2017, the Company completed its acquisition of all rights to Emflaza, or the Transaction. Emflaza is approved in the United States for the treatment of DMD in patients five years and older. The Transaction was completed pursuant to an asset purchase agreement, dated March 15, 2017, as amended on April 20, 2017, (the "Asset Purchase Agreement"), by and between the Company and Marathon Pharmaceuticals, LLC (now known as Complete Pharma Holdings, LLC), or Marathon. The Transaction was accounted for as an asset acquisition. 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. The Company assumed certain liabilities and obligations in the Transaction arising out of, or relating to, the assets acquired in the Transaction.

Upon the closing of the Transaction, the Company paid to Marathon total upfront consideration comprised of $75.0 million in cash, funded through cash on hand, and 6,683,598 shares of the Company's 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 Stock Market for the 15 trading-day period ending on the third trading day immediately preceding the closing. Marathon will be 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, and a single $50.0 million sales-based milestone, in each case subject to the terms and conditions of the Asset Purchase Agreement.

On August 23, 2018, the Company completed its acquisition of Agilis Biotherapeutics, Inc., or Agilis, pursuant to an Agreement and Plan of Merger, dated as of July 19, 2018 (the "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 "Merger").

Upon the closing of the Merger, the Company paid to Agilis equityholders total upfront consideration comprised of $49.2 million in cash and 3,500,907 shares of the Company's common stock (the "Closing Stock Consideration"). The Closing Stock Consideration was determined by dividing $150.0 million by the volume-weighted average price per share of the Company's common stock on the Nasdaq Global Select Market 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

1. The Company (Continued)

the Company 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. Under the Merger Agreement, the Company is required to pay $40.0 million of the development milestone payments no later than the second anniversary of the closing of the Merger, regardless of whether the applicable milestones have been achieved.

As of December 31, 2018, the Company had an accumulated deficit of approximately $938.9 million. The Company has financed its operations to date primarily through the private offering in August 2015 of 3.00% convertible senior notes due 2022 (see Note 7), public offerings of common stock in February 2014, October 2014, and April 2018, its initial public offering of common stock in June 2013, private placements of its convertible preferred stock, collaborations, bank debt, convertible debt financings, 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 generated revenue from net sales of Emflaza for the treatment of DMD in the United States. 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.

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.

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, certain accruals related to the Company's research and development expenses, stock-based compensation, valuation procedures for the convertible notes, allowance for doubtful accounts, inventory, acquired intangible assets, 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.

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 considers 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

2. Summary of significant accounting policies (Continued)

to maturity. The Company evaluates securities with unrealized losses to determine whether such losses, if any, are other than temporary.

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
Furniture, fixtures, and lab equipment	7 years

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.

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 credit losses.

Inventories and cost of product sales

In January 2017, the European Commission granted a one-year renewal of the Company's marketing authorization for Translarna for the treatment of nmDMD. Until this renewal, the Company had considered the authorization to be subject to risk and did not capitalize productions costs in inventory as it was not probable that such costs would be recovered. With the renewal, the Company considered recovery of the costs to be probable and began capitalizing production costs in inventory, effective January 1, 2017. Since January 1, 2017, production costs are expensed as cost of product sales when the related products are sold. The costs for a portion of the inventory available for sale were expensed as research and development costs prior to the January 2017 annual renewal of the Translarna marketing authorization and as such the cost of products sold and related gross margins prior to January 1, 2017 are not directly comparable to future cost of products sold and gross margin after January 1, 2017.

In April 2017, the Company completed the Transaction (see Note 3). 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. The Company began the commercialization of Emflaza in the United States shortly after the Transaction was completed. The Company utilizes third parties for the commercial distribution of Emflaza, including a third-party logistics company to warehouse Emflaza as well as a specialty pharmacy to sell and distribute Emflaza to patients. All of the Company's supply and manufacturing needs for Emflaza are fulfilled pursuant to exclusive supply agreements assumed by the Company upon close of the Transaction. Production costs are expensed as cost of product sales when the related products are sold.

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. Translarna and Emflaza product 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.

(In thousands except share and per share amount)

2. Summary of significant accounting policies (Continued)

The following table summarizes the components of the Company's inventory for the periods indicated:

	December 31, 2018	December 31, 2017
Raw materials	$ 1,431	$ 452
Work in progress	9,324	3,912
Finished goods	5,362	6,390
Total inventory	$ 16,117	$ 10,754

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 a $1.8 million inventory write down for the twelve month period ended December 31, 2018 primarily related to inventory labeling changes. No write down was recorded for the twelve month period ended December 31, 2017. 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 twelve month periods ended December 31, 2018 and December 31, 2017, 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 and royalty payments associated with net product sales.

Deferred rent

The Company has an operating lease for office space. Rent expense is recorded on a straight-line basis over the initial lease term. The difference between the actual cash paid and the straight-line rent expense is recorded as deferred rent. Leasehold improvements made related to this lease, subsequent to its inception, are amortized over the remaining lease term.

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

In May 2014, the Financial Accounting Standards Board ("FASB") issued Accounting Standards Update ("ASU") No. 2014-9, "Revenue from Contracts with Customers (Topic 606)". ASU No. 2014-9 eliminated transaction- and industry-specific revenue recognition guidance under FASB Accounting Standards Codification ("ASC") Subtopic 605-15, Revenue Recognition-Products (Topic 605) and replaced it with a principle-based approach for determining revenue recognition. ASC Topic 606 requires entities to recognize revenue to depict the transfer of promised goods or services to customers in an amount that reflects the consideration to which the entity expects to be entitled in exchange for those goods or services. On January 1, 2018, the Company adopted ASC Topic 606 using the modified retrospective approach, a practical expedient permitted under Topic 606, and applied this approach only to contracts that were not completed as of January 1, 2018. The Company calculated a one-time transition adjustment of $3.3 million, which was recorded on January 1, 2018 to the opening balance of accumulated deficit, related to the product sales of Emflaza. The ASC 606 transition adjustment recorded for Emflaza resulted in sales being recognized earlier than under Topic 605, as the deferred revenue recognition model (sell-through) is not allowed under Topic 606. The one-time adjustment consisted of $3.9 million in deferred revenue offset by $0.6 million of variable consideration. The information presented for the periods prior to January 1, 2018 has not been adjusted and is reported under Topic 605.

Periods prior to January 1, 2018

The Company recognizes revenue when amounts are realized or realizable and earned. Revenue is considered realizable and earned when the following criteria are met: (1) persuasive evidence of an arrangement exists; (2) delivery has occurred or services have been rendered; (3) the price is fixed or determinable; and (4) collection of the amounts due are reasonably assured.

2. Summary of significant accounting policies (Continued)

Net product sales

Prior to the second quarter of 2017, the Company's net product sales consisted of sales of Translarna for the treatment of nmDMD in territories outside of the U.S. The Company recognizes revenue from product sales when there is persuasive evidence that an arrangement exists, title to product and associated risk of loss has passed to the customer, the price is fixed or determinable, collectability is reasonably assured and the Company has no further performance obligations in accordance with FASB ASC Subtopic 605-15, Revenue Recognition—Products.

The Company has recorded revenue on sales where Translarna is available either on a commercial basis or through a reimbursed EAP program. Orders for Translarna are generally received from hospital and retail pharmacies and the Company's third-party partner distributors. Revenue is recognized when risk of ownership has transferred. The Company's third-party partner distributors act as intermediaries between the Company 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.

In May 2017, the Company began the commercialization of Emflaza in the U.S. The Company recorded product revenue related to the sales of Emflaza in the U.S. in accordance with ASC 605-15, when persuasive evidence of an arrangement exists, delivery has occurred and title of the product and associated risk of loss has passed to the customer, the price is fixed or determinable and collection from the customer has been reasonably assured. Due to the early stage of the product launch, the Company determined that it was not able to reliably make certain estimates, including returns, necessary to recognize product revenue upon shipment to distributors. As a result, the Company recorded net product revenue for Emflaza using a deferred revenue recognition model (sell-through). Under the deferred revenue model, the Company does not recognize revenue until Emflaza is shipped to the specialty pharmacy.

The Company records 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 the years ended December 31, 2017 and 2016 the Company recognized Translarna sales of $145.2 million and $81.4 million, respectively. For the year ended December 31, 2017, the Company recognized Emflaza sales of $28.8 million.

Collaboration and grant 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.

The Company evaluates all contingent consideration earned, such as a milestone payment, using the criteria as provided by ASC 605-28, Revenue Recognition—Milestone Method. At the inception of a collaboration arrangement, the Company evaluates if a milestone payment is substantive. The criteria requires that (1) the Company determines if the milestone is commensurate with either its performance to achieve the milestone or the enhancement of value resulting from its activities to achieve the milestone; (2) the milestone be related to past performance; and (3) the milestone be reasonable relative to all deliverable and payment terms of the collaboration arrangement. If these criteria are met then the contingent milestones can be considered a substantive milestone and will be recognized as revenue in the period that the milestone is achieved. The Company recognizes royalties as earned in accordance with the terms of various research and collaboration agreements. If not substantive, the contingent consideration is allocated to the existing units of accounting based on relative selling price and recognized following the same basis previously established for the associated unit of accounting.

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.

Periods commencing January 1, 2018

The Company's net product revenue 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.

2. Summary of significant accounting policies (Continued)

Net product revenue

The Company recognizes revenue when its performance obligations with its customers have been satisfied. The Company's performance obligations are to provide Translarna or Emflaza 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 either Translarna or Emflaza, 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 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 either product sales of Translarna or Emflaza. 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 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. Historically, returns of Translarna and Emflaza are immaterial to the financial statements. 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. For the year ended December 31, 2018, the Company recognized Translarna net sales of $171.0 million and Emflaza net sales of $92.0 million.

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.

Upon adoption of ASC Topic 606 on January 1, 2018, the Company elected the following practical expedients:

- Portfolio Approach - the Company applied the Portfolio Approach to contract reviews within its identified revenue streams that have similar characteristics and the Company believes this approach would not differ materially than if applying ASC Topic 606 to each individual contract.
- Significant Financing Component - the Company expects the period between when it transfers a promised good to a customer and when the customer pays for the good or service to be one year or less.
- Immaterial Performance Obligations - the Company disregards promises deemed to be immaterial in the context of the contract.
- Shipping and Handling Activities - 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 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 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.

2. Summary of significant accounting policies (Continued)

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 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.

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 allowance for doubtful accounts was $0.7 million as of December 31, 2018 and $0.8 million as of December 31, 2017. Bad debt expense was immaterial for the years ended December 31, 2018, 2017, and 2016.

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.

Nonrefundable 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 deferred research and development advance payments were $2.4 million and $0.5 million as of December 31, 2018 and 2017, 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

2. Summary of significant accounting policies (Continued)

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.

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.

Warrant liability

Warrants to purchase the Company's common stock with nonstandard antidilution provisions, regardless of the probability or likelihood that may conditionally obligate the issuer to ultimately transfer assets, are classified as liabilities and are recorded at their estimated fair value at each reporting period. Any change in fair value of these warrants is recorded as gain/(loss) on warrant valuation each reporting period in Other expense, net on the Company's statement of operations.

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 calculates expected volatility based on a historical volatility analysis of peers that were similar with respect to industry, stage of life cycle, size, and financial leverage and will continue to do so until the historical volatility of its common stock is sufficient to measure expected volatility for future option grants. The Company uses 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. 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 ASU 2016-9, the Company made a policy election to continue its methodology for estimating its forfeiture rate.

Income taxes

On December 22, 2017, the U.S. government enacted the 2017 Tax Cuts and Jobs Act (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, 2018.

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

2. Summary of significant accounting policies (Continued)

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.

The Company recorded a deferred tax liability in conjunction with the Merger, further discussed in Note 3, of $122.0 million 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’s asset and liability accounts 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.

Net (loss) income per share

Basic net (loss) income per share is calculated by dividing the net 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 ASC 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 obligations, other than changes due to payments, are recognized as a (gain) loss on fair value remeasurement of contingent consideration in the consolidated statements of operations.

2. Summary of significant accounting policies (Continued)

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 (net assets) 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 shall be measured based on the fair value of the consideration given) or the fair value of the assets (net assets) acquired, 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, 2018.

