bluebird bio, Inc.

2021
Annual Report

Fellow Shareholders –

Over the past fifteen months, bluebird has had no shortage of news to report to our investors – beginning in January 2021 with our plan to separate into two independent cell and gene therapy companies. Last November, we did just that: spinning off our oncology business and dedicating bluebird bio to severe genetic diseases, all while managing through one of the most challenging years in our history – one that sharpened our focus, reaffirmed our mission, and brought us closer than ever to realizing the promise of gene therapy for patients and their families.

We are proud to say that bluebird has the largest and deepest ex vivo gene therapy data set in the industry. Over the past decade, we have set the standard and advanced the field, amassing more than 500 patient years of experience, interrogating efficacy and safety in a thorough and transparent manner, establishing new patient-specific manufacturing and supply infrastructure, and navigating precedent-setting regulatory pathways for potential first-in-class gene therapies.

Our core three therapies – beti-cel for beta-thalassemia (beta-thal), eli-cel for cerebral adrenoleukodystrophy (CALD) and lovo-cel for sickle cell disease (SCD) have shown **robust, durable results and provide great hope to patients with severe genetic diseases and their families.** We showcased our progress for the hematology community at the American Society of Hematology (ASH) annual meeting in December, with an impressive three oral presentations and three simultaneous publications in the New England Journal of Medicine. Data from our SCD program showed 100% complete resolution of severe vaso-occlusive events in patients with SCD who received lovo-cel in Group C of our HGB-206 study. Data from our beta-thal program showed 89% transfusion independence in patients treated with beti-cel. Our studies reported on the longest available follow up of any gene therapy in development – up to three years for lovo-cel and seven years for beti-cel. These follow-up periods are significant because we can now demonstrate that our therapies improve quality of life through measures such as decreased pain and depression and increased social engagement for patients who reached transfusion independence or complete resolution of severe VOEs.

We also faced new hurdles. Early in 2021, our clinical programs for lovo-cel and beti-cel were put on clinical hold following a reported case of acute myeloid leukemia (AML) in a patient treated with lovo-cel for SCD. A comprehensive review quickly showed that lentiviral vector (LVV) mediated insertion likely did not play a role in the development of leukemia in this patient, and to date there have been no cases of insertional oncogenesis related to our BB305 vector. Working in close partnership with the FDA, NIH, international experts, investigators, and clinical trial sites, we were able to resume trials within just a few months. Throughout this process, we gained a deeper understanding of the pathophysiology of SCD that will allow bluebird, and all those researching and treating SCD, to better serve patients and the broader community. Currently, we are in active dialogue with the FDA about the resolution of a separate partial hold for patients with SCD under 18.

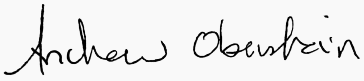
We have also undertaken a similarly thorough investigation related to the hold placed on our clinical program for CALD last August, following a diagnosis of myelodysplastic syndrome (MDS), a known risk of the Lenti-D LVV vector. Despite this risk, eli-cel remains the only potential treatment option for children without a matched donor and a critical source of hope for patients and families who receive the devastating diagnosis of CALD.

Our history and future are based on the strength of our LVV gene therapy platform. But to deliver on our ultimate goal and bring these therapies to patients, **our business has to be as good as our science**. That has led us to make a number of difficult decisions. Following two years of unsuccessful discussions with European reimbursement authorities, with great sadness and disappointment, we made the decision to withdraw from Europe. We right sized our cost structure, reduced our spending, and refocused our business on our near-term milestones. These decisions opened the door for us to be successful in the U.S., and we've emerged ready for the most event-filled year in bluebird bio's history.

Today, we're closer than ever to bringing potentially curative gene therapies to patients and their families. We are on track for two potential FDA approvals for beti-cel and eli-cel this year and a BLA submission for lovo-cel in the first quarter of 2023. These milestones will catapult bluebird forward as a commercial company and lay the foundation for the future of gene therapy.

At bluebird, **we persist for purpose.** I'd like to thank all of those who have been a part of this journey. We wouldn't be here without our birds – those who are with us, and those who have left the nest – and the ongoing collaboration with scientists, healthcare providers and most importantly, people living with severe genetic diseases,their families, and caregivers. Together, we are determined to build a brighter future without severe genetic disease.

Let's fly,



Andrew Obenshain

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UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, DC 20549

FORM 10-K

(Mark One)

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

For the fiscal year ended December 31, 2021
OR

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

For the transition period from _____ to _____
Commission File Number: 001-35966

bluebird bio, Inc.

(Exact Name of Registrant as Specified in Its Charter

Delaware	**13-3680878**
(State or Other Jurisdiction of Incorporation or Organization)	**(IRS Employer Identification No.)**
60 Binney Street	
Cambridge, Massachusetts	**02142**
(Address of Principal Executive Offices)	**(Zip Code)**

(339) 499-9300
(Registrant's Telephone Number, Including Area Code)

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

Title of each class	Trading Symbol(s)	Name of each exchange on which registered
Common Stock, $0.01 par value per share	BLUE	The NASDAQ Stock Market LLC

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 pursuant to Rule 405 of Regulation S-T (§ 232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit such files). **Yes** ☒ **No** ☐

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

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

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

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

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

The aggregate market value of common stock held by non-affiliates of the registrant based on the closing price of the registrant's common stock as reported on the Nasdaq Global Select Market on June 30, 2021, the last business day of the registrant's most recently completed second quarter, was $1,398,973,030.

As of February 28, 2022, there were 71,433,275 shares of the registrant's common stock, par value $0.01 per share, outstanding.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant's definitive Proxy Statement relating to its 2022 Annual Meeting of Stockholders are incorporated by reference into Part III of this Annual Report on Form 10-K where indicated. Such Proxy Statement will be filed with the U.S. Securities and Exchange Commission within 120 days after the end of the fiscal year to which this report relates.

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FORWARD-LOOKING STATEMENTS

This Annual Report on Form 10-K contains forward-looking statements that involve risks and uncertainties, as well as assumptions that, if they never materialize or prove incorrect, could cause our results to differ materially from those expressed or implied by such forward-looking statements. We make such forward-looking statements pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995 and other federal securities laws. All statements other than statements of historical facts contained in this Annual Report on Form 10-K are forward-looking statements. In some cases, you can identify forward-looking statements by words such as "anticipate," "believe," "contemplate," "continue," "could," "estimate," "expect," "intend," "may," "plan," "potential," "predict," "project," "seek," "should," "target," "would," or the negative of these words or other comparable terminology. These forward-looking statements include, but are not limited to, statements about:

- the initiation, timing, progress and results of our preclinical and clinical studies, and our research and development programs;
- our ability to advance product candidates into, and successfully complete, clinical studies;
- our ability to obtain adequate financing to fund our operations and to execute on our strategy;
- our ability to establish and scale commercial viral vector and drug product manufacturing capabilities, and to ensure adequate supply of our viral vectors and drug products;
- the timing or likelihood of regulatory filings and marketing approvals for our product candidates;
- the timing or success of commercialization of any approved products;
- our ability to obtain adequate pricing and reimbursement of any approved products;
- the implementation of our business model, strategic plans for our business, product candidates and technology;
- the scope of protection we are able to establish and maintain for intellectual property rights covering our product candidates and technology;
- estimates of our expenses, future revenues, capital requirements and our needs for additional financing;
- the potential benefits of strategic collaboration agreements and our ability to enter into strategic arrangements;
- our ability to maintain and establish collaborations and licenses;
- developments relating to our competitors and our industry;
- the impact of the COVID-19 pandemic;
- the effects, costs, and benefits of the separation of our portfolio of products and programs into two independent, publicly-traded companies; and
- other risks and uncertainties, including those listed under Part I, Item 1A. Risk Factors.

Any forward-looking statements in this Annual Report on Form 10-K reflect our current views with respect to future events or to our future financial performance and involve known and unknown risks, uncertainties and other factors that may cause our actual results, performance or achievements to be materially different from any future results, performance or achievements expressed or implied by these forward-looking statements. Factors that may cause actual results to differ materially from current expectations include, among other things, those listed under Part I, Item 1A. Risk Factors and elsewhere in this Annual Report on Form 10-K. Given these uncertainties, you should not place undue reliance on these forward-looking statements. Except as required by law, we assume no obligation to update or revise these forward-looking statements for any reason, even if new information becomes available in the future.

This Annual Report on Form 10-K also contains estimates, projections and other information concerning our industry, our business, and the markets for certain diseases, including data regarding the estimated size of those markets, and the incidence and prevalence of certain medical conditions. Information that is based on estimates, forecasts, projections, market research or similar methodologies is inherently subject to uncertainties and actual events or circumstances may differ materially from events and circumstances reflected in this information. Unless otherwise expressly stated, we obtained this industry, business,

market and other data from reports, research surveys, studies and similar data prepared by market research firms and other third parties, industry, medical and general publications, government data and similar sources.

Summary of the Material and Other Risks Associated with Our Business

Below is a summary of the material risks to our business, operations and the investment in our common stock. This summary does not address all of the risks that we face. Risks and uncertainties not presently known to us or that we presently deem less significant may also impair our business operations. Additional discussion of the risks summarized in this risk factor summary, and other risks that we face, can be found below under the heading "Risk Factors" and should be carefully considered, together with other information in this Annual Report on Form 10-K in its entirety before making investment decisions regarding our common stock.

- The FDA has placed our clinical studies of lovo-cel on partial clinical hold, and we have no assurance as to what the FDA may require, or the timing, if ever, of when the partial clinical hold may be lifted, or when we may resume enrolling pediatric patients in our clinical studies of lovo-cel.
- The FDA has placed our clinical studies of eli-cel on clinical hold, and we have no assurances as to what the FDA may require, or the timing, if ever, of when this clinical hold may be lifted, or the effect this clinical hold may have on FDA's ongoing review of the Biologics License Application ("BLA") for eli-cel.
- We have incurred significant losses since our inception and anticipate that we will continue to incur significant losses for the foreseeable future.
- There is substantial doubt regarding our ability to continue as a going concern. We will need to raise additional financing in upcoming periods, which may not be available on acceptable terms, or at all. Failure to obtain necessary capital when needed may force us to delay, limit or terminate our commercial readiness efforts, activities to support a potential commercial launch following any approval of our product candidates, or other operations.
- Our future success depends on our ability to retain key employees, consultants and advisors and to attract, retain and motivate qualified personnel.
- Insertional oncogenesis is a risk of gene therapies using viral vectors that can integrate into the genome, and several patients with CALD treated with eli-cel in our clinical studies have been diagnosed with myelodysplastic syndrome likely mediated by Lenti-D lentiviral vector ("LVV") insertion. These events may require us to halt or delay further clinical development of our product candidates, such as eli-cel, or to suspend or cease commercialization following marketing approval, if any, and the commercial potential of our product candidates may be materially and negatively impacted.
- We have limited experience as a commercial company and the marketing and sale of future products may be unsuccessful or less successful than anticipated.
- The commercial success of our future products will depend upon the degree of market acceptance by physicians, patients, third-party payers and others in the medical community. If we fail to obtain sufficient pricing or reimbursement approval for any future products, our revenues may be adversely affected and our business may suffer.
- If the market opportunities for our product or any future products are smaller than we believe they are, and if we are not able to successfully identify patients and achieve significant market share, our revenues may be adversely affected and our business may suffer.
- We rely on a complex supply chain for our product candidates. The manufacture and delivery of our LVV and drug products present significant challenges for us, and we may not be able to produce our vector and drug products at the quality, quantities, locations or timing needed to support our clinical programs or potential commercialization. In addition, we may encounter challenges with engaging or coordinating with qualified treatment centers needed to support potential commercialization.
- We cannot predict when or if we will obtain marketing approval to commercialize our product candidates, and the marketing approval of our product and any future products may ultimately be for more narrow indications than we expect.
- We face intense competition and rapid technological change and the possibility that our competitors may develop therapies that are more advanced or effective than ours, which may adversely affect our financial condition and our ability to successfully commercialize our product and any future products. If our competitors obtain orphan drug

exclusivity for products that regulatory authorities determine constitute the same drug and treat the same indications as our product or any future products, we may not be able to have competing products approved by the applicable regulatory authority for a significant period of time.