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 acquired in business combinations are capitalized. Several methods may be used to determine the estimated fair value of the IPR&D 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. IPR&D intangible assets that are determined to have had a drop in their fair value are adjusted downward and an impairment is recognized in the statement of operations. These assets are tested at least annually or sooner when a triggering event occurs that could indicate a potential impairment. The Company performed its annual test for its IPR&D assets and concluded that no impairment exists as of December 31, 2018.

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 on an annual basis or when a triggering event occurs that may indicate the carrying value of the goodwill is impaired. The Company performed its annual test for goodwill as of October 1, 2018 and concluded that no impairment exists as of December 31, 2018.

Recent accounting pronouncements

2. Summary of significant accounting policies (Continued)

In February 2016, the FASB issued No. 2016-2, “Leases (Topic 842)”. This standard will require organizations that lease assets with lease terms of more than 12 months to recognize assets and liabilities for the rights and obligations created by those leases on their balance sheets. The ASU will also require new qualitative and quantitative disclosures to help investors and other financial statement users better understand the amount, timing, and uncertainty of cash flows arising from leases. The standard is effective for public companies for fiscal years, and interim periods within those fiscal years, beginning after December 15, 2018, with early adoption permitted. The Company will adopt this guidance on January 1, 2019, as well as the package of practical expedients permitted under the transition guidance within the new standard. The Company believes that the adoption of ASU No. 2016-2 will not have a material impact on its consolidated results of operations, and expects to record approximately $10 - $15 million of lease assets and lease liabilities to the balance sheet.

In June 2016, the FASB issued ASU No. 2016-13, “Financial Instruments — Credit Losses (Topic 326): Measurement of Credit Losses on Financial Instruments”. This standard requires financial assets measured at amortized cost basis to be presented at the net amount expected to be collected. This standard is effective for public companies who are SEC filers for fiscal years beginning after December 15, 2019, including interim periods within those years. The Company expects to adopt this guidance when effective and is assessing what effect the adoption of ASU 2016-13 will have on its consolidated financial statements and accompanying notes.

In February 2018, the FASB issued ASU 2018-02, "Income Statement — Reporting Comprehensive Income (Topic 220): Reclassification of Certain Tax Effects from Accumulated Other Comprehensive Income". This standard permits the reclassification of tax effects stranded in other comprehensive income as a result of tax reform to retained earnings related to the change in federal tax rate in addition to other stranded effects that relate to the Tax Cuts and Job Act ("the Act") but do not directly relate to the change in the federal rate. ASU 2018-02 is effective for fiscal years beginning after December 15, 2018, including interim periods within those fiscal years with early adoption permitted for periods for which financial statements have not yet been issued or made available for issuance. The Company will adopt this guidance on January 1, 2019. The Company believes that the adoption of ASU No. 2018-02 will not have a material impact on its consolidated financial statements and accompanying notes.

In June 2018, the FASB issued ASU 2018-07, "Compensation — Stock Compensation (Topic 718), Improvements to Nonemployee Share-Based Payment Accounting". This standard expands the scope of ASC 718 to include share-based payments granted to nonemployees in exchange for goods or services used or consumed in the entity’s own operations and supersedes the guidance in ASC 505-50. The ASU retains the existing cost attribution guidance, which requires entities to recognize compensation cost for nonemployee awards in the same period and in the same manner they would if they paid cash for the goods or services, but it moves the guidance to ASC 718. ASU 2018-07 is effective for fiscal years beginning after December 15, 2018, including interim periods within those fiscal years with early adoption permitted for periods for which financial statements have not yet been issued or made available for issuance. The Company will adopt this guidance on January 1, 2019. The Company is currently assessing what effect the adoption of ASU No. 2018-07 will have on its consolidated financial statements and accompanying notes.

In August 2018, the FASB issued ASU 2018-13, "Fair Value Measurement (Topic 820), Disclosure Framework—Changes to the Disclosure Requirements for Fair Value Measurement". This standard eliminates certain disclosure requirements for fair value measurements for all entities, requires public entities to disclose certain new information and modifies some disclosure requirements. The new guidance is effective for all entities for fiscal years beginning after December 15, 2019 and for interim periods within those fiscal years. An entity is permitted to early adopt either the entire standard or only the provisions that eliminate or modify requirements. Entities can elect to early adopt in interim periods, including periods for which they have not yet issued financial statements or made their financial statements available for issuance. The Company expects to adopt this guidance when effective and is currently assessing what effect the adoption of ASU No. 2018-13 will have on its consolidated financial statements and accompanying notes.

In August 2018, the FASB issued ASU 2018-15,"Intangibles - Goodwill and Other - Internal-Use Software (Subtopic 350-40): Customer’s Accounting for Implementation Costs Incurred in a Cloud Computing Arrangement That Is a Service Contract". ASU 2018-15 requires a customer in a cloud computing arrangement that is a service contract to follow the internal-use software guidance in Accounting Standards Codification 350-40 to determine which implementation costs to defer and recognize as an asset. For public business entities, the guidance is effective for annual periods, and interim periods within those annual periods, beginning after December 15, 2019. For all other entities, it is effective for annual periods beginning after December 15, 2020 and interim periods in annual periods beginning after December 15, 2021. Early adoption is permitted, including adoption in any

2. Summary of significant accounting policies (Continued)

interim period for all entities. The Company expects to adopt this guidance when effective and is currently assessing what effect the adoption of ASU No. 2018-13 will have on its consolidated financial statements and accompanying notes.

In November 2018, the FASB issued ASU 2018-18,"Collaborative Arrangements (Topic 808): Clarifying the Interaction between Topic 808 and Topic 606". ASU 2018-18 provides guidance on whether certain transactions between collaborative arrangement participants should be accounted for with revenue under Topic 606. For public business entities, the guidance is effective for annual periods, and interim periods within those annual periods, beginning after December 15, 2019. For all other entities, it is effective for annual periods beginning after December 15, 2020 and interim periods in annual periods beginning after December 15, 2021. Early adoption is permitted, including adoption in any interim period for all entities. The Company expects to adopt this guidance when effective and is currently assessing what effect the adoption of ASU No. 2018-18 will have on its consolidated financial statements and accompanying notes.

Impact of recently adopted accounting pronouncements

In May 2014, the FASB issued ASU No. 2014-09, "Revenue from Contracts with Customers (Topic 606)". ASU No. 2014-09 eliminated transaction- and industry-specific revenue recognition guidance under FASB Accounting Standards Codification ("ASC") Subtopic 605-15, Revenue Recognition-Products and replaced it with a principle-based approach for determining revenue recognition. ASC Topic 606 requires entities to recognize revenue to depict the transfer of promised goods or services to customers in an amount that reflects the consideration to which the entity expects to be entitled in exchange for those goods or services. On January 1, 2018, the Company adopted ASC Topic 606 using the modified retrospective approach and applied this approach only to contracts that were not completed as of January 1, 2018. The Company calculated a one-time transition adjustment of $3.3 million, which was recorded on January 1, 2018 to deferred revenue and accumulated deficit, related to the product sales of Emflaza. The information presented for the periods prior to January 1, 2018 has not been restated and is reported under ASC Topic 605.

In November 2015, the FASB issued ASU No. 2015-17, "Income Taxes (Topic 740): Balance Sheet Classification of Deferred Taxes". This standard requires all deferred tax assets and liabilities to be classified as non-current on the balance sheet instead of separating deferred taxes into current and non-current amounts. In addition, valuation allowance allocations between current and non-current deferred tax assets are no longer required because those allowances also will be classified as non-current. This standard is effective for public companies for annual periods beginning after December 15, 2016. The Company adopted the guidance on January 1, 2017 on a prospective basis. As the Company's deferred tax assets are provided with full valuation allowance and the deferred tax liability is non-current as of December 31, 2018, adoption of this standard did not have a significant impact on the Company's financial statements.

In January 2016, the FASB issued ASU No. 2016-01, "Financial Instruments — Overall (Subtopic 825-10): Recognition and Measurement of Financial Assets and Financial Liabilities". This standard enhances the reporting model for financial instruments, which includes amendments to address aspects of recognition, measurement, presentation and disclosure. The new guidance affects all reporting organizations (whether public or private) that hold financial assets or owe financial liabilities. The Company adopted the guidance on January 1, 2018. In March 2018, the FASB issued ASU 2018-04, "Investments - Debt Securities (Topic 320) and Regulated Operations (Topic 980): Amendments to SEC Paragraphs Pursuant to the SEC Staff Accounting Bulletin ("SAB") No. 117 and SEC Release No. 33-9273 (SEC Update)". This standard supersedes SEC paragraphs in ASC 320, Investments-Debt Securities, as a result of the issuance of SAB 117 and also updates the Codification for a 2011 SEC release and is effective when a registrant adopts ASU 2016-01, which in the case of the Company was on January 1, 2018. The adoption of the guidance did not have a material impact on the consolidated financial statements and accompanying notes.

In March 2016, the FASB issued ASU No. 2016-9, "Compensation—Stock Compensation (Topic 718): Improvements to Employee Share-Based Payment Accounting". This standard requires the recognition of all income tax effects of awards in the income statement when the awards vest or are settled, with Additional Paid in Capital (APIC) pools to be eliminated. In addition, the standard will increase the amount an employer can withhold to cover income taxes on awards and still qualify for the exception to liability classification for shares used to satisfy the employer's statutory income tax withholding obligation as well as allowing companies to elect whether to account for forfeitures of share-based payments by recognizing forfeitures of awards as they occur or estimating the number of awards expected to be forfeited and adjusting the estimate when it is likely to change, as is currently required. This standard is effective for public companies for fiscal years beginning after December 15, 2016 and interim periods within those years. The Company adopted the guidance on January 1, 2017 and on a prospective basis, the Company records all

2. Summary of significant accounting policies (Continued)

excess tax benefits and deficiencies as income tax expense or benefit. Due to the Company's history of operating losses, the adoption did not result in changes to the Company's Net loss or Retained earnings. In connection with the adoption of ASU 2016-9, the Company made a policy election to continue its methodology for estimating its forfeiture rate.

In August 2016, the FASB issued ASU No. 2016-15, “Statement of Cash Flows (Topic 230): Classification of Certain Cash Receipts and Cash Payments”. This standard clarifies the presentation of certain specific cash flow issues in the Statement of Cash Flows. The Company adopted the guidance on January 1, 2018. The adoption of the guidance did not have a material impact on the consolidated financial statements and accompanying notes.

In November 2016, the FASB issued ASU 2016-16, “Intra-Entity Transfers of Assets Other Than Inventory”. ASU 2016-16 requires companies to account for the income tax effects of intercompany transfers of assets other than inventory (e.g., intangible assets) when the transfer occurs. The Company adopted the guidance on January 1, 2018. The adoption of the guidance did not have a material impact on the consolidated financial statements and accompanying notes.

In November 2016, the FASB issued ASU No. 2016-18, “Statement of Cash Flows (Topic 230): Restricted Cash”. This standard requires entities to show the changes in the total of cash, cash equivalents, restricted cash and restricted cash equivalents in the statement of cash flows and no longer present transfers between cash and cash equivalents and restricted cash and restricted cash equivalents in the statement of cash flows. The Company adopted the guidance on January 1, 2018. The adoption of the guidance did not have a material impact on the consolidated financial statements and accompanying notes.

In January 2017, the FASB issued ASU No. 2017-01, "Business Combinations (Topic 805): Clarifying the Definition of a Business". This standard changed the definition of a business to help entities determine whether a set of transferred assets and activities is a business. This standard is effective for public companies for fiscal years beginning after December 15, 2017, including interim periods within those fiscal years, with early adoption permitted. The Company elected to early adopt ASU No. 2017-01 and applied the guidance to the Transaction, which was accounted for as an asset acquisition under the revised guidance.