- We may not be successful in our efforts to identify or discover additional product candidates.
- Our business may be materially and adversely affected by the ongoing COVID-19 pandemic. The COVID-19 pandemic has had, and will likely continue to have, an impact on various aspects of our business and that of third parties on which we rely. The extent to which the COVID-19 pandemic impacts our business will depend in part on future developments, which are uncertain and unpredictable in nature.

PART I

Item 1. Business

Overview

In 2021, we completed the tax-free spin-off of our oncology programs and portfolio to become a company focused on the pursuit of curative gene therapies for severe genetic diseases. Today, bluebird bio, Inc. has industry-leading, late-stage clinical and research programs for the treatment of sickle cell disease ("SCD"), β-thalassemia and cerebral adrenoleukodystrophy ("CALD") and is advancing research to apply new technologies to these and other diseases. Using a proprietary lentiviral vector ("LVV") platform, we custom design each of our therapies to address the underlying cause of disease by introducing a functional copy of a gene to patients' own isolated hematopoietic stem cells ("HSCs"). In a rapidly advancing field, we have developed in-depth analytical methods to understand the safety of our LVV technologies, which are designed to deliver a sustained, lifelong response from a one-time treatment and to improve upon allogeneic hematopoietic stem cell transplant ("HSCT"), which carries significant limitations, including the ability to identify matched donors, risk of transplant-related graft-vs-host disease ("GVHD") and death, as well as to improve upon current treatment approaches used with patients not currently eligible to receive allogeneic HSCT. We have the largest and deepest *ex vivo* gene therapy data set in the industry, with more than 500 patient years of experience. We are also investing in research and development to expand the potential impact of our existing *ex vivo* programs through development of reduced toxicity conditioning and alternative HSC mobilization regimens, as well as in manufacturing process improvements. Long-term, we seek to build our pipeline by investing in *in vivo* applications of our LVV platform and advancement of our direct injection preclinical candidates.

European withdrawal

We announced our intent to wind down our operations in Europe and to focus on the U.S. market. The decision to discontinue operations in Europe resulted from prolonged negotiations with European payers and challenges to achieving appropriate value recognition and market access for ZYNTEGLO™ for the treatment of β-thalassemia. Following the exploration of potentially out-licensing the ex-U.S. rights to our three lead programs, we made the decision to withdraw the regulatory marketing authorizations for SKYSONA™ and ZYNTEGLO from the European Union and to withdraw our marketing applications for SKYSONA and ZYNTEGLO from the Medicines and Healthcare products Regulatory Agency (MHRA) in the United Kingdom. We are continuing the long-term follow-up of patients previously enrolled within the clinical trial programs in Europe as planned but do not intend to initiate any new clinical trials in Europe for β-thalassemia, CALD or SCD.

Our Programs

Lovotibeglogene autotemcel

We are developing lovotibeglogene autotemcel ("lovo-cel", formerly referred to as "LentiGlobin for SCD") as a one-time treatment for patients with SCD, a serious, progressive and debilitating genetic disease caused by a single mutation in the β-globin gene that leads to the production of abnormal sickle hemoglobin ("HbS"). HbS causes red blood cells ("RBCs") to become sickled and fragile, resulting in chronic hemolytic anemia, vasculopathy and unpredictable, painful vaso-occlusive events ("VOEs"), requiring frequent hospitalization. In the United States, the median age of death for someone with sickle cell disease is 43 to 46 years. Additionally, one in four people living with sickle cell disease experience a stroke by age 45.

Based on our discussions with the FDA, we believe that we may be able to seek approval for lovo-cel in the United States on the basis of clinical data from Group C of the HGB-206 Phase 1/2 clinical trial. We have treated all of the patients who will form the primary efficacy data set, with the demonstration of analytical comparability and validation of our commercial manufacturing process as the key remaining actions prior to submission of our planned BLA for lovo-cel.

Our approach in SCD involves the *ex vivo* insertion of the normal β-globin gene with the T87Q amino acid substitution into the patient's own HSCs using LVV, to enable formation of normally functioning hemoglobin A and normal RBCs in patients. T87Q serves as a distinct biomarker used to quantify expression levels of the functional β-globin protein in patients with SCD, while also providing anti-sickling properties. Lovo-cel has been granted Fast Track Designation for the treatment of SCD, Orphan Drug Designation for the treatment of SCD, Regenerative Medicine Advanced Therapy ("RMAT") Designation for the treatment of SCD, and Rare Pediatric Disease Designation for the treatment of SCD by the U.S. Food and Drug Administration ("FDA").

We are conducting, or have conducted, the following clinical studies to evaluate the safety and efficacy of lovo-cel in the treatment of patients with SCD:

- The HGB-206 study is a single-dose, open-label, non-randomized, multi-site Phase 1/2 clinical study in the United States to evaluate the safety and efficacy of lovo-cel. A total of 45 patients were treated with lovo-cel in this study across three treatment cohorts. Patients must have been at least twelve years of age at enrollment with a diagnosis of sickle cell disease, with β^S/β^S, β^S/β^+ or β^S/β^0 genotype. Patients must have had recurrent severe VOEs and must have failed to achieve clinical benefit from treatment with hydroxyurea. We refer to patients treated in the HGB-206 study under the amended study protocol utilizing HSCs from peripheral blood after mobilization with plerixafor as patients in "Group C" (n=36) rather than utilizing HSCs collected via bone marrow harvest, as in Groups A (n=7) and B (n=2). A refined manufacturing process designed to increase vector copy number and further protocol refinements made to improve engraftment potential of gene-modified stem cells were also used for Group C. The primary efficacy endpoint for this study is complete resolution of severe VOEs, between six and 18 months post-treatment, and the secondary efficacy endpoint for this study is globin response based on $\beta^{A\text{-}T87Q}$ expression and total hemoglobin. Safety endpoints include monitoring for laboratory parameters and frequency and severity of adverse events; the success and kinetics of HSC engraftment; the incidence of treatment related mortality and overall survival; the detection of vector-derived replication-competent lentivirus in any patient; and the characterization of events of insertional mutagenesis leading to clonal predominance or leukemia. Each patient will remain on study for approximately 24 months post-treatment and then will be invited to enroll in LTF-307, a long-term follow-up protocol that will assess safety and efficacy for an additional 13 years.

- HGB-210 is a single-dose, open-label, non-randomized, multi-site, Phase 3 clinical study in the United States to evaluate the efficacy and safety of lovo-cel in the treatment of patients with SCD, with a target enrollment of 35 pediatric and adult patients. We expect to include data from HGB-210 in our planned BLA submission for lovo-cel to demonstrate analytical comparability and validation of our commercial manufacturing process. Patients must be at least two years of age at enrollment with a diagnosis of sickle cell disease, with β^S/β^S, β^S/β^+ or β^S/β^0 genotype, subject to resolution of the partial clinical hold applicable to enrollment of pediatric patients. Patients must have recurrent severe VOEs and must have failed to achieve clinical benefit from treatment with hydroxyurea. The patients must also be eligible for HSCT. The primary efficacy endpoint for this study is complete resolution of severe VOEs, between six and 18 months post-treatment, and the secondary efficacy endpoint for this study includes globin response based on $\beta^{A\text{-}T87Q}$ expression and total hemoglobin. Safety endpoints include monitoring for laboratory parameters and frequency and severity of adverse events; the success and kinetics of HSC engraftment; the incidence of treatment related mortality and overall survival; the detection of vector-derived replication-competent lentivirus in any patient; and the characterization of events of insertional mutagenesis leading to clonal predominance or leukemia. Each patient will remain on study for approximately 24 months post-treatment and then will be invited to enroll in LTF-307, a long-term follow-up protocol that will assess safety and efficacy for an additional 13 years.

- HGB-205 is a completed proof-of-concept, single-center Phase 1/2 study in France of three patients with SCD which also enrolled patients with β-thalassemia. Those with SCD must have failed to achieve clinical benefit from treatment with hydroxyurea and have an additional poor prognostic risk factor (e.g., recurrent vaso-occlusive crises ("VOCs"), or acute chest syndrome). All patients must have been eligible for allogeneic HSCT, but without a matched sibling allogeneic HSCT donor. The primary objective of our HGB-205 study was to determine the safety, tolerability and success of engraftment of the drug product. The secondary objectives of the study were to quantify gene transfer efficiency and expression, and to measure the effects of treatment on disease-specific biological parameters and clinical events. In the case of patients with TDT and SCD, this meant the volume of RBC transfusions, and for patients with SCD, it also meant the number of VOCs and acute chest syndrome in each patient, compared with the two-year period prior to treatment. Safety evaluations performed during the study included success and kinetics of HSC engraftment, incidence of transplant-related mortality post-treatment, overall survival, detection of vector-derived replication-competent lentivirus in any patient and characterization of events of clonal predominance or leukemia/ lymphoma. Each patient remained on study for approximately 24 months post-treatment and then was invited to enroll in LTF-307, a long-term follow-up protocol that will assess safety and efficacy for an additional 13 years.

- LTF-307 is the long-term follow-up study for patients with SCD from our HGB-205, HGB-206, or HGB-210 studies who were treated with lovo-cel once they complete the original study protocol's follow-up period of approximately two years. Under LTF-307, patients will be followed for approximately an additional 13 years for a total of approximately 15 years post-treatment.

In December 2021, the FDA placed a partial clinical hold on our clinical program for lovo-cel for patients under the age of 18. The partial hold relates to our ongoing investigation into an adolescent patient with persistent, non-transfusion-dependent anemia 18 months post-treatment with lovo-cel. During the partial clinical hold, we anticipate continuing our clinical study

activities as planned for patients 18 and older in our HGB-206 Group C and HGB-210 studies, as well as follow-up activities for treated patients of all ages in all studies. Based on our discussions with the FDA, we believe that we may be able to seek approval for lovo-cel in the United States on the basis of clinical data from HGB-206 Group C, supportive data from HGB-210 for safety and analytical comparability and validation of our commercial manufacturing process. We have treated all of the patients who will form the primary efficacy dataset for the planned BLA submission, with the demonstration of analytical comparability and validation of our commercial manufacturing process as the key remaining actions prior to submission of our planned BLA for lovo-cel.

At the Annual Meeting of the American Society of Hematology in December 2021, we presented interim data from our lovo-cel program with a data cut-off date as of February 17, 2021, as summarized below:

- A total of 49 patients had been treated with lovo-cel, with up to six years of patient follow-up, in the HGB-205 (n=3), HGB-206 (n=44), and HGB-210 (n=2) clinical studies. The HGB-206 total included: Group A (n=7), Group B (n=2), and Group C (n=35), representing progressive adaptations to the manufacturing and treatment processes.