In January 2017, the FASB issued ASU 2017-04, "Simplifying the Test for Goodwill Impairment". This standard simplifies the accounting for goodwill impairment by requiring impairment charges to be based on the first step in today's two-step impairment test under ASC 350. Therefore, entities will record an impairment charge based on the excess of a reporting unit's carrying amount over its fair value. The guidance is effective for annual and interim impairment tests performed in periods beginning after December 15, 2019 for public business entities that meet the definition of an SEC filer, December 15, 2020 for public business entities that are not SEC filers, and December 15, 2021 for all other entities. Early adoption is permitted for all entities for annual and interim goodwill impairment testing dates on or after January 1, 2017. The guidance should be applied on a prospective basis. The Company early adopted this guidance in the fourth quarter ended December 31, 2018. The adoption of the guidance did not have a material impact on the consolidated financial statements and accompanying notes.

In May 2017, the FASB issued ASU No. 2017-09, "Stock Compensation (Topic 718): Scope of Modification Accounting". This standard clarifies when changes to the terms or conditions of a share-based payment award must be accounted for as a modification, with entities applying the modification accounting guidance if the value, vesting conditions or classification of the award changes. In addition to all disclosures about modifications that are required under the current guidance, entities will be also required to disclose that compensation expense has not changed if applicable. The Company adopted the guidance on January 1, 2018. The adoption of the guidance did not have a material impact on the consolidated financial statements and accompanying notes.

3. Acquisitions

Agilis Acquisition

On August 23, 2018, the Company completed its acquisition of Agilis pursuant to the Merger Agreement. Agilis was a privately-held biotechnology company advancing an innovative gene therapy platform for rare monogenic diseases that affect the central nervous system. Upon completion of the Merger, the Company acquired Agilis's lead product candidate, PTC-AADC, for the treatment of AADC deficiency, as well as three other gene therapies that were part of the Agilis platform.

Upon the closing of the Merger, the Company paid to Agilis equityholders total upfront consideration comprised of $49.2 million in cash and 3,500,907 shares of the Company’s common stock (the “Closing Stock Consideration”). The Closing Stock

(In thousands except share and per share amount)

3. Acquisitions (Continued)

Consideration was determined by dividing $150.0 million by the volume-weighted average price per share of the Company's common stock on the Nasdaq Global Select Market for the 10 consecutive trading-day period ending on the second trading-day immediately preceding the closing of the Merger. The fair value of the stock on the acquisition date was determined to be $155.9 million.

Pursuant to the Merger Agreement, Agilis equityholders may become 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 fair value of the contingent consideration payments at the acquisition date was estimated to be $290.5 million. Under the Merger Agreement, the Company is required to pay $40.0 million of the development milestone payments mentioned above no later than the second anniversary of the closing of the Merger, regardless of whether the applicable milestones have been achieved. The fair value of the deferred consideration payments at the closing date was estimated to be $38.1 million. Refer to Footnote 4 for further fair value considerations.

The Company evaluated the acquisition of Agilis under ASU No. 2017-01, *Business Combinations: Clarifying the Definition of a Business*. Because the business contained both inputs and processes necessary to manage products and provide economic benefits directly to its owners and substantially all the value of the acquisition did not relate to a similar group of assets, it was determined that the acquisition represents a business combination. Therefore, the transaction has been accounted for using the acquisition method of accounting. Under the acquisition method of accounting, the total purchase price of the acquisition is allocated to the net tangible and identifiable intangible assets acquired and liabilities assumed based on their fair values as of the date of acquisition.

The fair value of consideration totaled approximately $533.7 million summarized as follows:

	Fair Value	
Cash consideration	$	49,221
Fair value of PTC common stock issued		155,860
Estimated fair value of deferred consideration payable		38,100
Estimated fair value of contingent consideration payable		290,500
Total consideration	$	533,681

The Company recorded the assets acquired and liabilities assumed as of the date of acquisition based on the information available at that time. The Company finalized its accounting for the Merger during the three month period ended December 31, 2018. The following table presents the preliminary allocation of the purchase price to the estimated fair values of the assets acquired and liabilities assumed as of the acquisition date of August 23, 2018, the measurement period adjustments recorded during the period from the acquisition date through December 31, 2018, and the final allocation of the purchase price as of December 31, 2018.

(In thousands except share and per share amount)

3. Acquisitions (Continued)

	Preliminary Allocation as of the acquisition date of August 23, 2018	Measurement Period Adjustments	Final Allocation as of December 31, 2018
Cash and cash equivalents	$ 328	$ —	$ 328
Prepaid expenses and other current assets	181	—	181
Fixed assets	153	—	153
Other assets	38	—	38
Intangible assets - IPR&D	480,000	96,500	576,500
Accounts payable and accrued expenses	(3,828)	—	(3,828)
Deferred tax liability	(115,200)	(6,832)	(122,032)
Fair value of net assets acquired	$ 361,672	$ 89,668	$ 451,340
Goodwill	100,309	(17,968)	82,341
Total purchase price	$ 461,981	$ 71,700	$ 533,681

The Company incurred approximately $1.7 million in acquisition related expenses as of December 31, 2018, which were included in selling, general and administrative expenses in the consolidated statement of operations. The results of Agilis's operations have been included in the consolidated statements of operations beginning on the acquisition date of August 23, 2018.

The fair value of the IPR&D was capitalized as of the acquisition date and accounted for as indefinite-lived intangible assets until disposition of the assets or completion or abandonment of the associated research and development efforts. Accordingly, during the development period after the completion of the acquisition, these assets will not be amortized into earnings; rather, these assets will be subject to periodic impairment testing. Upon successful completion of the development efforts, the useful lives of the IPR&D assets will be determined and the assets will be considered definite-lived intangible assets and amortized over their expected useful lives.

The goodwill recorded is the excess of the purchase price of the net assets acquired net of any deferred tax adjustments. The Company currently has a deferred tax liability for the indefinite lived IPR&D intangible assets, which have no tax basis and, therefore, will not result in a future tax deduction. The goodwill is not deductible for income tax purposes.

The net loss of Agilis included in the consolidated statement of operations for the period August 23, 2018 through December 31, 2018 was $8.7 million.

Pro-Forma Financial Information Associated with the Agilis Acquisition (Unaudited)

The following table summarizes certain supplemental pro forma financial information for the twelve-month periods ended December 31, 2018 and 2017 as if the Merger had occurred as of January 1, 2017. The unaudited pro-forma financial information for the twelve-month period ended December 31, 2018 reflects adjustments of $1.7 million related to acquisition fees that are non-recurring in nature. There were no adjustments related to the twelve-month period ended December 31, 2017.

	Twelve Months Ended December 31,	
	2018	2017
Revenues	$ 264,734	$ 194,392
Net loss attributable to common stockholders	$ (138,083)	$ (93,333)

Emflaza Acquisition

(In thousands except share and per share amount)

3. Acquisitions (Continued)

On April 20, 2017, the Company completed its previously announced acquisition of all rights to Emflaza pursuant to an 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. The Company assumed certain liabilities and obligations in the Transaction arising out of, or relating to, the assets acquired in the Transaction.

The Company concluded that the Transaction included inputs and processes that did not constitute a business under the revised guidance of ASU No. 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 the Emflaza rights intangible asset and accounted for the Transaction as an asset acquisition under ASC 805-50.

The purchase price consisted of total upfront consideration comprised of $75.0 million in cash and 6,683,598 shares of the Company's common stock with a fair value of $75.2 million. In addition, the Company incurred approximately $2.2 million of acquisition costs, which are capitalized in an asset acquisition and included in the total consideration transferred.

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 addition, Marathon has the opportunity to receive a single $50.0 million sales-based milestone. In 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. Refer to Note 18 for further details.

The following tables present the total purchase consideration and the preliminary allocation of the purchase consideration for the Transaction as of April 20, 2017 (the “Acquisition Date”):

Cash consideration	$	75,000
Fair value of PTC common stock issued to Marathon (6,683,598 shares)		75,190
Acquisition costs		2,163
Total preliminary consideration transferred	$	152,353

Purchase price	$	152,353

Total fair value of tangible assets acquired and liabilities assumed:		
Inventory		3,980
Emflaza rights	$	148,373

The Emflaza rights intangible asset is being amortized to cost of product sales over its expected useful life of approximately seven years. Given the inherent uncertainty of the Company's sales projections, the Company amortizes the asset on a straight line basis. Refer to Note 18 for further details.

4. Fair value of financial instruments and investments

Fair value of certain investments is based upon market prices using quoted prices in active markets for identical assets quoted on the last day of the year. In establishing the estimated fair value of the remaining investments, the Company used the fair value as determined by its investment advisors using observable inputs other than quoted prices.

The Company reviews its investments on a periodic basis for other-than-temporary impairments. This review is subjective, as it requires management to evaluate whether an event or change in circumstances has occurred in that period that may have a significant adverse effect on the fair value of the investment.

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, 2018 and 2017:

PTC Therapeutics, Inc.

Notes to consolidated financial statements (Continued)

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(In thousands except share and per share amount)

4. Fair value of financial instruments and investments (Continued)

	December 31, 2018			
	Total	Quoted prices in active markets for identical assets (level 1)	Significant other observable inputs (level 2)	Significant unobservable inputs (level 3)
Marketable securities	$ 58,088	$ —	$ 58,088	$ —
Warrant liability	$ —	$ —	$ —	$ —
Stock appreciation rights liability	$ 3,814	$ —	$ —	$ 3,814
Deferred consideration payable	$ 37,700	$ —	$ 37,700	$ —
Contingent consideration payable- development and regulatory milestones	$ 257,040	$ —	$ —	$ 257,040
Contingent consideration payable- net sales milestones and royalties	$ 53,200	$ —	$ —	$ 53,200

	December 31, 2017			
	Total	Quoted prices in active markets for identical assets (level 1)	Significant other observable inputs (level 2)	Significant unobservable inputs (level 3)
Marketable securities	$ 79,454	$ —	$ 79,454	$ —
Warrant Liability	$ 1	$ —	$ —	$ 1
Stock appreciation rights liability	$ 1,665	$ —	$ —	$ 1,665

The Company uses the market approach to measure fair value for its financial assets. The market approach uses prices and other relevant information generated by market transactions involving identical or comparable assets. The Company's marketable securities investments classified as Level 2 primarily utilize broker quotes in a nonactive market to value these securities. No transfers of assets between Level 1 and Level 2 of the fair value measurement hierarchy occurred during the years ended December 31, 2018 and 2017.

The following is a summary of marketable securities accounted for as available-for-sale securities at December 31, 2018 and 2017:

	December 31, 2018			
	Amortized Cost	Gross Unrealized		Fair Value
		Gains	Losses	
Commercial paper	$ 31,657	$ 43	$ (1)	$ 31,699
Corporate debt securities	26,399	—	(10)	26,389
Total	$ 58,056	$ 43	$ (11)	$ 58,088

	December 31, 2017			
	Amortized Cost	Gross Unrealized		Fair Value
		Gains	Losses	
Commercial paper	$ 13,775	$ 52	$ —	$ 13,827
Corporate debt securities	65,657	—	(30)	65,627
Total	$ 79,432	$ 52	$ (30)	$ 79,454

Unrealized gains and losses are reported as a component of accumulated other comprehensive (loss) income in stockholders' equity. During the year ended December 31, 2018, the Company did not have any realized gains or losses from the sale of marketable securities. The cost of securities sold is based on the specific identification method. The Company evaluates investments with

(In thousands except share and per share amount)

4. Fair value of financial instruments and investments (Continued)

unrealized losses to determine if the losses are other than temporary. At December 31, 2018, the Company held securities with an unrealized loss position that were not considered to be other-than-temporarily impaired as the Company has the ability and intent to hold such investments until recovery of their amortized cost bases, which may be maturity. The Company has determined that it is not more likely than not that the Company will be required to sell the investments before such recovery.

In addition, the Company considered the financial condition, credit ratings and near-term prospects of the issuers, and the magnitude of the losses as compared to the cost and the length of time the investments have been in an unrealized loss position when determining if the losses are other than temporary.