- The 35 Group C patients had up to 37.6 months of follow-up (median of 17.3; min-max: 3.7-37.6 months), for a total of 54.8 patient-years of experience. In HGB-206 Group C, no severe VOEs were reported with up to 36 months of follow-up in patients with a history of at least four severe VOEs and at least six months of follow-up. Following engraftment, median total hemoglobin for these patients increased from 8.5 g/dL at baseline to ≥11 g/dL from six through up to 36 months post-infusion; notably, HbS in all patients was less than 60% of total hemoglobin, and gene therapy-derived anti-sickling hemoglobin, HbA^{T87Q}, contributed at least 40% of total hemoglobin. All evaluable patients (n=25) continued to experience complete resolution of severe VOEs through up to 36 months of follow-up, compared with a median of 3.5 per year (min-max: 2.0-13.5) in the 24 months before enrollment.

- The safety data for lovo-cel remained generally consistent with the risks of autologous stem cell transplantation and myeloablative single-agent busulfan conditioning, as well as underlying SCD. There were no reports of GVHD, graft failure, replication-competent lentivirus, or vector-mediated insertional oncogenesis in any patient treated in HGB-206. One non-serious, Grade 2 adverse event ("AE") of febrile neutropenia was considered related to lovo-cel. There were no serious AEs related to lovo-cel in Group C. In HGB-206 Group C, one patient with underlying cardiopulmonary disease and SCD-related complications died 20 months post-treatment; the investigator and an independent monitoring committee agreed his death was unlikely related to lovo-cel. In HGB-206 Group A, two patients treated with lovo-cel developed acute myeloid leukemia ("AML"). Following investigation of the cases, it was determined that these were unlikely related to lentiviral insertion from lovo-cel. The underlying increased risk of hematologic malignancies in SCD, combined with the transplant procedure and associated proliferative stress, as well as continued hematopoietic stress due to minimal clinical benefit in these two Group A patients (drug product manufactured using stem cells collected via bone marrow harvest and using a previous manufacturing process which has since been discontinued) may have contributed to the development of acute myeloid leukemia.

- In HGB-206 Group C, key hemolysis markers approached normal levels, suggesting a reduction in hemolysis: lactate dehydrogenase and indirect bilirubin levels normalized, reticulocyte counts approached normal levels, and haptoglobin levels were detected at last visit.

- Based on exploratory assay data evaluating HbA^{T87Q} and HbS protein in individual RBCs to assess pancellularity of HbA^{T87Q}, a mean of 85% of RBCs containing $\beta^{A\text{-}T87Q}$ was observed in ten patients with at least 24 months of follow-up, suggesting near-pancellular HbA^{T87Q} distribution and with pancellularity observed to be increasing over time. Within HbA^{T87Q}-containing RBCs, the median HbA^{T87Q} was estimated to be 15.3 pg per RBCs (range: 11.7 to 22.7).

- Integration site analysis data in HGB-206 Group C also demonstrated greater diversity detected in lentiviral vector insertion sites, which is attributed to improvements implemented for Group C.

Betibeglogene autotemcel

The BLA for betibeglogene autotemcel ("beti-cel") is currently under review by the FDA for β-thalassemia in patients who receive regular RBC transfusions. The BLA for beti-cel was accepted for filing and granted priority review and the Prescription Drug User Fee Act ("PDUFA") goal date is August 19, 2022.

β-thalassemia is a rare genetic disease caused by a mutation in the β-globin gene resulting in the production of defective RBCs. The disease is characterized by severe anemia, and the ineffective production of RBCs can lead to a range of multi-systemic complications, including but not limited to splenomegaly, marrow expansion, bone deformities, and iron overload in major organs (as a result of blood transfusions needed to treat the disease). Patients with β-thalassemia require time-consuming,

highly-specialized care for life with many patients receiving RBC transfusions every two to four weeks. More than 80 percent of people with β-thalassemia are living with at least one complication from their disease, and patients have a mortality rate that is five times that of the general population. Our approach involves using LVV to insert the normal β-globin gene with a single amino acid substitution into the patient's own HSCs *ex vivo,* to enable formation of normal RBCs, in patients. Beti-cel refers to the β-thalassemia patients' own cells that have undergone our *ex vivo* manufacturing process resulting in genetically modified HSCs.

The BLA is based on data from patients treated in our Phase 3 HGB-207 and HGB-212 studies, as well as the phase 1/2 HGB-204 and HGB-205 studies. Beti-cel has been granted Orphan Drug status by the FDA for the treatment of β-thalassemia and was granted Fast Track designation for the treatment of β-thalassemia major. The FDA previously granted beti-cel Orphan Drug status, Breakthrough Therapy designation and Rare Pediatric Disease designation for the treatment of transfusion-dependent β-thalassemia.

We are conducting, or have conducted, the following clinical studies to evaluate the safety and efficacy of beti-cel in the treatment of patients with β-thalassemia:

- HGB-207 is an ongoing single-dose, open-label, non-randomized, international, multi-site phase 3 clinical study to evaluate the safety and efficacy of beti-cel to treat patients with transfusion-dependent β-thalassemia ("TDT") and non-β^0/β^0 genotypes. Twenty-three patients were enrolled and completed dosing in the study, consisting of 15 adolescent and adult patients between 12 and 50 years of age at enrollment, and eight pediatric patients less than 12 years of age at enrollment. Age at enrollment ranged from four to 34 years old. To be enrolled, patients with TDT and non-β^0/β^0 genotypes must have received at least 100 mL/kg/year of RBCs or at least eight transfusions per year for the past two years. All patients must have been eligible for allogeneic HSCT, but without a matched family HSCT donor. The primary endpoint of this study is the proportion of treated patients who achieve transfusion independence, defined as weighted average hemoglobin levels ≥9.0 g/dL without any RBC transfusions for a continuous period of at least 12 months at any time during the study after treatment. The secondary endpoints of this study are designed to quantify gene transfer efficiency and expression, and to measure the effects of treatment with beti-cel on transfusion requirements and clinical events. Safety evaluations performed during the study include success and kinetics of platelet and neutrophil engraftment, incidence of transplant-related mortality post-treatment, overall survival, detection of vector-derived replication-competent lentivirus in any patient and characterization of events of clonal predominance or leukemia. Each patient will remain on study for approximately 24 months post-treatment and then will be invited to enroll in LTF-303, a long-term follow-up protocol that will assess safety and efficacy for an additional 13 years.

- HGB-212 is an ongoing single-dose, open-label, non-randomized, international, multi-site phase 3 clinical study to evaluate the efficacy and safety of beti-cel to treat patients with TDT who have either a β^0/β^0, β^0/IVS-I-110, or IVS-I-110/IVS-I-110 genotypes. Eighteen patients were enrolled and completed dosing in the study, consisting of ten adolescent and adult patients between twelve and 50 years of age at enrollment, and eight patients less than twelve years of age at enrollment. To be eligible, patients must have received at least 100 mL/kg/year of RBCs or at least eight transfusions per year for the past two years. All patients must have been clinically stable and eligible to undergo HSCT and been treated and followed for at least the last two years in a specialized center that maintained detailed medical records, including transfusion history. The primary endpoint of this study is the proportion of treated patients who meet the definition of transfusion independence. The secondary endpoints of this study are designed to measure the proportion of patients who meet the definition of transfusion reduction, which is defined as demonstration of reduction in volume of RBC transfusion requirements (in mL/kg) in the post-treatment time period of months 12 to 24 compared to the average annual transfusion requirement in the 24 months prior to enrollment, to quantify gene transfer efficiency and expression, and to measure the effects of treatment with beti-cel on transfusion requirements post-treatment and clinical events. Each patient will remain on study for approximately 24 months post-treatment and then will be invited to enroll in LTF-303, a long-term follow-up protocol that will assess safety and efficacy for an additional 13 years.

- HGB-204 is a completed, single-dose, open-label, non-randomized, multi-site Phase 1/2 clinical study in the United States, Australia and Thailand to evaluate the safety and efficacy of beti-cel in increasing hemoglobin production and the proportion of treated patients who meet the definition of transfusion independence. This study was completed in February 2018, and patients in this study were enrolled in a long-term follow-up protocol to assess safety and efficacy beyond the study follow-up period. Eighteen adults and adolescents were treated in the study. To be eligible for enrollment in this study, patients were between 12 and 35 years of age with a diagnosis of TDT and received at least 100 mL/kg/year of RBCs or at least eight transfusions per year in each of the two years preceding enrollment. The patients were also medically eligible for allogeneic HSCT. Efficacy was evaluated primarily by the production of ≥2.0 g/dL of hemoglobin A containing $\beta^{A\text{-}T87Q}$-globin for the six-month period between 18- and 24-months post-treatment.

Exploratory efficacy endpoints included RBC transfusion requirements per month and per year, post-treatment. Safety evaluations performed during the study included success and kinetics of HSC engraftment, incidence of transplant-related mortality post-treatment, overall survival, detection of vector-derived replication-competent lentivirus in any patient and characterization of events of insertional mutagenesis leading to clonal predominance or leukemia. Subjects were monitored by regular screening. Each patient remained on study for approximately 24 months from time of consent and then was invited to enroll in LTF-303, a long-term follow-up protocol that is assessing safety and efficacy for an additional 13 years.

- HGB-205 is a completed, proof-of-concept, single-dose, open-label, non-randomized, Phase 1/2 clinical study conducted at a single site in France to examine the safety and efficacy of beti-cel in four patients with β-thalassemia that also enrolled patients with SCD. Each patient remained on study for approximately 24 months from time of consent and then was invited to enroll in LTF-303, a long-term follow-up protocol that is assessing safety and efficacy for an additional 13 years.

- LTF-303 is the long-term follow-up study for patients with β-thalassemia from our HGB-204, HGB-205, HGB-207, or HGB-212 studies who were treated with beti-cel once they complete the original study protocol's follow-up period of approximately two years. Under LTF-303, patients will be followed for approximately an additional 13 years for a total of approximately 15 years post-treatment.

In December 2021, we presented the following updated long-term follow up clinical data from HGB-204, HGB-205, HGB-207, HGB-212, and LTF-303 at the ASH Annual Meeting, with a data cut-off date as of August 18, 2021:

- A total of 63 pediatric, adolescent and adult patients, including 20 patients with at least five years of follow-up, 11 with at least six years and three with up to seven years across β^0/β^0 and non-β^0/β^0 genotypes, have been treated with beti-cel across our clinical studies. After participating in and completing the two years of follow-up in any of the Phase 1/2 (HGB-204, HGB-205) or Phase 3 studies (HGB-207, HGB-212), patients treated with beti-cel were invited to enroll in LTF-303. 57 of 63 beti-cel-treated patients across age groups and genotypes spanning a broad range of the most severe β^0/β^0 and non-β^0/β^0 genotypes were enrolled in LTF-303 (22 treated in Phase 1/2 studies, 35 treated in Phase 3 studies) with a median post-infusion follow-up of 41.5 months (min-max: 23-87.5). Twenty patients enrolled in LTF-303 had at least five years of follow-up.