The unrealized losses and fair values of available-for-sale securities that have been in an unrealized loss position for a period of less than and greater than 12 months as of December 31, 2018 are as follows:

	December 31, 2018					
	Securities in an unrealized loss position less than 12 months		Securities in an unrealized loss position greater than 12 months		Total	
	Unrealized losses	Fair Value	Unrealized losses	Fair Value	Unrealized losses	Fair Value
Commercial Paper	$ (1)	$ 1,993	$ —	$ —	$ (1)	$ 1,993
Corporate debt securities	(7)	14,230	(3)	10,087	$ (10)	$ 24,317
Total	$ (8)	$ 16,223	$ (3)	$ 10,087	$ (11)	$ 26,310

The unrealized losses and fair values of available-for-sale securities that have been in an unrealized loss position for a period of less than and greater than 12 months as of December 31, 2017 are as follows:

	December 31, 2017					
	Securities in an unrealized loss position less than 12 months		Securities in an unrealized loss position greater than 12 months		Total	
	Unrealized losses	Fair Value	Unrealized losses	Fair Value	Unrealized losses	Fair Value
Corporate debt securities	$ (28)	$ 59,108	$ (2)	$ 6,519	$ (30)	$ 65,627

Marketable securities on the balance sheet at December 31, 2018 and 2017 mature as follows:

	December 31, 2018	
	Less Than 12 Months	More Than 12 Months
Commercial paper	$ 31,699	$ —
Corporate debt securities	26,389	—
Total Marketable securities	$ 58,088	$ —

	December 31, 2017	
	Less Than 12 Months	More Than 12 Months
Commercial paper	$ 13,827	$ —
Corporate debt securities	55,550	10,077
Total Marketable securities	$ 69,377	$ 10,077

The Company classifies all of its securities as current as they are all available for sale and are available for current operations.

Convertible 3.0% senior notes

In August 2015, the Company issued $150.0 million of 3.0% convertible senior notes due August 15, 2022 (the "Convertible Notes"). Interest is payable semi-annually on February 15 and August 15 of each year, beginning on February 15, 2016. The

4. Fair value of financial instruments and investments (Continued)

Company separately accounted for the liability and equity components of the Convertible Notes by allocating the proceeds between the liability component and equity component, as further discussed in Note 7. 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 Convertible Notes at December 31, 2018 and 2017 was $146.6 million and $115.7 million, respectively.

The carrying amounts reported in the consolidated balance sheets for cash and cash equivalents, accounts receivable, accounts payable and borrowings under the credit and security agreement with MidCap Financial Trust and other financial institutions (as further discussed in Note 7) approximate fair value because of the immediate or short-term maturity of these financial instruments. The carrying amounts for the credit and security agreement approximate fair value based on market activity for other debt instruments with similar characteristics and comparable risk.

Deferred consideration payable

Pursuant to the Merger Agreement, Agilis equityholders may become entitled to receive contingent consideration payments from the Company based on the achievement of certain development milestones up to an aggregate maximum amount of $60.0 million and 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. The Company is required to pay $40.0 million of development milestone payments no later than the second anniversary of the closing of the Merger, regardless of whether the applicable milestones have been achieved. The fair value of the deferred consideration payable at December 31, 2018 was estimated to be $37.7 million by applying 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 candidates. As of December 31, 2018, $19.4 million of the deferred consideration payable was classified as current on the balance sheet.

Level 3 valuation

The warrant liability is classified in Other long-term liabilities on the Company's balance sheet. The warrant liability is marked-to-market each reporting period with the change in fair value recorded as a gain or loss within Other expense, net on the Company's statement of operations until the warrants are exercised, expire or other facts and circumstances lead the warrant liability to be reclassified as an equity instrument. The fair value of the warrant liability is determined at each reporting period by utilizing the Black-Scholes option pricing model.

The stock appreciation rights (SARs) liability is classified in Other liabilities on the Company's consolidated balance sheets. The SARs liability is marked-to-market each reporting period with the change in fair value recorded as compensation expense on the Company's consolidated statements of operations until the SARS vest. The fair value of the SARs liability is determined at each reporting period by utilizing the Black-Scholes option pricing model.

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 is 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. 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.

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Notes to consolidated financial statements (Continued)

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4. Fair value of financial instruments and investments (Continued)

The table presented below is a summary of changes in the fair value of the Company's Level 3 valuation for the warrant liability, SARs liability, and the contingent consideration payable for the years ended December 31, 2018 and 2017:

	Level 3 liabilities			
	Warrants	SARs	Contingent consideration payable- development and regulatory milestones	Contingent consideration payable- net sales milestones and royalties
Beginning balance as of December 31, 2016	$ 1	$ 865	$ —	$ —
Change in fair value	—	1,864	—	—
Payments	—	(1,064)	—	—
Ending balance as of December 31, 2017	$ 1	$ 1,665	$ —	$ —
Additions	—	—	263,500	27,000
Change in fair value	(1)	4,140	(6,460)	26,200
Payments	—	(1,991)	—	—
Ending balance as of December 31, 2018	$ —	$ 3,814	$ 257,040	$ 53,200

The following significant unobservable inputs were used in the valuation of the warrant liability, SARs liability, and the contingent consideration payable for the years ended December 31, 2018 and 2017:

	December 31, 2018			
	Fair Value	Valuation Technique	Unobservable Input	Range
Warrants	—	Option-pricing model	Volatility	59.39% - 60.48%
			Risk free interest rate	2.6%
			Strike price	$128.00 - $2,520.00
			Fair value of common stock	$34.32
			Expected life	0.59 - 0.72 years
SARs	$3,814	Option-pricing model	Volatility	46.53% - 59.59%
			Risk free interest rate	2.44% - 2.63%
			Strike price	$6.76 - $30.86
			Fair value of common stock	$34.32
			Expected life	0.01 - 1.01 years
Contingent consideration payable- development and regulatory milestones	$257,040	Probability-adjusted discounted cash flow	Potential development and regulatory milestones	$0 - $555 million
			Probabilities of success	25% - 94%
			Discount rates	5.8% - 8.0%
			Projected years of payments	2020 - 2026
Contingent considerable payable- net sales milestones and royalties	$53,200	Option-pricing model with Monte Carlo simulation	Potential net sales milestones	$0 - $150 million
			Probabilities of success	25% - 89%
			Potential percentage of net sales for royalties	2% - 6%
			Discount rate	14.0%
			Projected years of payments	2021 - 2038

PTC Therapeutics, Inc.

Notes to consolidated financial statements (Continued)

December 31, 2018

(In thousands except share and per share amount)

4. Fair value of financial instruments and investments (Continued)

	December 31, 2017			
	Fair Value	**Valuation Technique**	**Unobservable Input**	**Range**
Warrants	$1	Option-pricing model	Volatility	69%
			Risk free interest rate	$1.89
			Strike price	$128.00 - $2,520.00
			Fair value of common stock	$16.68
			Expected life	1.60 - 1.70 years
SARs	$1,665	Option-pricing model	Volatility	31% - 70%
			Risk free interest rate	1.28% - 1.89%
			Strike price	$6.76 - $30.86
			Fair value of common stock	$16.68
			Expected life	0.00 - 2.00 years

The contingent consideration is classified as a Level 3 liability as its 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 approach, including but not limited to, assumptions involving probability adjusted sales estimates for the Agilis 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, 2018 and 2017:

	December 31,	
	2018	**2017**
Leasehold improvements	$ 2,384	$ 14,078
Computer equipment and software	4,609	5,471
Furniture, fixtures, and lab equipment	9,965	20,776
Assets in process	3,219	895
	20,177	41,220
Less accumulated depreciation and amortization	(7,483)	(32,844)
Total	$ 12,694	$ 8,376

Depreciation expense was approximately $2.6 million, $2.3 million, and $3.3 million for the years ended December 31, 2018, 2017, and 2016, respectively.

6. Accounts payable and accrued expenses

(In thousands except share and per share amount)

Accounts payable and accrued expenses at December 31, 2018 and 2017 consist of the following:

	December 31,	
	2018	2017
Employee compensation, benefits, and related accruals	$ 27,629	$ 17,711
Consulting and contracted research	11,267	5,137
Professional fees	5,574	2,116
Sales allowances and other related costs	29,417	22,257
Royalties and rebates	31,874	11,657
Accounts payable	6,001	15,282
Other	16,437	2,286
Total	$ 128,199	$ 76,446

7. Debt

2017 Credit Facility

In May 2017, the Company entered into a credit and security agreement (the "Credit Facility") with MidCap Financial Trust, a Delaware statutory trust (“MidCap”), as administrative agent and MidCap and certain other financial institutions as lenders thereunder (the “Credit Agreement”) that provides for a senior secured term loan facility of $60.0 million, of which $40.0 million was drawn by the Company on May 5, 2017. The Company’s ability to draw on the remaining $20.0 million under the senior secured term loan facility expired on December 31, 2018. The Company capitalized approximately $0.4 million of debt issuance costs, which were netted against the carrying value of the Credit Facility and will be amortized over the term of the Credit Facility using the effective interest rate method.

Borrowings under the Credit Agreement bear interest at a rate per annum equal to LIBOR (with a LIBOR floor rate of 1.00%) plus 6.15%. The Company is obligated to make interest only payments (payable monthly in arrears) through April 30, 2019. Commencing on May 1, 2019 and continuing for the remaining twenty-four months of the facility, the Company will be required to make monthly interest payments and monthly principal payments. The principal payments are to be made based on straight-line amortization of the principal over the twenty-four month period. The maturity date of the Credit Agreement is May 1, 2021, unless terminated earlier.

The Credit Facility is subject to certain financial covenants. As of December 31, 2018, the Company was in compliance with all required covenants.

Convertible Notes

In August 2015, the Company issued, at par value, $150.0 million aggregate principal amount of 3.0% convertible senior notes due 2022. The Convertible Notes bear cash interest at a rate of 3.0% per year, payable semi-annually on February 15 and August 15 of each year, beginning on February 15, 2016. The 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 Convertible Notes are governed by an indenture (the Convertible Notes Indenture) with U.S Bank National Association as trustee (the Convertible Notes Trustee).

Holders may convert their 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)

7. Debt (Continued)

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.

On or after February 15, 2022, until the close of business on the business day immediately preceding the maturity date, holders may convert their Convertible Notes at any time, regardless of the foregoing circumstances. Upon conversion, the Company will pay cash up to the aggregate principal amount of the Convertible Notes to be converted and deliver shares of its common stock in respect of the remainder, if any, of its conversion obligation in excess of the aggregate principal amount of Convertible Notes being converted.

The conversion rate for the Convertible Notes was initially, and remains, 17.7487 shares of the Company's common stock per $1,000 principal amount of the 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 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 Convertible Notes to be redeemed, plus accrued and unpaid interest to, but excluding, the redemption date. No sinking fund is provided for the Convertible Notes, which means that the Company is not required to redeem or retire the Convertible Notes periodically. There have been no redemptions to date.

If the Company undergoes a "fundamental change" (as defined in the Indenture governing the Convertible Notes Indenture), subject to certain conditions, holders of the Convertible Notes may require the Company to repurchase for cash all or part of their Convertible Notes at a repurchase price equal to 100% of the principal amount of the Convertible Notes to be repurchased, plus accrued and unpaid interest to, but excluding, the fundamental change repurchase date.

The Convertible Notes Indenture contains customary events of default with respect to the Convertible Notes, including that upon certain events of default (including the Company's failure to make any payment of principal or interest on the Convertible Notes when due and payable) occurring and continuing, the Convertible Notes Trustee by notice to the Company, or the holders of at least 25% in principal amount of the outstanding Convertible Notes by notice to the Company and the Convertible Notes Trustee, may, and the Convertible Notes Trustee at the request of such holders (subject to the provisions of the Convertible Notes Indenture) shall, declare 100% of the principal of and accrued and unpaid interest, if any, on all the 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 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.

The Company accounts for the Convertible Notes as a liability and equity component where the carrying value of the liability component will be valued based on a similar instrument. In accounting for the issuance of the Convertible Notes, the Company separated the 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 does 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 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, is amortized to interest expense over the seven-year term of the Convertible Notes. The

(In thousands except share and per share amount)

7. Debt (Continued)

equity component is not re-measured as long as it continues to meet the conditions for equity classification. The equity component recorded at issuance related to the Convertible Notes is $57.5 million and was recorded in additional paid-in capital.

In accounting for the transaction costs related to the issuance of the Convertible Notes, the Company allocated the total costs incurred to the liability and equity components of the Convertible Notes based on their relative values. Transaction costs attributable to the liability component are amortized to interest expense over the seven-year term of the 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 Notes.

The Convertible Notes consist of the following:

	Year ended December 31,	
Liability component	**2018**	**2017**
Principal	$ 150,000	$ 150,000
Less: Debt issuance costs	(1,746)	(2,121)
Less: Debt discount, net (1)	(35,054)	(42,572)
Net carrying amount	$ 113,200	$ 105,307

(1) Included in the consolidated balance sheets within convertible senior notes (due 2022) and amortized to interest expense over the remaining life of the Convertible Notes using the effective interest rate method.

The fair value of the Convertible Notes was approximately $146.6 million as of December 31, 2018. The Company estimates the fair value of its Convertible Notes utilizing market quotations for debt that have quoted prices in active markets. As of December 31, 2018, the remaining contractual life of the Convertible Notes is approximately 3.6 years.

The following table sets forth total interest expense recognized related to the Convertible Notes:

	Year ended December 31,	
	2018	**2017**
Contractual interest expense	$ 4,500	$ 4,500
Amortization of debt issuance costs	375	337
Amortization of debt discount	7,518	6,755
Total	$ 12,393	$ 11,592
Effective interest rate of the liability component	11.0%	11.0%

8. Capital structure

Common stock

In April 2018, the Company closed an underwritten public offering of its common stock pursuant to a registration statement on Form S-3. The Company issued and sold an aggregate of 4,600,000 shares of common stock under the registration statement at a public offering price of $27.04 per share, including 600,000 shares issued upon exercise by the underwriters of their option to purchase additional shares. The Company received net proceeds of approximately $117.9 million after deducting underwriting discounts and commissions and other offering expenses payable by the Company.

As of December 31, 2018, the Company's number of authorized shares of common stock was 125,000,000.

Warrants

All of the Company's outstanding warrants are classified as liabilities as of December 31, 2018 and 2017 because they contain non-standard antidilution provisions.

PTC Therapeutics, Inc.

Notes to consolidated financial statements (Continued)

December 31, 2018

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8. Capital structure (Continued)

The following is a summary of the Company's outstanding warrants as of December 31, 2018:

	Warrant shares	Exercise price	Expiration
Common stock	7,030	$ 128.00	2019
Common stock	130	$ 2,520.00	2019

The following is a summary of the Company's outstanding warrants as of December 31, 2017:

	Warrant shares	Exercise price	Expiration
Common stock	7,030	$ 128.00	2019
Common stock	130	$ 2,520.00	2019

9. Earnings per share

Basic earnings per share is computed by dividing net loss available to common stockholders by the weighted-average number of common shares outstanding. Diluted earnings per share is computed by dividing net loss available to common stockholders by the weighted-average number of common shares plus the effect of dilutive potential common shares outstanding during the period.

The following table sets forth the computation of basic and diluted earnings per share for common stockholders:

	Year ended December 31,		
	2018	2017	2016
Numerator			
Net loss	$ (128,081)	$ (79,000)	$ (142,110)
Denominator			
Denominator for basic and diluted net loss per share	46,576,313	39,183,073	34,044,584
Net loss per share:			
Basic and diluted	$ (2.75) *	$ (2.02) *	$ (4.17) *

* For the years ended December 31, 2018, 2017, and 2016, 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,		
	2018	2017	2016
Stock Options	8,534,358	6,448,642	5,854,316
Unvested restricted stock	571,479	393,011	271,651
Total	9,105,837	6,841,653	6,125,967

10. Stock award plan

In 2009, the Company's shareholders approved the 2009 Equity and Long-Term Incentive Plan, which provides for the granting of stock option awards, restricted stock awards, and other stock-based and cash-based awards, subject to certain adjustments and annual increases.

On March 5, 2013, the Company's Board of Directors approved the 2013 Stock Incentive Plan, which provides for the granting of stock option awards, stock appreciation rights, restricted stock, restricted stock units and other stock-based awards in

10. Stock award plan (Continued)

the aggregate of 739,937 shares of common stock. On March 5, 2013, the Board approved a grant of 735,324 shares of restricted stock and 4,613 stock options. There are no additional shares available for issuance under this plan.

In May 2013, the Company's Board of Directors and stockholders increased by 2,500,000 the number of shares authorized under the 2009 Equity and Long Term Incentive Plan, which provides for the granting of stock option awards, restricted stock awards, and other stock-based and cash-based awards. There are no additional shares available for issuance under this 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, 2018, awards for 729,689 shares of common stock were available for issuance.

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 three- or four-year period.

Inducement stock option awards

Pursuant to the Nasdaq inducement grant exception, during the year ended December 31, 2018, the Company issued options to purchase an aggregate of 1,352,800 shares of common stock to certain new hire employees at a weighted-average exercise price of $37.35 per share. Additionally, during the year ended December 31, 2018, the Company issued restricted stock units to certain new hire employees that upon vesting, will be converted into an aggregate of 7,000 shares of common stock. An aggregate of 202,432 of options previously granted as inducement awards were forfeited during the year ended December 31, 2018 in connection with employee separations from the Company.

PTC Therapeutics, Inc.

Notes to consolidated financial statements (Continued)

December 31, 2018

(In thousands except share and per share amount)

10. Stock award plan (Continued)

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, 2015	4,826,477	$ 37.20		
Granted	1,500,645	$ 27.90		
Exercised	(89,216)	$ 10.85		
Forfeited	(383,590)	$ 47.42		
Outstanding at December 31, 2016	5,854,316	$ 34.71		
Granted	1,913,873	$ 12.34		
Exercised	(202,085)	$ 10.80		
Forfeited	(1,117,462)	$ 33.65		
Outstanding at December 31, 2017	6,448,642	$ 29.00		
Granted	3,181,623	$ 26.64		
Exercised	(633,973)	$ 18.61		
Forfeited	(461,934)	$ 35.36		
Outstanding at December 31, 2018	8,534,358	$ 28.58	7.37	$ 88,454
Vested or expected to vest at December 31, 2018	3,881,360	$ 24.81	8.79	$ 44,893
Exercisable at December 31, 2018	4,410,211	$ 32.01	6.02	$ 40,854

The fair values of grants made in the years ended December 31, 2018, 2017 and 2016 were contemporaneously estimated on the date of grant using the following assumptions:

	2018	2017	2016
Risk-free interest rate	2.25% - 3.10%	1.84% - 2.45%	1.30% - 2.24%
Expected volatility	64% - 90%	76% - 81%	67% - 78%
Expected term	5.03 - 10.00 years	5.04 - 10.00 years	5.05 - 10.00 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, 2018, 2017 and 2016 was $17.48, $8.45, and $17.31 per share, respectively.

Restricted Stock Awards—Restricted stock awards 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.

Restricted Stock Units—Restricted stock units are granted subject to certain restrictions, including in some cases service or time conditions (restricted stock). The grant-date fair value of restricted stock units, 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)

10. Stock award plan (Continued)

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, 2017	393,011	$ 15.64
Granted	354,691	$ 19.09
Vested	(114,295)	$ 16.36
Forfeited	(61,928)	$ 17.24
Unvested at December 31, 2018	571,479	$ 17.61

Stock Appreciation Rights—Stock appreciation rights (SARs) entitle the holder to receive, upon exercise, an amount of the Company's common stock or cash (or a combination thereof) determined by reference to appreciation, from and after the date of grant, in the fair market value of a share of the Company's common stock over the measurement price based on the exercise date.

In May 2016, a total of 897,290 SARs were granted to non-executive employees (the 2016 SARs). The 2016 SARs will vest annually in equal installments over four years and will be settled in cash on each vest date, requiring the Company to remeasure the SARs at each reporting period until vesting occurs. For the period ending December 31, 2018, the Company recorded $4.1 million in compensation expense related to the 2016 SARs.

Employee Stock Purchase Plan—In June 2016, the Company established an Employee Stock Purchase Plan (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. The total number of shares available for purchase under the Plan is one 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, 2018, the Company recorded $1.0 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,		
	2018	2017	2016
Research and development	$ 16,096	$ 15,456	$ 16,812
Selling, general and administrative	17,156	15,103	18,197
Total	$ 33,252	$ 30,559	$ 35,009

As of December 31, 2018, there was approximately $62.6 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 2.96 years.

11. 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.

PTC Therapeutics, Inc.

Notes to consolidated financial statements (Continued)

December 31, 2018

(In thousands except share and per share amount)

11. Other comprehensive income(loss) and accumulated other comprehensive items (Continued)

The following table summarizes other comprehensive income (loss) and the changes in accumulated other comprehensive items, by component, for the years ended December 31, 2018, 2017, and 2016, respectively.

	Unrealized (Losses)/Gains On Marketable Securities, net of tax	Foreign Currency Translation	Total Accumulated Other Comprehensive Items
Balance at December 31, 2015	$ (589)	$ (611)	$ (1,200)
Other comprehensive income (loss) before reclassifications	386	(671)	(285)
Amounts reclassified from other comprehensive items	—	—	—
Other comprehensive income (loss)	386	(671)	(285)
Balance at December 31, 2016	$ (203)	$ (1,282)	$ (1,485)
Other comprehensive income before reclassifications	225	5,229	5,454
Amounts reclassified from other comprehensive items	—	—	—
Other comprehensive income	225	5,229	5,454
Balance at December 31, 2017	$ 22	$ 3,947	$ 3,969
Other comprehensive income (loss) before reclassifications	9	(2,516)	(2,507)
Amounts reclassified from other comprehensive items	—	—	—
Other comprehensive income (loss)	9	(2,516)	(2,507)
Balance at December 31, 2018	$ 31	$ 1,431	$ 1,462

12. Revenue recognition

Net product sales

During the twelve months ended December 31, 2018, net product sales in the United States were $92.0 million consisting solely of Emflaza, and net product sales not in the United States were $171.0 million and consisting solely of Translarna.

The following table presents changes in the Company's contract liabilities from December 31, 2017 to December 31, 2018:

	Balance as of December 31, 2017	Additions	Deductions	ASC 606 Adjustment	Balance as of December 31, 2018
Deferred Revenue	$ 11,891	$ 6,417	$ (1,433)	$ (3,937)	$ 12,938

The Company did not have any contract assets for the During the twelve months ended December 31, 2018.

During the twelve months ended December 31, 2018, the Company recognized revenue in the period from:

	December 31, 2018
Amounts included in contract liabilities at the beginning of the period	$ —
Performance obligations satisfied in previous period	—
Performance obligations satisfied in current period	263,005
Total product revenue	$ 263,005

The Company has not made significant changes to the judgments made in applying ASC Topic 606 for the twelve months ended December 31, 2018.

Remaining performance obligations

12. Revenue recognition (Continued)

Remaining performance obligations represent the transaction price for goods the Company has yet to provide. As of December 31, 2018, the aggregate amount of transaction price allocated to remaining performance obligations relating to Translarna net product revenue was $12.9 million. The Company expects to recognize revenue over the next one to three years as the specific timing for satisfying the performance obligations is contingent upon a number of factors, including customers' needs and schedules.

The impact of adoption using the modified retrospective method on the Company's consolidated financial statements is as follows:

PTC Therapeutics, Inc.

Notes to consolidated financial statements (Continued)

December 31, 2018

(In thousands except share and per share amount)

12. Revenue recognition (Continued)

i. Consolidated balance sheets

		Impact of changes in accounting policies	
	As reported December 31, 2018	Adjustments	As reported Balances without adoption of Topic 606
Assets			
Current assets:			
Cash and cash equivalents	$ 169,498	$ —	$ 169,498
Marketable securities	58,088	—	58,088
Trade receivables, net	67,907	—	67,907
Inventory	16,117	(84)	16,033
Prepaid expenses and other current assets	9,247	—	9,247
Total current assets	320,857	(84)	320,773
Fixed assets, net	12,694	—	12,694
Intangible assets, net	701,031	—	701,031
Goodwill	82,341	—	82,341
Deposits and other assets	2,299	—	2,299
Total assets	$ 1,119,222	$ (84)	$ 1,119,138
Liabilities and stockholders' equity			
Current liabilities:			
Accounts payable and accrued expenses	$ 128,199	$ (2,120)	$ 126,079
Current portion of long-term debt	11,667	—	11,667
Deferred revenue	3,716	10,563	14,279
Other current liabilities	3,814	—	3,814
Deferred consideration payable- current	19,400	—	19,400
Total current liabilities	166,796	8,443	175,239
Deferred revenue - long-term	9,722	—	9,722
Long-term debt	141,347	—	141,347
Contingent consideration payable	310,240	—	310,240
Deferred consideration payable - long-term	18,300	—	18,300
Deferred tax liability	122,032	—	122,032
Other long-term liabilities	58	—	58
Total liabilities	768,495	8,443	776,938
Stockholders' equity:			
Common stock	51	—	51
Additional paid-in capital	1,288,137	—	1,288,137
Accumulated other comprehensive income	1,462	—	1,462
Accumulated deficit	(938,923)	(8,527)	(947,450)
Total stockholders' equity	350,727	(8,527)	342,200
Total liabilities and stockholders' equity	$ 1,119,222	$ (84)	$ 1,119,138

PTC Therapeutics, Inc.