- Of the 57 patients enrolled in LTF-303, 46 patients achieved transfusion independence: 15/22 (68%) patients treated in Phase 1/2 and 31/35 (89%) patients treated in Phase 3. All 46 patients who achieved transfusion independence maintained it through last follow-up in LTF-303, demonstrating the long-term durability of beti-cel. Phase 1/2 patients had a median duration of ongoing transfusion independence of 65.9 months (min-max: 19.8-84.5) and Phase 3 patients had a median ongoing transfusion independence duration of 32 months (min-max: 18.2-49.1). Weighted average hemoglobin in patients who achieved transfusion independence reached normal or near-normal levels in the Phase 1/2 studies (10.3 g/dL; min-max: 9.1-13.2) and in the Phase 3 studies (11.6 g/dL; min-max: 9.5-13.7).

- Patients with β-thalassemia who require regular blood transfusions need to reduce excess iron caused by chronic blood transfusions, including by chelation (pharmacological removal). Prior to beti-cel infusion, all patients in our clinical studies were on iron chelation. Importantly, the majority of patients who achieved transfusion independence (n=46/57) that restarted iron chelation after infusion have since stopped (59%, 20/34); and 24% of those who achieved transfusion independence (11/46) were able to receive phlebotomy (blood removal), which is another method for iron reduction that is only possible for patients who have sufficient hemoglobin levels without RBC transfusions. We believe this result supports the potential for beti-cel to reduce the treatment burden associated with iron management.

- The majority of AEs and SAEs in the beti-cel clinical development program were unrelated to beti-cel and consistent with the known side effects of HSC collection and busulfan conditioning regimen (including several SAEs of veno-occlusive disease that resolved with treatment). Adverse reactions considered related to beti-cel were few and consisted primarily of non-serious infusion-related reactions that occurred on the day of infusion (e.g., abdominal pain, hot flush, dyspnea, tachycardia and non-cardiac chest pain) and cytopenias (e.g. thrombocytopenia, leukopenia and neutropenia). Pain in extremity shortly after treatment was also documented. One of these AEs was a SAE of thrombocytopenia considered possibly related to beti-cel and resolved. There were no deaths, no vector-derived replication-competent lentivirus, and no events of insertional oncogenesis or malignancy.

In June 2019, the European Commission granted conditional marketing authorization for beti-cel, marketed as ZYNTEGLO gene therapy, for the treatment of patients 12 years and older with transfusion-dependent β-thalassemia who do not have a β^0/β^0 genotype, for whom HSCT is appropriate but an HLA-matched related HSC donor is not available. We have

submitted a request for the withdrawal of the marketing authorization for ZYNTEGLO in the European Union, to be effective in the first half of 2022.

Elivaldogene autotemcel

The BLA for elivaldogene autotemcel (“eli-cel”) is currently under review by the FDA for treatment of patients less than 18 years of age with early CALD who do not have an available and willing HLA-matched sibling HSC donor. The BLA for eli-cel was accepted for filing and granted priority review, and the PDUFA goal date is September 16, 2022

CALD is the most severe form of adrenoleukodystrophy, a rare X-linked metabolic disorder caused by mutations in the *ABCD1* gene, which results in accumulation of very long-chain fatty acids ("VLCFAs") in plasma and tissues, leading to a range of clinical outcomes. CALD involves a progressive destruction of myelin, the protective sheath of the nerve cells in the brain that are responsible for thinking and muscle control. Symptoms of CALD usually occur in early childhood and progress rapidly if untreated, leading to severe loss of neurological function and eventual death in most patients. Our approach involves the *ex vivo* insertion of a functional copy of the *ABCD1* gene into the patient’s own HSCs via LVV . Following engraftment, we expect the transduced HSCs to differentiate into other cell types, including macrophages and cerebral microglia, which produce functional ALDP. We believe that the functional ALDP can then enable the local degradation of VLCFAs in the brain, which in turn can stabilize the disease by preventing further cerebral inflammation and demyelination that are characteristics of CALD.

Our eli-cel program has been subject to an ongoing clinical hold since mid-2021 when we received a report of myelodysplastic syndrome ("MDS"). We believe this initial case of MDS was related to eli-cel and likely mediated by Lenti-D LVV insertion. Consistent with this known risk, additional treatment-related cases of MDS have subsequently been reported, and all patients who received eli-cel in the clinical program continue to be monitored in accordance with study protocols. On February 23, 2022, the FDA notified us that the clinical hold on the eli-cel program would remain in place, and requested additional information about safety events and monitoring in the eli-cel clinical program. The FDA previously granted eli-cel Orphan Drug designation, Rare Pediatric Disease designation, and Breakthrough Therapy designation.

The BLA for eli-cel is supported by efficacy and safety data from 32 patients dosed in ALD-102, the completed Phase 2/3 Starbeam study, and 23 patients dosed in ALD-104, the Phase 3 study, which has enrolled a total of 35 patients. All patients who completed ALD-102, as well as those who will complete ALD-104, are invited to participate in LTF-304, a long-term follow-up study. In ALD-102, 90.6% (29/32) of patients met the primary endpoint of Major Functional Disabilities ("MFD")-free survival at 24 months. Two patients withdrew from study ALD-102 at investigator discretion, and one additional subject experienced rapid disease progression early in the study, resulting in MFDs and subsequent death. The median duration of follow-up was 3.5 years (42.3 months; 13.4, 83.7). Adverse reactions attributed to eli-cel observed in clinical trials have included MDS, cystitis viral, pancytopenia, and vomiting. There have been no reports of graft-versus-host-disease, graft failure or rejection, transplant-related mortality, or replication competent lentivirus in the 55 patients who have received eli-cel in clinical studies as of the data cut-off date.

The ALD-103 study is a completed observational prospective/ partially retrospective data collection study of 59 patients with CALD ≤17 years of age who received allogeneic HSCT. This study was designed to collect efficacy and safety outcomes data in patients who had undergone allogeneic HSCT in a period that is contemporaneous with ALD-102. We anticipate that eli-cel safety and efficacy will be evaluated by the FDA in light of the data collected in ALD-102 and ALD-104 in conjunction with ALD-103 as well as our completed retrospective observational ALD-101 study.

In July 2021, the European Commission granted marketing authorization for eli-cel as a one-time gene therapy for the treatment of early cerebral adrenoleukodystrophy in patients less than 18 years of age with an *ABCD1* genetic mutation, and for whom a human leukocyte antigen ("HLA")-matched sibling HSC donor is not available. We have withdrawn the marketing authorization of SKYSONA in the European Union, effective in December 2021.

Manufacturing activities

We have entered into multi-year agreements with external manufacturing partners to support our programs in the United States. We have multi-year agreements with SAFC Carlsbad, Inc. ("SAFC", a subsidiary of MilliporeSigma), and Thermo Fisher Scientific, Inc. (previously Novasep) in the production of LVV. In addition, we have entered into multi-year agreements with Lonza Houston, Inc. and Minaris Regenerative Medicine ("Minaris") to produce drug product. In addition, we rely on specialized third-party testing organizations to confirm the quality of LVV and drug product prior to their use in clinical trials and in the commercial context.

We believe our team of technical personnel has extensive manufacturing, analytical and quality experience as well as strong project management discipline to effectively oversee these contract manufacturing activities, and to compile

manufacturing and quality information for our regulatory submissions and commercialization efforts. For the treatment of patients with our drug product in the commercial setting following approval if and when received, we are collaborating with participating apheresis centers in the United States, which we refer to as qualified treatment centers, to be centers for collection of HSCs from the patient and for infusion of drug product to the patient.

Adherent cell culture is used to manufacture beti-cel and eli-cel LVV. Large-scale suspension bioreactor process is currently used to manufacture clinical supply of lovo-cel LVV, while adherent cell culture for the manufacture of LVV was used initially in the clinical development of lovo-cel. We are also planning a clinical study to demonstrate the comparability of using cryopreserved patient starting material for the manufacture of drug product, which, if successful, would expand the patient population that our therapies could potentially serve following marketing approval, if and when received.

Commercial operations

We are building our commercialization organization in the United States, with a goal of delivering our gene therapies, if and once approved, to patients through qualified treatment centers. In the course of preparing to treat our first commercial patients, we have established commercial capabilities in the United States by adding employees with broad experience in quality assurance and compliance, medical education, marketing, supply chain, sales, public policy, patient services, market access and product reimbursement. Our commercialization activities include active engagements with stakeholders across the healthcare system, including those with public and private payers, patient advocates and organizations, professional societies, and healthcare providers, to explore new payment models that we hope will enable access for more patients. Ultimately, we intend to leverage our commercial infrastructure to support the potential for multiple product launches in the United States.

While we have largely established the appropriate quality systems, compliance policies, systems and procedures, as well as internal systems and infrastructure necessary for supporting our complex supply chain and commercialization activities, we expect that we may make additional targeted investments as we continue our efforts to build our network of qualified treatment centers, establishing patient-focused programs, educating healthcare professionals, and securing reimbursement.

The timing and conduct of our commercialization activities will be dependent upon regulatory interactions, marketing approvals if and when received for our therapies, and on agreements we have made or may make in the future with strategic collaborators.

Pipeline activities and strategic collaborations

Our near-term research and development activities are focused on efforts to expand the potential impact of our existing *ex vivo* programs through reduced toxicity conditioning and HSC mobilization regimens, as well as manufacturing process improvements. Our long-term investments in research and development are focused on potential *in vivo* applications of LVV technology. We seek to build our pipeline by investing in our *in vivo* LVV platform as well as by advancing our direct injection preclinical candidates.

Currently, our strategic collaborations include those with:

- Magenta Therapeutics, Inc., to evaluate the utility of MGTA-145 in combination with plerixafor for mobilization and collection of stem cells in adults and adolescents with SCD, through a proof-of-concept clinical trial; and
- Forty Seven, Inc., a subsidiary of Gilead Sciences, Inc., to pursue clinical proof-of-concept for an antibody-based conditioning regimen in combination with our *ex vivo* lentiviral gene therapy platform.

Intellectual property

We strive to protect and enhance the proprietary technology, inventions, and improvements that are commercially important to the development of our business, including seeking, maintaining, and defending patent rights, whether developed internally or licensed from third parties. We also rely on trade secrets relating to our proprietary technology platform and on know-how, continuing technological innovation and in-licensing opportunities to develop, strengthen and maintain our proprietary position in the field of gene therapy that may be important for the development of our business. We additionally rely on regulatory protection afforded through orphan drug designations, data exclusivity, market exclusivity, and patent term extensions where available.

Our commercial success may depend in part on our ability to obtain and maintain patent and other proprietary protection for commercially important technology, inventions and know-how related to our business; defend and enforce our patents; preserve the confidentiality of our trade secrets; and operate without infringing the valid enforceable patents and proprietary rights of third parties. Our ability to stop third parties from making, using, selling, offering to sell or importing our products

may depend on the extent to which we have rights under valid and enforceable patents or trade secrets that cover these activities. With respect to both licensed and company-owned intellectual property, we cannot be sure that patents will be granted with respect to any of our pending patent applications or with respect to any patent applications filed by us in the future, nor can we be sure that any of our existing patents or any patents that may be granted to us in the future will be commercially useful in protecting our commercial products and methods of manufacturing the same.