Notes to consolidated financial statements (Continued)

December 31, 2018

(In thousands except share and per share amount)

12. Revenue recognition (Continued)

Consolidated statements of operations

	Impact of changes in accounting policies Twelve Months Ended		
	As reported for the period ended December 31, 2018	Adjustments	As reported Balances without adoption of Topic 606
Revenues:			
Net product revenue	$ 263,005	$ (5,177)	$ 257,828
Collaboration and grant revenue	1,729	—	1,729
Total revenues	264,734	(5,177)	259,557
Operating expenses:			
Cost of product sales, excluding amortization of acquired intangible asset	12,670	(84)	12,586
Amortization of acquired intangible asset	22,877	—	22,877
Research and development	171,984	—	171,984
Selling, general and administrative	153,548	—	153,548
Change in the fair value of deferred and contingent consideration	19,340	—	19,340
Total operating expenses	380,419	(84)	380,335
Loss from operations	(115,685)	(5,093)	(120,778)
Interest expense, net	(12,554)	—	(12,554)
Other income, net	129	—	129
Loss before income tax expense	(128,110)	(5,093)	(133,203)
Income tax benefit	29	—	29
Net loss attributable to common stockholders	$ (128,081)	$ (5,093)	$ (133,174)

iii. Consolidated statements of comprehensive loss

	Impact of changes in accounting policies Twelve Months Ended		
	As reported for the period ended December 31, 2018	Adjustments	As reported Balances without adoption of Topic 606
Net loss	$ (128,081)	$ (5,093)	$ (133,174)
Other comprehensive loss:			
Unrealized gain on marketable securities, net of tax	9	—	9
Foreign currency translation loss	(2,516)	—	(2,516)
Comprehensive loss	$ (130,588)	$ (5,093)	$ (135,681)

(In thousands except share and per share amount)

12. Revenue recognition (Continued)

iv. Consolidated statements of cash flows

	Impact of changes in accounting policies		
	As reported for the period ended December 31, 2018	Adjustments	Balances without adoption of Topic 606
Cash flows from operating activities			
Net loss	$ (128,081)	$ (5,093)	$ (133,174)
Adjustments to reconcile net loss to net cash used in operating activities:			
Depreciation and amortization	26,087	—	26,087
Change in valuation of deferred and contingent consideration	19,340	—	19,340
Amortization of premiums on investments	(433)	—	(433)
Amortization of debt issuance costs	524	—	524
Share-based compensation expense	33,252	—	33,252
Non-cash interest expense	7,518	—	7,518
Disposal of asset	2	—	2
Unrealized foreign currency transaction (gains) losses, net	(59)	—	(59)
Changes in operating assets and liabilities:			
Inventory, net	(5,823)	(84)	(5,907)
Prepaid expenses and other current assets	(1,609)	—	(1,609)
Trade receivables, net	(29,589)	—	(29,589)
Deposits and other assets	(1,093)	—	(1,093)
Accounts payable and accrued expenses	43,877	(2,120)	41,757
Other long-term liabilities	1,932	—	1,932
Deferred revenue	6,514	7,297	13,811
Net cash used in operating activities	(27,641)	—	(27,641)
Cash flows from investing activities			
Purchases of fixed assets	(7,097)	—	(7,097)
Purchases of marketable securities	(68,614)	—	(68,614)
Sale & redemption of marketable securities	90,423	—	90,423
Acquisition of product rights	(8,433)	—	(8,433)
Business acquisition, net of cash acquired	(48,892)	—	(48,892)
Net cash used in investing activities	(42,613)	—	(42,613)
Cash flows from financing activities			
Proceeds from exercise of options	10,868	—	10,868
Proceeds from shares issued under employee stock purchase plan	2,787	—	2,787
Net proceeds from public offerings	117,916	—	117,916
Net cash provided by financing activities	131,571	—	131,571
Effect of exchange rate changes on cash	(3,611)	—	(3,611)
Net increase in cash and cash equivalents	57,706	—	57,706
Cash and cash equivalents, beginning of period	111,792	—	111,792
Cash and cash equivalents, end of period	$ 169,498	$ —	$ 169,498

Collaboration revenue

12. Revenue recognition (Continued)

The Company has ongoing collaborations with the Spinal Muscular Atrophy Foundation (SMA Foundation) and F. Hoffman-La Roche Ltd and Hoffman- La Roche Inc. (collectively, Roche) and early stage discovery arrangements with other institutions. The following are the key terms to the Company's (i) ongoing collaborations and (ii) early stage discovery and development arrangements.

Roche and SMA Foundation

In November 2011, the Company and the SMA Foundation entered into a licensing and collaboration agreement with Roche for a spinal muscular atrophy program. Under the terms of the agreement, Roche acquired an exclusive worldwide license to the Company's spinal muscular atrophy program, which includes 3 compounds currently in preclinical development, as well as potential back-up compounds. The Company received a nonrefundable upfront cash payment of $30.0 million during the research term, which was terminated effective December 31, 2014, after which Roche provided the Company with funding, based on an agreed- upon full-time equivalent rate, for an agreed-upon number of full- time equivalent employees that the Company contributed to the research program.

The Company identified 2 material promises in the collaboration agreement, the license and the research activities. The Company evaluated whether these material promises are distinct and determined that the license does not have standalone functionality and there is a significant integration of the license and research activities. As such, both promises were bundled into one distinct performance obligation. As a result, the Company deferred the $30.0 million upfront payment which was recognized over the estimated performance period of 2 years, which was the contracted research period. As of adoption of ASC Topic 606 on January 1, 2018, all performance obligations had been satisfied and the balance of the remaining deferred upfront payment was fully recognized.

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 August 2013, a lead development compound, RG7800, was selected to move into IND-enabling studies, which triggered a milestone payment to the Company from Roche of $10.0 million. Under ASC Topic 605, the Company considered this milestone event substantive because the applicable criteria of its revenue recognition policy would be satisfied and recorded it as collaboration revenue for the year ended December 31, 2013.

In January 2014, the Company announced the initiation of a Phase 1 clinical program in its spinal muscular atrophy collaboration with Roche and the SMA Foundation which triggered a $7.5 million milestone payment from Roche. Under ASC Topic 605, the Company considered this milestone event substantive because the applicable criteria of its revenue recognition policy would be satisfied and recorded it as collaboration revenue for the year ended December 31, 2014.

In November 2014, the Company announced the initiation of a Phase 2 study in adult and pediatric patients in its spinal muscular atrophy collaboration with Roche and the SMA Foundation which triggered a $10 million payment from Roche. Under ASC Topic 605, the Company considered this milestone event substantive because the applicable criteria of its revenue recognition policy would be satisfied and recorded it as collaboration revenue for the year ended December 31, 2014.

In October 2017, the Company announced that the Sunfish, a two-part clinical trial in pediatric and adult type 2 and type 3 spinal muscular atrophy initiated in the fourth quarter of 2016 with Roche and SMA Foundation, had transitioned into the pivotal second part of its study. The achievement of this milestone triggered a $20.0 million payment to the Company from Roche. Under ASC Topic 605, the Company considered this milestone event substantive because the applicable criteria of its revenue recognition policy would be satisfied and recorded it as collaboration revenue for the year ended December 31, 2017.

The remaining potential research and development event milestones that can be received as of December 31, 2018 is $87.5 million. The remaining potential sales milestones as of December 31, 2018 is $325.0 million upon achievement of certain sales events. In addition, the Company is eligible to receive up to double digit royalties on worldwide annual net sales of a commercial product.

(In thousands except share and per share amount)

12. Revenue recognition (Continued)

For the twelve months ended December 31, 2018, 2017, and 2016, the Company recognized revenue related to the licensing and collaboration agreement with Roche of $0.2 million, $20.3 million, and $0.4 million, respectively.

Early stage collaboration and discovery agreements

From time to time, the Company has arrangements with several organizations pursuant to which the Company uses its discovery technologies to help identify potential drug candidates. The Company does not take ownership of the potential compounds, but rather provides research services to the collaborator using its specialized technology platform.

Generally, these arrangements are structured such that the collaborator and the Company work together to jointly select targets from which to apply its discovery technologies. The research period for the Company to apply its technology is generally 3 to 4 years. The Company will typically receive a nonrefundable, upfront cash payment and the collaborator agrees to provide funding for research activities performed on its behalf.

Generally, the 2 material promises in these arrangements are the license and the research activities. The Company evaluated whether these material promises are distinct and determined that the license does not have standalone functionality and there is a significant integration of the license and research activities. As such, both promises are bundled into one distinct performance obligation. As of adoption of ASC Topic 606 on January 1, 2018, all deferred revenue related to these arrangements had been recognized. For the twelve months ended December 31, 2018, 2017, and 2016, the Company did not recognize any revenue related to discovery agreements.

The Company is eligible to receive additional payments from its early stage discovery research arrangements if the discovery compounds are ultimately developed and commercialized. The aggregate potential payments the Company is eligible for if all products are developed is $143.0 million and up to $252.0 million in sales milestones upon achievement of specified sales events and up to double digit royalties on worldwide annual net sales of the licensed product. The Company will recognize revenue when it is probable the milestones will be achieved (see Note 2). For the twelve months ended December 31, 2018, 2017, and 2016, the Company did not recognize any revenue related to early stage collaborations.

Grant revenue

The Company receives grant funding from various institutions and governmental bodies. The grants are typically for early discovery research, and typically the grant program lasts from two to five years. The Company records revenue as the research activities are performed. If the granting agency provides for an upfront payment, the amount is deferred and recognized as revenue as the expenditures are incurred. For the year ended December 31, 2018 and 2017, the Company did not recognize any grant revenue. For the year ending December 31, 2016, the Company recognized $0.9 million in grant revenue.

13. Income taxes

The loss from operations before tax (expense) benefit consisted of the following for the years ended December 31, 2018, 2017, and 2016:

	2018	2017	2016
Domestic	(68,461)	(54,588)	(61,446)
Foreign	(59,649)	(23,077)	(80,095)
Total	(128,110)	(77,665)	(141,541)

(In thousands except share and per share amount)

13. Income taxes (Continued)

The Income Tax Provision consisted of the following for the years ended December 31, 2018, 2017 and 2016:

	2018	2017	2016
Current:			
U.S. Federal	$ —	$ —	$ —
U.S. State and Local	(38)	(6)	(2)
Foreign	(669)	(1,131)	(766)
Deferred:			
U.S. Federal	—	(198)	199
U.S. State and Local	—	—	—
Foreign	736	—	—
Total tax benefit (expense)	$ 29	$ (1,335)	$ (569)

A reconciliation of the U.S. statutory income tax rate to the Company's effective tax rate is as follows:

	December 31,		
	2018	2017	2016
Federal income tax provision at statutory rate	21.00%	34.00 %	34.00 %
State income tax provision, net of federal benefit	0.05	(1.01)	3.05
Permanent differences	(6.41)	(8.48)	(3.70)
Research and development	6.49	19.53	16.66
Change in valuation allowances	2.20	29.10	(30.72)
Change in deferred tax assets	(14.22)	(64.12)	—
Foreign tax rate differential	(9.10)	(10.33)	(19.84)
Benefit allocated from other comprehensive income	—	(0.26)	0.14
Other	0.01	(0.15)	0.01
Effective income tax rate	0.02%	(1.72)%	(0.40)%

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 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:

	2018	2017
Assets:		
Noncurrent deferred income taxes	$ 736	$ —
Liabilities:		
Noncurrent deferred income taxes	(122,032)	—
Deferred income taxes - net	$ (121,296)	$ —

(In thousands except share and per share amount)

13. Income taxes (Continued)

The significant components of the Company's deferred tax assets and liabilities at December 31, 2018 and 2017 are as follows:

	2018	2017
Deferred tax assets:		
Accrued expense	$ 714	$ 625
Amortization	5,148	2,116
Depreciation	1,601	1,749
Federal tax credits	89,070	80,961
State tax credits	5,473	7,148
Federal net operating losses	62,159	61,068
State net operating losses	165	11,884
Foreign net operating losses	736	—
Capitalized research and development costs	2,093	3,332
Share based compensation and other	21,411	18,815
Total gross deferred tax assets	188,570	187,698
Less valuation allowance	(180,481)	(177,631)
Total deferred tax assets, net of valuation allowance	$ 8,089	$ 10,067
Deferred tax liabilities:		
Convertible debt	$ (7,353)	$ (9,927)
OCI unrealized (gains)/losses	—	(140)
Indefinite lived intangible	(122,032)	—
Total gross deferred tax liabilities	(129,385)	(10,067)
Net deferred tax assets (liabilities)	$ (121,296)	$ —

At December 31, 2018 and 2017, the Company recorded valuation allowance against its net deferred tax assets of approximately $180.5 million and $177.6 million, respectively. The change in the valuation allowance during the years ended December 31, 2018 and 2017 was approximately $2.8 million and $5.4 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, 2018, the Company incurred approximately $296.0 million, $202.4 million, $5.9 million of federal, state, and foreign 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, 2018, research and development credit carryforwards for federal and state purposes are approximately $15.2 million and $6.6 million, respectively. In addition, the Orphan Drug Credit Carryover available as of December 31, 2018 is approximately $74.0 million. As a result of U.S. tax reform legislation, federal net operating losses generated in 2018 carryforward indefinitely, however, the Company has federal net operating losses that pre-date U.S. tax reform legislation which begin to expire in 2021 and federal credit carryforwards that begin to expire in 2019. State net operating loss carryforwards begin to expire in 2030, and the state credit carryforwards began to expire in 2016. 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

13. Income taxes (Continued)

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. In summary, there are $296.0 million of NOLs available, out of which $231.5 million are limited by IRC Section 382. At December 31, 2018, there is $194.5 million available for immediate use and an additional $5.7 million will free up in 2019.

The income tax expense for the years ended December 31, 2018 and 2017 differed from the amounts computed by applying the U.S. federal income tax rate of 21% and 34% respectively, to loss before tax expense as a result of foreign taxes, nondeductible expenses, 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, 2018 the Company did not have any unrecognized tax benefits and has not accrued any interest or penalties through 2018. The Company does not expect to have any unrecognized tax benefits within the next twelve months. 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.

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. U.S. federal income taxes have not been provided on undistributed earnings of our international subsidiaries as it is our intention to reinvest any earnings into the respective subsidiaries. It is not practicable to estimate the amount of tax that might be payable if some or all of such earnings were to be repatriated due to the legal structure and complexity of U.S. and local tax laws. As of December 31, 2018 and December 31, 2017 there are no undistributed earnings.

We have completed our accounting for the income tax effects of U.S. tax reform legislation and included measurement period adjustments in 2018. 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 which resulted in a provisional benefit of $46.1 million which was offset by an associated change in the valuation allowance.

14. Commitments and contingencies

Operating leases

The Company leases office space in South Plainfield, New Jersey for its principal office under three noncancelable operating leases through May 2022, August 2024 and October 2024 in addition to office space in various countries for international employees primarily through workspace providers. Rent expense was approximately $2.7 million, $2.2 million, and $2.2 million for the years ended December 31, 2018, 2017, and 2016, respectively. The Company also leases certain office equipment under operating leases.

(In thousands except share and per share amount)

14. Commitments and contingencies (Continued)

Future minimum lease payments as of December 31, 2018 are as follows:

2019	$ 3,216
2020	2,900
2021	2,409
2022	2,082
2023 and thereafter	3,321
Total	$ 13,928

Other 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 program funding agreement, to the extent that the Company develops and commercializes program intellectual property 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 program 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, if the Company outlicenses rights to a collaboration product, 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 a specified amount.

Pursuant to the Merger Agreement with Agilis, the Company is required to pay $40.0 million of development milestone payments no later than the second anniversary of the closing of the Merger, regardless of whether the applicable milestones have been achieved. The Company may also be obligated to pay additional development, regulatory approval, and net sales milestones and net sales royalties. Refer to Note 3 for further details.

The Company also has a Collaboration and License Agreement with Akcea for the commercialization of Tegsedi and Waylivra, and products containing those compounds in countries in Latin America and the Caribbean. Pursuant to the agreement, the Company paid Akcea an upfront licensing fee, which included an initial payment of $12.0 million. An additional $6.0 million is payable within 30 days after receipt of regulatory approval of Waylivra from the FDA or the EMA, whichever occurs earlier. In addition, Akcea is 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, the Brazilian Health Regulatory Authority, subject to a maximum aggregate amount of $8.0 million for all such products. Akcea is also entitled to receive royalty payments subject to certain terms set forth in the Akcea Collaboration and License 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 has royalty payments associated with Translarna and Emflaza product net sales, payable quarterly or annually in accordance with the terms of the related agreements.

(In thousands except share and per share amount)

14. Commitments and contingencies (Continued)

From time to time in the ordinary course of our business, we are subject to claims, legal proceedings and disputes, including as a result of patients seeking to participate in our clinical trials or otherwise gain access to our product candidates. We are not currently aware of any material legal proceedings against us.

15. 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, 2018		
	United States	Non-US	Total
Total assets	$ 1,013,977	$ 105,245	$ 1,119,222
Property and equipment, net	$ 10,497	$ 2,197	$ 12,694
Revenue	$ 93,694	$ 171,040	$ 264,734

	Year Ended December 31, 2017		
	United States	Non-US	Total
Total assets	$ 278,108	$ 113,545	$ 391,653
Property and equipment, net	$ 6,272	$ 2,104	$ 8,376
Revenue	$ 49,155	$ 145,237	$ 194,392

16. 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 provides an 92% matching contribution for up to the first 6% of each contributing employee's base salary contributions. The Company made matching contributions to the 401(k) plan and recorded expense of approximately $2.2 million, $1.6 million and $1.1 million for the years ended December 31, 2018, 2017 and 2016, respectively.

17. Restructuring

In March 2016, the Company commenced implementation of a reorganization of its operations intended to improve efficiency and better align the Company's costs and employment structure with its strategic plans. The Company completed its reorganization in June 2016 and recorded a one-time charge of $2.5 million for the year ended December 31, 2016. The total $2.5 million in one-time charges is related to work-force reduction, recorded in research and development and selling, general and administrative expenses in the accompanying statement of operations. All restructuring payments were made prior to December 31, 2017 and as such, the balance of accrued restructuring expenses was $0 as of December 31, 2017 and December 31, 2018, 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 No. 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.

(In thousands except share and per share amount)

18. Intangible assets and goodwill (Continued)

The Emflaza rights intangible asset is being amortized to cost of product sales over its expected useful life of approximately 7 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 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 twelve month period ended December 31, 2018, the Company recorded $14.4 million of milestone payments due to net sales of Emflaza, which were added to the cost basis for the Emflaza rights intangible asset and will be amortized prospectively on a straight-line basis over the remaining life of the asset. As of December 31, 2018, a milestone payable to Marathon of $6.0 million was recorded on the balance sheet within accrued expenses.

For the twelve month periods ended December 31, 2018 and 2017, the Company recognized amortization expense of $22.9 million and $15.4 million, respectively, related to the Emflaza rights intangible asset, resulting in accumulated amortization of $38.3 million as of December 31, 2018.The estimated future amortization of the Emflaza rights intangible asset is expected to be as follows:

	As of December 31, 2018
2019	$ 24,283
2020	24,276
2021	24,277
2022	24,277
2023 and thereafter	27,418
Total	$ 124,531

Indefinite-lived intangibles

In connection with the acquisition of Agilis (Note 3), 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 Agilis platform also includes a gene therapy 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. An investigational new drug ("IND") submission with the FDA for this program is expected in late 2019. Additionally, the Agilis platform includes two other gene therapy 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 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.

Goodwill

As a result of the 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. Refer to Note 3 for further details.

Collaboration and Licensing Agreement

(In thousands except share and per share amount)

18. Intangible assets and goodwill (Continued)

On August 1, 2018, the Company entered into a Collaboration and License Agreement with Akcea for the commercialization of Tegsedi and Waylivra, and products containing those compounds in countries in Latin America and the Caribbean. Pursuant to the agreement, the Company paid Akcea an upfront licensing fee, which included an initial payment of $12.0 million. An additional $6.0 million is payable within 30 days after receipt of regulatory approval of Waylivra from the United States Food and Drug Administration or the European Medicines Agency, whichever occurs earlier. The Company evaluated the agreement under the guidance in ASC 730 and concluded that the acquired rights to commercialize the products had no alternative future use as of the date of the Merger. Accordingly, the $12.0 million was charged to research and development expense in the consolidated statements of operations for the twelve month period ended December 31, 2018. The Company recently filed a request for marketing authorizations for Tegsedi with ANVISA. Waylivra is currently under regulatory review in the EU.

19. Subsequent events

In January 2019, the Company closed an underwritten public offering of its common stock pursuant to a registration statement on Form S-3. The Company issued and sold an aggregate of 7,563,725 shares of common stock under the registration statement 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 approximately $224.1 million after deducting underwriting discounts and commissions and other offering expenses payable by the Company.

20. Selected quarterly financial data (Unaudited)

The following financial information reflects all normal recurring adjustments, which are, in the opinion of management, necessary for a fair statement of the results of the interim periods. Summarized quarterly data for 2018 and 2017 are as follows:

	For the quarters ending			
	March 31	June 30	September 30	December 31
2018:				
Net product revenue	$ 55,981	$ 68,170	$ 53,021	$ 85,833
Collaboration and grant revenue	81	573	570	505
Operating expenses	72,805	74,317	101,821	131,476
Loss from operations	(16,743)	(5,574)	(48,230)	(45,138)
Net loss	(19,263)	(9,520)	(50,969)	(48,330)
Basic and diluted net loss per common share(1)	$ (0.46)	$ (0.21)	$ (1.06)	$ (0.96)
2017:				
Net product revenue	$ 26,442	$ 47,891	$ 41,780	$ 57,953
Collaboration and grant revenue	105	71	73	20,077
Operating expenses	52,902	60,459	72,745	72,578
(Loss) income from operations	(26,355)	(12,497)	(30,892)	5,452
Net (loss) income	(29,057)	(17,475)	(33,738)	1,270
Basic and diluted net (loss) income per common share(1)(2)	$ (0.85)	$ (0.44)	$ (0.82)	$ 0.03

(1) The amounts were computed independently for each quarter and the sum of the quarters may not total the annual amounts.

(2) Diluted net income per common share for the quarter ending December 31, 2017 excludes the conversion of the Convertible Notes as the effect of their inclusion is anti-dilutive during the period.

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 Principal Financial Officer (principal financial officer), evaluated the effectiveness of our disclosure controls and procedures as of December 31, 2018. 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, 2018, our Chief Executive Officer and Principal 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 Principal Financial Officer (principal financial officer), assessed the effectiveness of our internal control over financial reporting as of December 31, 2018. 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, 2018 based on those criteria.

The effectiveness of our internal control over financial reporting as of December 31, 2018, 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, 2018 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, 2018, 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, 2018, 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, 2018 and 2017, 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, 2018, and the related notes and our report dated March 1, 2019 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

March 1, 2019

Item 9B. Other Information.