We have developed or in-licensed numerous patents and patent applications and possess substantial know-how and trade secrets relating to the development and commercialization of gene therapy products. Our proprietary intellectual property, including patent and non-patent intellectual property, is generally directed to, for example, certain genes, transgenes, methods of transferring genetic material into cells, genetically modified cells, processes to manufacture our lentivirus-based product candidates and other proprietary technologies and processes related to our lead product development candidates. In connection with the wind down of our operations in Europe, we have decided to let the non-U.S. patents and patent applications that we own lapse by ceasing further prosecution of our pending ex-U.S. patent applications and not paying future maintenance fees for ex-U.S. patents when due. As of January 25, 2022, our patent portfolio includes the following:

- approximately 144 patents or patent applications that we own or have exclusively in-licensed from third parties, including 13 that are co-owned with MIT, related to LVVs and vector systems;
- approximately 40 patents or patent applications that we have non-exclusively in-licensed from third parties related to LVVs and vector systems;
- approximately 154 patents or patent applications that we own or have exclusively in-licensed from third parties related to LVV or drug product manufacturing and associated assays;
- approximately 7 patents or patent applications that we have non-exclusively in-licensed from third parties related to LVV or drug product manufacturing and associated assays; and
- approximately 27 patents or patent applications that we own or have exclusively in-licensed from third parties related to therapeutic cellular product candidates and assays.

Our objective is to continue to expand our U.S. portfolio of patents and patent applications in order to protect our gene therapy product candidates manufacturing processes. Examples of the products and technology areas covered by our intellectual property portfolio are described below. See also "—License agreements." From time to time, we also evaluate opportunities to sublicense our portfolio of patents and patent applications that we own or exclusively license, and we may enter into such licenses from time to time.

Beti-cel and lovo-cel

The beti-cel and lovo-cel programs include the following patent portfolios described below.

- **Pasteur Institute.** The Pasteur patent portfolio contains patent applications directed to FLAP/cPPT elements and LVV utilized to produce beti-cel and lovo-cel. As of January 25, 2022, we had an exclusive license to two issued U.S. patents. We expect the issued composition of matter patents to expire in 2022 and 2023 in the United States (excluding possible patent term extensions).
- **RDF.** The in-licensed patent portfolio from Research Development Foundation ("RDF") in part, contains patents and patent applications directed to aspects of our LVV that may be utilized to produce beti-cel and lovo-cel. As of January 25, 2022, we had an exclusive license (from RDF) to seven issued U.S. patents and two pending U.S. patent applications related to our LVV platform. Corresponding foreign patents and patent applications related to our LVV platform include issued patents in Canada, Europe, and Israel. We expect the issued composition of matter patents to expire from 2022-2027 in the United States, and in 2022 in the rest of the world (excluding possible patent term extensions). Further, we expect composition of matter patents, if issued from the pending patent applications and if the appropriate maintenance, renewal, annuity or other governmental fees are paid, to expire in 2022 (excluding possible patent term extensions). We expect any other patents and patent applications in this portfolio other than composition of matter patents, if issued, and if the appropriate maintenance, renewal, annuity, or other governmental fees are paid, to expire in 2022 (worldwide, excluding possible patent term extensions).
- **MIT/bluebird bio.** This co-owned patent portfolio contains patents and patent applications directed to certain specific compositions of matter for lentiviral β-globin expression vectors. As of January 25, 2022, we co-owned four issued U.S. patents and one pending U.S. patent application, as well as corresponding foreign patents issued in Europe and Hong Kong. We expect the issued composition of matter patents to expire in 2023 (excluding possible patent term extensions). Further, we expect composition of matter patents, if issued from the pending patent applications and if the

appropriate maintenance, renewal, annuity or other governmental fees are paid, to expire in 2023 (excluding possible patent term extensions). We expect any other patents and patent applications in this portfolio, if issued, and if the appropriate maintenance, renewal, annuity, or other governmental fees are paid, to expire in 2023 (worldwide, excluding possible patent term extensions). We note that we have an exclusive license to MIT's interest in this co-owned intellectual property.

- **Children's Medical Center Corporation ("CMCC")/bluebird bio.** This co-owned patent portfolio contains patent applications directed to certain specific compositions of matter for treating β-thalassemia and SCD. As of January 25, 2022, we co-owned one pending U.S. patent application, as well as nine corresponding foreign patent applications. We expect any composition of matter or methods patents, if issued from the pending patent application, and if the appropriate maintenance, renewal, annuity or other governmental fees are paid, to expire in 2038 (worldwide, excluding possible patent term extensions). We expect any other patents and patent applications in this portfolio, if issued, and if the appropriate maintenance, renewal, annuity, or other governmental fees are paid, to expire in 2038 (worldwide, excluding possible patent term extensions). We note that we have an option to exclusively license CMCC's interest in this co-owned intellectual property.

Our β-thalassemia and SCD research programs also include in-licensed patents and patent applications that are directed to certain specific compositions of matter and methods for treating β-thalassemia/SCD. As of January 25, 2022, we had an exclusive license to three issued U.S. patents and one pending U.S. patent application as well as 29 corresponding foreign patents and 12 pending corresponding foreign applications. We expect the issued composition of matter patents to expire in 2035 in the United States and in the rest of the world (excluding possible patent term extensions). Further, we expect any composition of matter or method patents, if issued from the pending patent applications, if applicable, and if the appropriate maintenance, renewal, annuity or other governmental fees are paid, to expire in 2035 (worldwide, excluding possible patent term extensions). We expect any other patents in this portfolio, if issued, and if the appropriate maintenance, renewal, annuity, or other governmental fees are paid, to expire from 2035 (worldwide, excluding possible patent term extensions). In addition, as of January 25, 2022, we had a non-exclusive license to five issued U.S. patents, three pending corresponding foreign patent applications and 32 issued foreign patents. We expect the issued composition of matter and method patents to expire in 2029 in the United States and in the rest of the world (excluding possible patent term extensions).

Eli-cel

The eli-cel program includes the following patent portfolios described below.

- **Pasteur Institute**. The in-licensed Pasteur patent portfolio contains the patents and patent applications described above directed towards aspects of LVV utilized to produce eli-cel.

- **RDF.** The in-licensed RDF patent portfolio contains the patents and patent applications described above directed towards aspects of LVV that may be utilized to produce eli-cel.

- **bluebird bio**. The bluebird bio patent portfolio contains patents and patent applications directed to compositions of matter for eli-cel vectors and compositions and methods of using the vectors and compositions in cell-based gene therapy of adrenoleukodystrophy or adrenomyeloneuropathy. As of January 25, 2022, we owned three U.S. patents and 26 issued foreign patents. We expect the issued composition of matter patents for eli-cel vectors to expire in 2032 (excluding possible patent term extensions).

Lentiviral platform (e.g., LVV, manufacturing, and cell therapy products)

The lentiviral platform, which is potentially applicable across our programs in severe genetic disease, includes the following patent portfolios described below.

- **Pasteur Institute.** The Pasteur patent portfolio contains the patents and patent applications described above.

- **RDF.** The in-licensed RDF patent portfolio contains the patents and patent applications described above.

- **SIRION.** The in-licensed patent portfolio from SIRION Biotech GmbH ("SIRION") contains patents and patent applications directed to methods of manufacturing ex vivo gene therapy products with LVV. As of January 25, 2022, we had an exclusive license to two issued U.S. patents, one pending U.S. patent application and two corresponding foreign patent applications and 45 issued corresponding foreign patents. We expect the issued method patents to expire in 2033 (excluding possible patent term extensions). We expect any other composition of matter and methods patents, if issued from the pending patent applications and if the appropriate maintenance, renewal, annuity or other

governmental fees are paid, to expire in 2033 (excluding possible patent term extensions). We expect any other patents and patent applications in this portfolio, if issued, and if the appropriate maintenance, renewal, annuity, or other governmental fees are paid, to expire in 2033 (worldwide, excluding possible patent term extensions).

- **bluebird bio.** Another component of the bluebird bio patent portfolio includes LVV and drug product manufacturing platforms and is potentially applicable across our programs. This portion of the portfolio contains patents and patent applications directed to improved methods for transfection and transduction of therapeutic cells. As of January 25, 2022, we owned three issued U.S. patents, three pending U.S. patent applications and 30 corresponding foreign patent applications and 61 issued corresponding foreign patents. We expect the issued method patents to expire from 2032-2037 (excluding possible patent term extensions). We expect composition of matter and method patents, if issued from the pending patent applications and if the appropriate maintenance, renewal, annuity or other governmental fees are paid, to expire from 2032-2037 (excluding possible patent term extensions). We expect any other patents and patent applications in this portfolio, if issued, and if the appropriate maintenance, renewal, annuity, or other governmental fees are paid, to expire from 2032-2037 (worldwide, excluding possible patent term extensions).

- **2seventy bio.** The 2seventy bio patent portfolios include LVV manufacturing platforms and improvements and are potentially applicable across our programs. As of January 25, 2022, we had a non-exclusive license to three patent families that include one pending U.S. patent application and four corresponding foreign patent applications, one pending PCT application, and one U.S. provisional patent application. We expect any composition of matter or methods patents, if issued from a corresponding nonprovisional application or national stage application, or corresponding foreign applications, if applicable, and if the appropriate maintenance, renewal, annuity or other governmental fees are paid, to expire from 2040-2042 (worldwide, excluding possible patent term extensions). We expect any other patents and patent applications in this portfolio, if issued, and if the appropriate maintenance, renewal, annuity, or other governmental fees are paid, to expire from 2040-2042 (worldwide, excluding possible patent term extensions).

The term of individual patents depends upon the legal term of the patents in the countries in which they are obtained. In most countries in which we file, the patent term is 20 years from the date of filing the non-provisional application. In the United States, a patent's term may be lengthened by patent term adjustment, which compensates a patentee for administrative delays by the U.S. Patent and Trademark Office in granting a patent, or may be shortened if a patent is terminally disclaimed over an earlier-filed patent.

The term of a patent that covers an FDA-approved drug may also be eligible for patent term extension, which permits patent term restoration of a U.S. patent as compensation for the patent term lost during the FDA regulatory review process. The Hatch-Waxman Act permits a patent term extension of up to five years beyond the expiration of the patent. The length of the patent term extension is related to the length of time the drug is under regulatory review. A patent term extension cannot extend the remaining term of a patent beyond a total of 14 years from the date of product approval and only one patent applicable to an approved drug may be extended. Moreover, a patent can only be extended once, and thus, if a single patent is applicable to multiple products, it can only be extended based on one product. Similar provisions are available in Europe and other foreign jurisdictions to extend the term of a patent that covers an approved drug. When possible, depending upon the length of clinical trials and other factors involved in the filing of a BLA, we expect to apply for patent term extensions for patents covering our product candidates and their methods of use.

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 entering into confidentiality agreements with our employees, consultants, scientific advisors and third parties. 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 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

Inserm-Transfert

In May 2009, we entered into an exclusive license with Inserm-Transfert, which is a wholly-owned subsidiary of Institut national de la santé et de la recherche médicale, for use of certain patents and know-how related to the *ABCD1* gene and

corresponding protein, for use in the field of human ALD therapy. Inserm-Transfert is referred to herein as Inserm. The last patent in the Inserm licensed patent portfolio expired in February of 2016.

Upon commercialization of our products covered by the in-licensed intellectual property, which we expect would include eli-cel, we will be obligated to pay Inserm a percentage of net sales as a royalty for the longer of the life of any patents covering the product or 10 years from first commercial sale. This royalty is in the low single digits. The royalties payable to Inserm are subject to reduction for any third-party payments required to be made, with a minimum floor in the low single digits.

We are required to use all commercially reasonable efforts to develop licensed products and introduce them into the commercial market as soon as practical, consistent with our reasonable business practices and judgment in compliance with an agreed upon development plan. We have assumed certain development, regulatory and commercial milestone obligations and must report on our progress in achieving these milestones on an annual basis.