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", "Section 16(a) Beneficial Ownership Reporting Compliance", "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 2019 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 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", "2018 Director Compensation", "Corporate Governance—Risk Oversight" and "Corporate Governance—Compensation Committee Interlocks and Insider Participation" in our Proxy Statement for the 2019 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 2019 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 2019 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 2019 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, 2018 and 2017
- Consolidated Statements of Operations for the years ended December 31, 2018, 2017 and 2016
- Consolidated Statements of Comprehensive Loss for the years ended December 31, 2018, 2017 and 2016
- Consolidated Statements of Stockholders' Equity for the years ended December 31, 2018, 2017 and 2016
- Consolidated Statements of Cash Flows for the years ended December 31, 2018, 2017 and 2016
- 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)
3.1	Restated Certificate of Incorporation of the Registrant (incorporated by reference to Exhibit 3.3 to the Registration Statement on Form S-1, as amended (File No. 333-188657), of the Registrant)
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	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)
10.1+	1998 Employee, Director and Consultant Stock Option Plan, as amended (incorporated by reference to Exhibit 10.1 to the Registration Statement on Form S-1, as amended (File No. 333-188657), of the Registrant)
10.2+	Form of Incentive Stock Option Certificate under 1998 Employee, Director and Consultant Stock Option Plan (incorporated by reference to Exhibit 10.2 to the Registration Statement on Form S-1, as amended (File No. 333-188657), of the Registrant)
10.3+	Form of Non-Qualified Stock Option Certificate under 1998 Employee, Director and Consultant Stock Option Plan (incorporated by reference to Exhibit 10.3 to the Registration Statement on Form S-1, as amended (File No. 333-188657), of the Registrant)
10.4+	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)

Exhibit Number	Description of Exhibit
10.5+	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)
10.6+	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)
10.7+	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)
10.8+	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)
10.9+	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)
10.10+	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)
10.11+	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)
10.12+	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)
10.13+	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)
10.14+	Form of Nonqualified Stock Option Agreement Inducement Grant Agreement—2014-2019 (incorporated by reference to Exhibit 10.14 to the Annual Report on Form 10-K filed by the Registrant on March 2, 2015)
10.15+	Form of Incentive Stock Option Agreement under 2013 Long Term Incentive Plan—2014-2019 (incorporated by reference to Exhibit 10.15 to the Annual Report on Form 10-K filed by the Registrant on March 2, 2015)
10.16+	Form of Nonstatutory Stock Option Agreement under 2013 Long Term Incentive Plan—2014-2019 (incorporated by reference to Exhibit 10.16 to the Annual Report on Form 10-K filed by the Registrant on March 2, 2015)
10.17+	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)
10.18+	Form of Restricted Stock Unit Agreement under 2013 Long Term Incentive Plan —2016-2019 (incorporated by reference to Exhibit 10.32 to the Annual Report on Form 10-K filed by the Registrant on February 29, 2016)
10.19+	Form of Restricted Stock Agreement under 2013 Long Term Incentive Plan —2017-2019 (incorporated by reference to Exhibit 10.19 to the Annual Report on Form 10-K filed by the Registrant on March 16, 2017)
10.20+	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)
10.21	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)
10.22†	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)

Exhibit Number	Description of Exhibit
10.23†	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)
10.24†	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)
10.25†	Funding Agreement, dated as of December 21, 2011, by and between the Registrant and The Wellcome Trust Limited (incorporated by reference to Exhibit 10.17 to the Registration Statement on Form S-1, as amended (File No. 333-188657), of the Registrant)
10.26+	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)
10.27+	Consulting Services Agreement between PTC Therapeutics, Inc. and Spiegel Consulting LLC, dated April 22, 2016 (incorporated by reference to Exhibit 10.1 to the Current Report on Form 8-K filed by the Registrant on April 27, 2016)
10.28+	Inducement Stock Option Award—Nonstatutory Stock Option Agreement dated February 27, 2014 between the Registrant and Robert J. Spiegel (incorporated by reference to Exhibit 99.2 to the Registration Statement on Form S-8 (File No. 333-194323), of the Registrant)
10.29+	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)
10.30+	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)
10.31†	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)
10.32†	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)
10.33	Credit and Security Agreement, dated May 5, 2017, by and among PTC Therapeutics Inc., MidCap Financial Trust and the additional lenders thereto (incorporated by reference to Exhibit 10.1 to the Current Report on Form 8-K filed by the Registrant on May 8, 2017)
10.34	Amendment No. 1 and Limited Consent to Credit and Security Agreement, dated of as July 19, 2018, by and among PTC Therapeutics, Inc., MidCap Financial Trust, and the Lenders as defined therein (incorporated by reference to Exhibit 10.2 to the Current Report on Form 8-K filed by Registrant on July 19, 2018)
10.35	Pledge Agreement, dated May 5, 2017, by and among PTC Therapeutics Inc., each of the subsidiaries listed thereto as pledgers and MidCap Financial Trust (incorporated by reference to Exhibit 10.2 to the Current Report on Form 8-K filed by the Registrant on May 8, 2017)
10.36	Intellectual Property Security Agreement, dated May 5, 2017, by and among PTC Therapeutics Inc. and MidCap Financial Trust (incorporated by reference to Exhibit 10.3 to the Current Report on Form 8-K filed by the Registrant on May 8, 2017)
10.37+	Employment Agreement, as amended, between the Registrant and Marcio Souza (incorporated by reference to Exhibit 10.6 to the Quarterly Report on Form 10-Q filed by the Registrant on August 9, 2017)
10.38+	Employment Agreement, as amended, between the Registrant and Christine Utter (incorporated by reference to Exhibit 10.7 to the Quarterly Report on Form 10-Q filed by the Registrant on August 9, 2017)
10.39†	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)

Exhibit Number	Description of Exhibit
10.40†	License and Technology Transfer Agreement, dated December 23, 2015, 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)
10.42†	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)
10.43	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)
10.44	2016 Employee Stock Purchase Plan (incorporated by reference to Exhibit A to the Definitive Proxy Statement on Schedule 14A filed by the Registrant on April 28, 2016)
21.1	Subsidiaries of the Registrant (incorporated by reference to Exhibit 10.19 to the Annual Report on Form 10-K filed by the Registrant on March 16, 2017)
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	XBRL Instance Document
101.SCH	XBRL Taxonomy Extension Schema Document
101.CAL	XBRL Taxonomy Extension Calculation Linkbase Document
101.LAB	XBRL Taxonomy Extension Label Linkbase Database
101.PRE	XBRL Taxonomy Extension Presentation Linkbase Document
101.DEF	XBRL Taxonomy Extension Definition Linkbase Document

† 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.

Stockholders may obtain (without charge) a copy of this Annual Report on Form 10-K (including the financial statements and financials 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: March 1, 2019

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: March 1, 2019

By: /s/ STUART W. PELTZ
Stuart W. Peltz
Chief Executive Officer and Director

Dated: March 1, 2019

By: /s/ CHRISTINE UTTER
Christine Utter
Principal Financial Officer
(Principal Financial and Accounting Officer)

Dated: March 1, 2019

By: /s/ MICHAEL SCHMERTZLER
Michael Schmertzler
Director

Dated: March 1, 2019

By: /s/ ALLAN JACOBSON
Allan Jacobson
Director

Dated: March 1, 2019

By: /s/ STEPHANIE S. OKEY
Stephanie S. Okey
Director

Dated: March 1, 2019

By: /s/ EMMA REEVE
Emma Reeve
Director

Dated: March 1, 2019

By: /s/ DAVID P. SOUTHWELL
David P. Southwell
Director

Dated: March 1, 2019	By:	/s/ GLENN D. STEELE Glenn D. Steele *Director*
Dated: March 1, 2019	By:	/s/ DAWN SVORONOS Dawn Svoronos *Director*
Dated: March 1, 2019	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-3 No. 333-220151) of PTC Therapeutics, Inc.,
(8) 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),
(9) Registration Statement (Form S-8 No. 333-229126) pertaining to the 2013 Long Term Incentive Plan Inducement Grant Awards (January 2018 - December 2018)

of our reports dated March 1, 2019, 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, 2018.

/s/ ERNST & YOUNG LLP

Iselin, New Jersey
March 1, 2019

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: March 1, 2019

By: /s/ STUART W. PELTZ
Stuart W. Peltz
Chief Executive Officer
(Principal Executive Officer)

Exhibit 31.2

CERTIFICATIONS

I, Christine Utter, 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: March 1, 2019

By: /s/ CHRISTINE UTTER
Christine Utter
Principal Financial Officer
(Principal Financial and Accounting 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, 2018 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: March 1, 2019

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, 2018 as filed with the Securities and Exchange Commission on the date hereof (the "Report"), the undersigned, Christine Utter, Principal Financial 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: March 1, 2019

By: /s/ CHRISTINE UTTER
Christine Utter
Principal Financial Officer
(Principal Financial and Accounting 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
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
Chief Financial Officer
Constellation Pharmaceuticals, Inc.

David P. Southwell
Chief Executive Officer
Tscan Therapeutics, Inc.

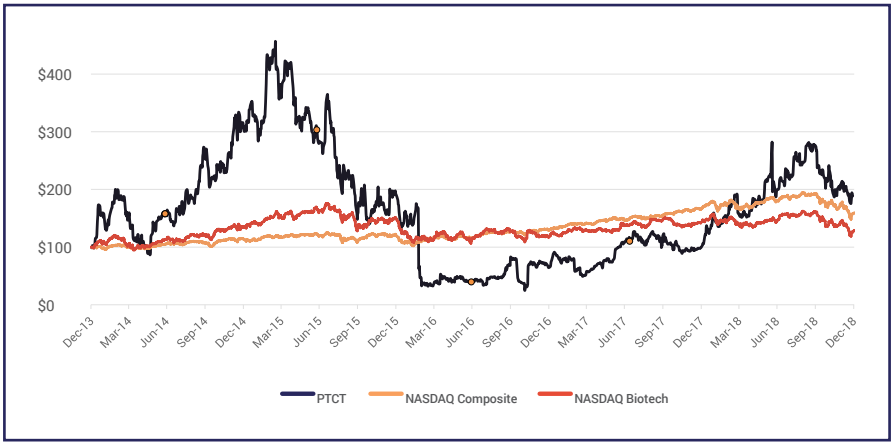
Glenn D. Steele, Jr., M.D., Ph.D.
Chairman
xG Health Solutions

Dawn Svoronos
Former President of Europe/Canada
Merck

Jerome B. Zeldis, M.D., Ph.D.
Chief Medical Officer & President of Clinical Development
Sorrento Therapeutics, 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, 2018 through December 31, 2018, 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, 2013	Dec 31, 2014	Dec 31, 2015	Dec 31, 2016	Dec 31, 2017	Dec 31, 2018
PTC Therapeutics, Inc. (PTCT)	$100	$305	$191	$64	$98	$202
NASDAQ Composite (IXIC)	$100	$113	$120	$129	$165	$159
NASDAQ Biotechnology Index (NBI)	$100	$134	$149	$117	$142	$128

Executive Committee

Stuart W. Peltz, Ph.D.
Chief Executive Officer

Neil Almstead, Ph.D.
Chief Technical Operations Officer

Mark E. Boulding
Executive Vice President and Chief Legal Officer

Mary Frances Harmon
Senior Vice President
Corporate Relations

Mark J. Pykett, V.M.D., Ph.D.
Chief Scientific Officer

Martin Rexroad
Senior Vice President
Human Resources

Megan Sniecinski
Senior Vice President
Business Operations and Program Management

Marcio Souza
Chief Operating Officer

Christine Utter
Principal Financial Officer and Treasurer

Stockholder Information

Market Information
PTC's common stock trades on the NASDAQ Global Market under the ticker symbol PTCT.

Global Corporate Headquarters
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 4 Ireland

Annual Meeting
The Annual Meeting of Stockholders will be held on Wednesday, June 12th at 9am Eastern Time at the Embassy Suites Hotel, 121 Centennial Ave, Piscataway Township, NJ 08854

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

Global Corporate Headquarters
PTC Therapeutics, Inc.
100 Corporate Court
South Plainfield, NJ 07080 USA

PTC Therapeutics International Limited
5th Floor
3 Grand Canal Plaza
Grand Canal Street Upper
Dublin 4 Ireland

For more information visit
www.ptcbio.com