We may unilaterally terminate the license agreement at any time. Either party may terminate the agreement in the event of the other party's material breach which remains uncured after 60 days of receiving written notice of such breach or in the event the other party becomes the subject of a voluntary or involuntary petition in bankruptcy and such petition is not dismissed with prejudice within 120 days after filing. In addition, Inserm may terminate the license agreement in the event that we cannot prove within 60 days of written notice from Inserm that we have been diligent in developing the licensed products and introducing them into the commercial market.

Absent early termination, the agreement will automatically terminate upon the expiration of all issued patents and filed patent applications within the patent rights covered by the agreement or 10 years from the date of first commercial sale of a licensed product, whichever is later. The license grant ceases in connection with any such termination. The longest-lived patent rights licensed to us under the agreement expired in 2016.

Institut Pasteur

We have entered into a license with Institut Pasteur for certain patents relating to the use of DNA sequences, LVV and recombinant cells in the field of *ex vivo* gene therapy and CAR T cell-based therapy in a range of indications, excluding vaccinations. This agreement was amended twice in 2012, again in 2013 and most recently in 2015. The Institut Pasteur licensed patent portfolio includes two U.S. patents. The issued patents have statutory expiration dates in 2022 and 2023. The license is exclusive for products containing human and non-human LVV. Institut Pasteur retains the right, on behalf of itself, its licensees and research partners, to conduct research using the licensed intellectual property.

We have the right to grant sublicenses outright to third parties under the agreement. For the first sublicense including a product targeting β-hemoglobinopathies (including β-thalassemia and SCD) or ALD (including CALD and adrenomyeloneuropathy), we must pay Institut Pasteur an additional payment of €3.0 million. If we receive any income (cash or non-cash) in connection with sublicenses for products targeting indications other than β-hemoglobinopathies (including β-thalassemia and SCD) or ALD (including CALD and adrenomyeloneuropathy), we must pay Institut Pasteur a percentage of such income varying from low single digits if the sublicense also includes licenses to intellectual property controlled by us, and a percentage of sublicense income in the mid-range double digits if the sublicense does not include licenses to intellectual property controlled by us.

Upon commercialization of our products covered by the in-licensed intellectual property, which we expect would include beti-cel, lovo-cel, and eli-cel, we will be obligated to pay Institut Pasteur a percentage of net sales as a royalty. This royalty varies depending on the indication of the product but in any event is in the low single digits. In addition, starting in 2016 we must make under this agreement an annual maintenance payment which is creditable against royalty payments on a year-by-year basis. If the combined royalties we would be required to pay to Institut Pasteur and third parties is higher than a pre-specified percentage, we may ask Institut Pasteur to re-negotiate our royalty rates under this relationship.

We are required to use all reasonable commercial efforts (as compared to a company of similar size and scope) to develop and commercialize one or more products in the license field and to obtain any necessary governmental approvals in respect of, and market the products in license field, if any. Additionally, we have assumed certain development and regulatory milestone obligations. We must report on our progress towards achieving these milestones on an annual basis. We may unilaterally terminate the license agreement at any time by sending Institut Pasteur 90 days prior written notice. Either party may terminate the license in the event of the other party's substantial breach which remains uncured after 60 days of receiving written notice of such breach. Institut Pasteur may also terminate the agreement in the event bankruptcy proceedings are opened against us and not dismissed within 60 days.

Absent early termination, the agreement will automatically terminate upon the expiration of the last licensed patents or five years after first market authorization of the first product, whichever occurs later. In the event the agreement is terminated, while the license grant would cease, we would retain the right to manufacture, import, use and sell licensed products for a certain period of time post-termination. In addition, our ownership stake in certain jointly made improvements covered by the licensed patents would survive termination of the agreement. The longest-lived patent rights licensed to us under the agreement are currently expected to expire in 2023.

Stanford University

In July 2002, we entered into a non-exclusive license agreement with the Board of Trustees of the Leland Stanford Junior University, referred to herein as Stanford, which we amended and restated in April 2012. Under this agreement, we are granted a license to use the HEK293T cell line for any commercial or non-commercial use for research, nonclinical and clinical development purpose and human and animal gene therapy products.

We have the right to grant sublicenses outright to third parties under the agreement. For each such sublicense we grant, we must pay Stanford a fee (unless the sublicense is to a collaborating partner, contract manufacturer or contract research organization).

Upon commercialization of our products covered by the in-licensed intellectual property, which we expect would include beti-cel, lovo-cel, and eli-cel, we will be obligated to pay Stanford a percentage of net sales as a royalty. This royalty varies with net sales but in any event is in the low single digits and is reduced for each third-party license that requires payments by us with respect to a licensed product, provided that the royalty to Stanford is not less than a specified percentage which is less than one percent. Since April 2013, we have been paying Stanford an annual maintenance fee, which will be creditable against our royalty payments.

We may unilaterally terminate the agreement by giving Stanford 30 days' written notice. Stanford may also terminate the license agreement if after 30 days of providing notice we are delinquent on any report or payment, are not using commercially reasonable efforts to develop, manufacture and/or commercialize one or more licensed products, are in material breach of any provision or provide any false report. Termination of this agreement may require us to utilize different cell types for vector manufacturing, which could lead to delays.

Absent early termination, the license will expire in April 2037. We may elect to extend the term for an additional 25 years so long as we have a commercial product on the market at that time and we are in material compliance with the license agreement.

Massachusetts Institute of Technology

In December 1996, we entered into an exclusive license with the Massachusetts Institute of Technology, referred to herein as MIT, for use of certain patents in any field. This license agreement was amended in December 2003, May 2004 and June 2011. The licensed patent portfolio includes at least 13 U.S. and foreign patents and patent applications. Any patents within this portfolio that have issued or may yet issue would have a statutory expiration date from in 2023. This license also has been amended to include a case jointly owned by MIT and us wherein we received the exclusive license to MIT's rights in this case. MIT retains the right to practice the intellectual property licensed under the agreement for noncommercial research purposes.

We have the right to grant sublicenses outright to third parties under the agreement. In the event we sublicense the patent rights, we must pay MIT a percentage of all payments we receive from the sublicensee. This percentage varies from mid-single digits to low double digits.

Upon commercialization of our products covered by the in-licensed intellectual property, which we expect would include beti-cel and lovo-cel, we will be obligated to pay MIT a percentage of net sales by us or our sublicensees as a royalty. This royalty is in the low single digits and is reduced for royalties payable to third parties, provided that the royalty to MIT is not less than a specified percentage that is less than one-percent. In addition, we make under this agreement an annual maintenance payment which may be credited against the royalty payments.

We are required to use diligent efforts to market licensed products and to continue active, diligent development and marketing efforts for licensed products during the term of the agreement. We have assumed certain milestones with respect to raising capital investment and regulatory progress. We must report on our progress on achieving these milestones on an annual basis.

We may unilaterally terminate the license agreement upon six months' notice to MIT. MIT may terminate the agreement if we cease to carry on our business, or in the event of our material breach which remains uncured after 90 days of receiving written notice of such breach (30 days in the case of nonpayment). In the event the agreement is terminated, while the license grant would cease, we would retain a right to complete manufacture of any licensed products in process and sell then-existing inventory. In addition, MIT would grant our sublicensees a direct license following such termination. With respect to jointly owned intellectual property, any termination would allow MIT to grant licenses to any third-party to such intellectual property, without our approval, unless a sublicensee was already in place, in which case, MIT would grant our sublicensees a direct license.

Research Development Foundation

In December 2011, we entered into an exclusive license with RDF to use certain patents that involve LVV. The RDF licensed patent portfolio includes at least 31 U.S. and foreign patents and patent applications. Any patents within this portfolio that have issued or may yet issue would have an expected statutory expiration date between 2021 and 2027. RDF retains the right, on behalf of itself and other nonprofit academic research institutions, to practice and use the licensed patents for any academic, non-clinical research and educational purposes. We have the right to grant sublicenses outright to third parties under the agreement.

Upon commercialization of our products covered by the in-licensed intellectual property, which we expect would include beti-cel, lovo-cel, and eli-cel, we are obligated to pay RDF a percentage of net sales as a royalty. This royalty is in the low single digits and is reduced by half if during the following ten years from the first marketing approval the last valid claim within the licensed patent that covers the licensed product expires or ends.

We are required to use commercially reasonable and diligent efforts for a company of our size and resources to develop or commercialize one or more licensed products, including our first licensed product by 2016 and a second licensed product by 2018. These diligence efforts include minimum annual royalty payments to RDF, which are creditable against earned royalties otherwise due to RDF, and payments upon regulatory milestones.

RDF may terminate the agreement in the event of our material breach which remains uncured after 90 days of receiving written notice of such breach (30 days in the case of nonpayment) or in the event we become bankrupt, our business or assets or property are placed in the hands of a receiver, assignee or trustee, we institute or suffer to be instituted any procedure in bankruptcy court for reorganization or rearrangement of our financial affairs, make a general assignment for the benefit of creditors, or if we or an affiliate or a sublicensee institutes any procedure challenging the validity or patentability of any patent or patent application within the licensed patents, the agreement will immediately terminate.

Absent early termination, the agreement will continue until its expiration upon the later of there being no more valid claims within the licensed patents or the expiration of our royalty obligations on licensed products that are subject to an earned royalty, if such earned royalty is based on the minimum 10-year royalty period described above. In the event the agreement is terminated, while the license grant would cease, RDF will grant our sublicensees a direct license. The longest lived patent rights licensed to us under the agreement are in one U.S. patent currently expected to expire in 2027.

SIRION

In December 2015, we entered into a license agreement with SIRION, pursuant to which we exclusively licensed certain patents and patent applications directed towards aspects of manufacturing gene therapy products. Any patents within this portfolio that have issued or may yet issue would have an expected statutory expiration date in 2033. We have the right to grant sublicenses to third parties, subject to certain conditions. Upon commercialization of our products covered by the in-licensed intellectual property, which we expect would include beti-cel and lovo-cel, we will be obligated to pay SIRION a percentage of net sales as a royalty in the low single digits. We are required to use commercially reasonable efforts to research and develop one or more licensed products in the license field during the term of the agreement, and we must report on our progress in achieving those milestones on a periodic basis. We may be obligated to pay up to $13.4 million in the aggregate upon the achievement of certain development and regulatory milestones. We may unilaterally terminate the license agreement at any time with prior written notice to SIRION. SIRION may terminate the license in the event of our material breach upon notice and following an opportunity for us to cure the material breach. SIRION may also terminate the agreement in the event bankruptcy proceedings are opened against us and are not dismissed within a specified period of time. Absent early termination, the agreement will automatically terminate upon the expiration of the patent rights covered by the agreement. The longest lived patent rights licensed to us under the Agreement are currently expected to expire in 2033.

Orchard Therapeutics Limited

In April 2017, we entered into a license agreement with GlaxoSmithKline Intellectual Property Development Limited ("GSK") pursuant to which GSK non-exclusively licensed certain of our patent rights related to LVV technology to develop and commercialize gene therapies for Wiscott-Aldrich syndrome and metachromatic leukodystrophy, two rare genetic diseases. Effective April 2018, this license agreement was assigned by GSK to Orchard Therapeutics Limited ("Orchard"). Financial terms of the agreement included an upfront payment to us as well as potential development and regulatory milestone payments and low single digit royalties on net sales of covered products.

Competition

The biotechnology and pharmaceutical industries are characterized by intense and rapidly changing competition to develop new technologies and proprietary products. Not only must we compete with other companies that are focused on gene therapy products but any products that we may commercialize will have to compete with existing therapies and new therapies that may become available in the future. Many of our competitors, either alone or with their strategic partners, have substantially greater financial, technical and human resources than we do and significantly greater experience in the discovery and development of product candidates, obtaining FDA and other regulatory approvals of therapies and the commercialization of those therapies. Accordingly, our competitors may be more successful than us in obtaining approval for therapies and achieving widespread market acceptance. Our competitors' therapies may be more effective, or more effectively marketed and sold, than any therapy we may commercialize and may render our treatments obsolete or non-competitive before we can recover the expenses of developing and commercializing any of our therapies.

These competitors also compete with us in recruiting and retaining qualified scientific and management personnel and establishing clinical study sites and patient registration for clinical studies, 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.

We anticipate that we will face intense and increasing competition as new therapies enter the market and advanced technologies become available. We expect any therapies that we develop and commercialize to compete on the basis of, among other things, efficacy, safety, convenience of administration and delivery, price, the level of generic competition and the availability of reimbursement from government and other third-party payers.

Our commercial opportunity could be reduced or eliminated if our competitors develop and commercialize therapies that are safer, more effective, have fewer or less severe side effects, are more convenient or are less expensive than any therapies that we may develop. Our competitors also may obtain FDA or other regulatory approval for their therapies more rapidly than we may obtain approval for ours, which could result in our competitors establishing a strong market position before we are able to enter the market. In addition, our ability to compete may be affected in many cases by insurers or other third-party payers seeking to encourage the use of generic products. If our therapeutic product candidates are approved, we expect that they will be priced at a significant premium over current standard of care. Depending on how successful these competitive efforts are, it is possible they may increase the barriers to adoption and success for our therapies. These efforts include the following:

Sickle cell disease — The current standard of care for the treatment of SCD in the developed world is chronic blood transfusions or hydroxyurea (a generic drug). In addition, patients treated with chronic blood transfusions often receive iron chelation therapy to help manage the iron overload. We are aware of ongoing studies that continue to evaluate the efficacy and safety of hydroxyurea in various populations. In addition, a limited number of patients with SCD receive allogeneic HSCT treatment, particularly if a sufficiently well-matched source of donor cells is identified. There are a number of academic and industry-sponsored research and development programs to improve the tolerability and safety of allogeneic HSCT with less well-matched sources of donor cells, while increasing the availability of suitable donors. Emmaus Life Sciences, Inc. received FDA approval for and has launched Endari (L-glutamine) for the treatment of SCD. In addition to the FDA approved HbS polymerization inhibitor (voxelotor, Global Blood Therapeutics, Inc.) and the FDA / EMA approved antibody to p-selectin (crizanlizumab, Novartis), a number of different therapeutic approaches for the chronic treatment of SCD are under investigation targeting the various aspects of SCD pathophysiology, including: a pyruvate kinase receptor activator, mitapivat, being developed by Agios Pharmaceuticals, Inc. and being evaluated by the FDA with a New Drug Application under priority review; another pyruvate kinase receptor activator, FT-4202, in a Phase 1 study supported by Forma Therapeutics; a PDE9 inhibitor, IMR-687, in a Phase 2 study supported by IMARA Inc.; and a selective small molecule inhibitor of ectoderm development protein designed to increase the expression of fetal hemoglobin, FTX-6058, in a phase 1 study supported by Fulcrum Therapeutics, Inc. There are also several different groups developing gene therapy options for sickle cell disease. These include: CRISPR Therapeutics AG's (in collaboration with Vertex Pharmaceuticals Incorporated) ongoing Phase 1/2 study for its CTX-001, which leverages the CRISPR/Cas9 gene editing platform to disrupt the BCL11A erythroid enhancer,

Aruvant Sciences, Inc.'s ongoing Phase 1/2 study for its ARU-1801, which leverages LVV encoding γ-globin, Editas Medicine, Inc.'s ongoing Phase 1/2 study for its EDIT-301, which leverages the CRISPR/Cas12a gene editing platform to target the HBG1/2 promoter to upregulate HbF, and Graphite Bio's ongoing Phase 1/2 study for its GPH101, which leverages a gene correction platform (CRISPR / homology directed repair) to restore normal hemoglobin production. There are several other groups developing gene therapy approaches for SCD in early phases of development, including Beam Therapeutics, Sangamo BioSciences Inc., Intellia Therapeutics, Inc. (in collaboration with Novartis), and Children's Hospital of Philadelphia.

β-thalassemia — The current standard of care for the treatment of β-thalassemia in the developed world is chronic blood transfusions to address the patient's anemia. In addition, such patients often receive iron chelation therapy to help manage the iron overload associated with their chronic blood transfusions. Novartis and Chiesi, who provide the leading iron chelation therapies, are seeking to develop improvements to their product profile and accessibility. A number of different approaches are under investigation that seek to improve the current standard of care treatment options, including a protein that aims to improve red blood cell production and small molecule that aims to improve red blood cell metabolism. Reblozyl (luspatercept), a subcutaneously-delivered protein therapeutic marketed by Acceleron Pharma, Inc. (recently acquired by Merck) and BMS that targets molecules in the TGF-β superfamily, has been approved in the United States for the treatment of anemia in adult patients with beta thalassemia who require regular RBC transfusions, and was recently approved in the EU for the treatment of adult patients with transfusion-dependent anemia associated with β-thalassemia. Additionally, Agios has announced that an application for Mitapivat, an oral pyruvate kinase receptor activator, has been accepted for filing and granted priority review by the FDA. Some patients with β-thalassemia receive HSCT treatment, particularly if a sufficiently well-matched source of donor cells is identified. In addition, there are a number of academic and industry-sponsored research and development programs to improve the outcomes of allogeneic HSCT, or the tolerability and safety of haploidentical HSCT, while increasing the availability of suitable donors. There are also several different groups developing gene therapy options for β-thalassemia. These include: CRISPR Therapeutics AG (in collaboration with Vertex Pharmaceuticals Incorporated) is conducting an ongoing Phase 1/2 study for its CTX-001, which leverages the CRISPR/Cas9 gene editing platform to disrupt the BCL11A erythroid enhancer; and the San Raffaele Telethon Institute for Gene Therapy (in collaboration with Orchard Therapeutics) is currently investigating its gene therapy in a Phase 2 study of adults and pediatric patients with transfusion dependent β-thalassemia, although Orchard Therapeutics has announced that this program has been deprioritized as of May 2020.

CALD — The current standard of care for the treatment of CALD is allogeneic HSCT. We understand that various academic centers around the world are seeking to develop improvements to allogeneic HSCT, such as Magenta Therapeutic, Inc.'s cord blood expansion technology which is currently being investigated in a Phase 2 clinical trial for the treatment of inherited metabolic disorders, including adrenoleukodystrophy. Other possible treatments being investigated include Orpheris, Inc.'s OP-101, Minoryx Therapeutics' MIN-102 (leriglitazone), and Viking Therapeutics' VK0214.

Government regulation

In the United States, biological products, including gene therapy products, are subject to regulation under the Federal Food, Drug, and Cosmetic Act ("FD&C Act") and the Public Health Service Act ("PHS Act") and other federal, state, local and foreign statutes and regulations. Both the FD&C Act and the PHS Act and their corresponding regulations govern, among other things, the testing, manufacturing, safety, efficacy, purity, potency, labeling, packaging, storage, record keeping, distribution, import, export, reporting, record keeping, post-approval monitoring, advertising and other promotional practices involving biological products. FDA approval must be obtained before marketing of biological products. 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 and we may not be able to obtain the required regulatory approvals.

U.S. biological products development process

The process required by the FDA before a biological product may be marketed in the United States generally involves the following:

- completion of nonclinical laboratory tests and animal studies according to good laboratory practices ("GLPs"), and other applicable regulations;
- submission to the FDA of an investigational new drug application ("IND"), which must become effective before human clinical studies may begin;
- approval by an institutional review board ("IRB"), or ethics committee at each clinical site before the trial commences;

- performance of adequate and well-controlled human clinical studies according to the FDA's regulations commonly referred to as good clinical practices ("GCPs") and any additional requirements for the protection of human research subjects and their health information, to establish the safety, purity and potency or efficacy of the proposed biological product for its intended use;

- preparation and submission to the FDA of a BLA for marketing approval that includes substantial evidence of safety, purity, and potency from results of nonclinical testing and clinical studies;

- satisfactory completion of an FDA inspection of the manufacturing facility or facilities where the biological product is produced to assess compliance with GMP, to assure that the facilities, methods and controls are adequate to preserve the biological product's identity, strength, quality and purity and, if applicable, the FDA's good tissue practices ("GTPs") for the human cellular and tissue products;

- potential FDA audit of the nonclinical and clinical study sites that generated the data in support of the BLA; and

- FDA review and approval, or licensure, of the BLA.

Before testing any biological product candidate, including a gene therapy product, in humans, the product candidate enters the preclinical testing stage. Preclinical tests, also referred to as nonclinical studies, include laboratory evaluations of product chemistry, toxicity and formulation, as well as animal studies to assess the potential safety and activity of the product candidate. The conduct of the preclinical tests must comply with federal regulations and requirements including GLPs, where applicable.

The clinical study sponsor must submit the results of the preclinical tests, together with manufacturing information, analytical data, any available clinical data or literature and a proposed clinical protocol, to the FDA as part of the IND. Some preclinical testing may continue even after the IND is submitted. The IND automatically becomes effective 30 days after receipt by the FDA, unless the FDA places the clinical study on a clinical hold within that 30-day time period. In such a case, the IND sponsor and the FDA must resolve any outstanding concerns before the clinical study can begin. The FDA may also impose clinical holds on a biological product candidate at any time before or during clinical studies due to safety concerns or non-compliance. If the FDA imposes a clinical hold, studies may not recommence without FDA authorization and then only under terms authorized by the FDA. Accordingly, we cannot be sure that submission of an IND will result in the FDA allowing clinical studies to begin, or that, once begun, issues will not arise that suspend or terminate such studies.

In addition to the IND submission process, under the National Institutes of Health ("NIH"), Guidelines for Research Involving Recombinant DNA Molecules ("NIH Guidelines"), supervision of human gene transfer trials includes evaluation and assessment by an institutional biosafety committee ("IBC"), a local institutional committee that reviews and oversees research utilizing recombinant or synthetic nucleic acid molecules at that institution. The IBC assesses the safety of the research and identifies any potential risk to public health or the environment, and such review may result in some delay before initiation of a clinical trial. While the NIH Guidelines are not mandatory unless the research in question is being conducted at or sponsored by institutions receiving NIH funding of recombinant or synthetic nucleic acid molecule research, many companies and other institutions not otherwise subject to the NIH Guidelines voluntarily follow them.

Clinical studies involve the administration of the biological product candidate to healthy volunteers or patients under the supervision of qualified investigators, generally physicians not employed by or under the study sponsor's control. Clinical studies are conducted under protocols detailing, among other things, the objectives of the clinical study, dosing procedures, subject selection and exclusion criteria, and the parameters to be used to monitor subject safety, including stopping rules that assure a clinical study will be stopped if certain adverse events should occur. Each protocol and any amendments to the protocol must be submitted to the FDA as part of the IND. Clinical studies must be conducted and monitored in accordance with the FDA's regulations comprising the GCP requirements, including the requirement that all research subjects provide informed consent. Further, each clinical study must be reviewed and approved by an IRB at or servicing each institution at which the clinical study will be conducted. An IRB is charged with protecting the welfare and rights of study participants and considers such items as whether the risks to individuals participating in the clinical studies are minimized and are reasonable in relation to anticipated benefits. The IRB also approves the form and content of the informed consent that must be signed by each clinical study subject or his or her legal representative and must monitor the clinical study until completed.

Human clinical studies are typically conducted in three sequential phases that may overlap or be combined:

- *Phase 1*. The biological product is initially introduced into healthy human subjects or patients with the target disease or condition. These studies are designed to test the safety, dosage tolerance, absorption, metabolism and distribution of the investigational product in humans, the side effects associated with increasing doses, and if possible, to gain early evidence on effectiveness.

- *Phase 2*. The biological product is evaluated in a limited patient population with the specified disease or condition to identify possible adverse effects and safety risks, to preliminarily evaluate the efficacy of the product for specific targeted diseases and to determine dosage tolerance, optimal dosage and dosing schedule.

- *Phase 3*. The biological product is administered to an expanded patient population to further evaluate dosage,to provide statistically significant evidence of clinical efficacy, and to further test for safety, generally at geographically dispersed clinical study sites. These clinical studies are intended to establish the overall risk/benefit ratio of the product and provide an adequate basis for product labeling.

Post-approval clinical studies, sometimes referred to as phase 4 clinical studies, may be conducted after initial marketing approval. These clinical studies are used to gain additional experience from the treatment of patients in the intended therapeutic indication, particularly for long-term safety follow-up. For example, the FDA recommends that sponsors of certain gene therapy clinical trials observe subjects for potential gene therapy-related delayed adverse events for a 15-year period, including a minimum of five years of annual examinations followed by ten years of annual queries, either in person or by questionnaire, of study subjects.

During all phases of clinical development, regulatory agencies require extensive monitoring and auditing of all clinical activities, clinical data, and clinical study investigators. Annual progress reports detailing the results of the clinical studies must be submitted to the FDA. Written IND safety reports must be promptly submitted to the FDA, the NIH and the investigators for serious and unexpected adverse events, any findings from other studies, tests in laboratory animals or in vitro testing that suggest a significant risk for human subjects, or any clinically important increase in the rate of a serious suspected adverse reaction over that listed in the protocol or investigator brochure. The sponsor must submit an IND safety report within 15 calendar days after the sponsor determines that the information qualifies for reporting. The sponsor also must notify the FDA of any unexpected fatal or life-threatening suspected adverse reaction within seven calendar days after the sponsor's initial receipt of the information. The FDA or the sponsor or its data safety monitoring board may suspend a clinical study at any time on various grounds, including a finding that the research subjects or patients are being exposed to an unacceptable health risk. Similarly, an IRB can suspend or terminate approval of a clinical study at its institution if the clinical study is not being conducted in accordance with the IRB's requirements or if the biological product candidate has been associated with unexpected serious harm to patients.

Concurrent with clinical studies, companies usually complete additional animal studies and must also develop additional information about the physical characteristics of the biological product as well as finalize a process for manufacturing the product in commercial quantities in accordance with GMP requirements. To help reduce the risk of the introduction of adventitious agents with use of biological products, the PHS Act emphasizes the importance of manufacturing control for products whose attributes cannot be precisely defined. The manufacturing process must be capable of consistently producing quality batches of the product candidate and, among other things, the sponsor must develop methods for testing the identity, strength, quality, potency and purity of the final biological product. Additionally, appropriate packaging must be selected and tested and stability studies must be conducted to demonstrate that the biological product candidate does not undergo unacceptable deterioration over its shelf life.

U.S. review and approval processes

After the completion of clinical studies of a biological product, FDA approval of a BLA must be obtained before commercial marketing of the biological product. The BLA must include results of product development, laboratory and animal studies, human studies, information on the manufacture and composition of the product, proposed labeling and other relevant information. In addition, under the Pediatric Research Equity Act ("PREA") as amended, a BLA or supplement to a BLA must contain data to assess the safety and effectiveness of the biological 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 grant deferrals for submission of data or full or partial waivers. Unless otherwise required by regulation, PREA does not apply to any biological product for an indication for which orphan designation has been granted. The testing and approval processes require substantial time and effort and there can be no assurance that the FDA will accept the BLA for filing and, even if filed, that any approval will be granted on a timely basis, if at all.

Within 60 days following submission of the application, the FDA reviews a BLA submitted to determine if it is substantially complete before the agency accepts it for filing. The FDA may refuse to file any BLA that it deems incomplete or not properly reviewable at the time of submission and may request additional information. In this event, the BLA must be resubmitted with the additional information. The resubmitted application also is subject to review before the FDA accepts it for filing. Once the submission is accepted for filing, the FDA begins an in-depth substantive review of the BLA. The FDA reviews the BLA to determine, among other things, whether the proposed product is safe and potent, or effective, for its intended use,

and has an acceptable purity profile, and whether the product is being manufactured in accordance with GMP to assure and preserve the product's identity, safety, strength, quality, potency and purity. The FDA may refer applications for novel biological products or biological products that present difficult questions of safety or efficacy to an advisory committee, typically a panel that includes clinicians and other experts, for review, evaluation and a recommendation as to whether the application should be approved and under what conditions. The FDA is not bound by the recommendations of an advisory committee, but it considers such recommendations carefully when making decisions. During the biological product approval process, the FDA also will determine whether a Risk Evaluation and Mitigation Strategy ("REMS") is necessary to assure the safe use of the biological product. If the FDA concludes a REMS is needed, the sponsor of the BLA must submit a proposed REMS; the FDA will not approve the BLA without a REMS, if required.

Before approving a BLA, the FDA will inspect the facilities at which the product is manufactured. The FDA will not approve the product unless it determines that the manufacturing processes and facilities are in compliance with GMP requirements and adequate to assure consistent production of the product within required specifications. For a gene therapy product, the FDA also will not approve the product if the manufacturer is not in compliance with the GTPs. These are FDA regulations that govern the methods used in, and the facilities and controls used for, the manufacture of human cells, tissues, and cellular and tissue based products ("HCT/Ps") which are human cells or tissue intended for implantation, transplant, infusion, or transfer into a human recipient. The primary intent of the GTP requirements is to ensure that cell and tissue based products are manufactured in a manner designed to prevent the introduction, transmission and spread of communicable disease. FDA regulations also require tissue establishments to register and list their HCT/Ps with the FDA and, when applicable, to evaluate donors through screening and testing. Additionally, before approving a BLA, the FDA will typically inspect one or more clinical sites to assure that the clinical studies were conducted in compliance with IND study requirements and GCP requirements. To assure GMP, GTP and GCP compliance, an applicant must incur significant expenditure of time, money and effort in the areas of training, record keeping, production, and quality control.

Notwithstanding the submission of relevant data and information, the FDA may ultimately decide that the BLA does not satisfy its regulatory criteria for approval and deny approval. Data obtained from clinical studies are not always conclusive and the FDA may interpret data differently than we interpret the same data. If the agency decides not to approve the BLA in its present form, the FDA will issue a complete response letter that usually describes all of the specific deficiencies in the BLA identified by the FDA. The deficiencies identified may be minor, for example, requiring labeling changes, or major, for example, requiring additional clinical studies. Additionally, the complete response letter may include recommended actions that the applicant might take to place the application in a condition for approval. If a complete response letter is issued, the applicant may either resubmit the BLA, addressing all of the deficiencies identified in the letter, withdraw the application, or request a hearing.

If a product receives regulatory approval, the approval may be significantly limited to specific diseases and dosages or the indications for use may otherwise be limited, which could restrict the commercial value of the product. Further, the FDA may require that certain contraindications, warnings or precautions be included in the product labeling. The FDA may impose restrictions and conditions on product distribution, prescribing, or dispensing in the form of a risk management plan, or otherwise limit the scope of any approval. In addition, the FDA may require post marketing clinical studies, sometimes referred to as phase 4 clinical studies, designed to further assess a biological product's safety and effectiveness, and testing and surveillance programs to monitor the safety of approved products that have been commercialized.

One of the performance goals agreed to by the FDA under the PDUFA is to review 90% of standard BLAs in 10 months and 90% of priority BLAs in six months, whereupon a review decision is to be made. The FDA does not always meet its PDUFA goal dates for standard and priority BLAs and its review goals are subject to change from time to time. The review process and the PDUFA goal date may be extended by three months, such as in the case of our BLAs for beti-cel and eli-cel upon FDA request, or the BLA sponsor otherwise provides additional information or clarification regarding information already provided in the submission within the last three months before the PDUFA goal date.

Orphan drug designation

Under the Orphan Drug Act, the FDA may grant orphan designation to a drug or biological product intended to treat a rare disease or condition, which is generally 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 a drug or biological product available in the United States for this type of disease or condition will be recovered from sales of the product. Orphan product designation must be requested before submitting an NDA or BLA. After the FDA grants orphan product designation, the identity of the therapeutic agent and its potential orphan use are disclosed publicly by the FDA. Orphan product designation does not convey any advantage in or shorten the duration of the regulatory review and approval process.

If a product that has orphan designation subsequently receives the first FDA approval for the disease or condition for which it has such designation, the product is entitled to orphan product exclusivity, which means that the FDA may not approve any other applications to market the same drug or biological product for the same indication for seven years, except in limited circumstances, such as a showing of clinical superiority to the product with orphan exclusivity. Competitors, however, may receive approval of different products for the indication for which the orphan product has exclusivity or obtain approval for the same product but for a different indication for which the orphan product has exclusivity. Orphan product exclusivity also could block the approval of one of our products for seven years if a competitor obtains approval of the same biological product as defined by the FDA or if our product candidate is determined to be contained within the competitor's product for the same indication or disease. If a drug or biological product designated as an orphan product receives marketing approval for an indication broader than what is designated, it may not be entitled to orphan product exclusivity.

Expedited development and review programs

The FDA has a Fast Track program that is intended to expedite or facilitate the process for reviewing new drugs and biological products that meet certain criteria. Specifically, new drugs and biological products are eligible for Fast Track designation if they are intended to treat a serious or life-threatening condition and demonstrate the potential to address unmet medical needs for the condition. Fast Track designation applies to the combination of the product and the specific indication for which it is being studied. The sponsor of a new drug or biologic may request the FDA to designate the drug or biologic as a Fast Track product at any time during the clinical development of the product. Unique to a Fast Track product, the FDA may consider for review sections of the marketing application on a rolling basis before the complete application is submitted, if the sponsor provides a schedule for the submission of the sections of the application, the FDA agrees to accept sections of the application and determines that the schedule is acceptable, and the sponsor pays any required user fees upon submission of the first section of the application.

Any product submitted to the FDA for marketing, including under a Fast Track program, may be eligible for other types of FDA programs intended to expedite development and review, such as priority review and accelerated approval. Under the Breakthrough Therapy program, products intended to treat a serious or life-threatening disease or condition may be eligible for the benefits of the Fast Track program when preliminary clinical evidence demonstrates that such product may have substantial improvement on one or more clinically significant endpoints over existing therapies. Additionally, FDA will seek to ensure the sponsor of a breakthrough therapy product receives timely advice and interactive communications to help the sponsor design and conduct a development program as efficiently as possible. Any product is eligible for priority review if it has the potential to provide safe and effective therapy where no satisfactory alternative therapy exists or a significant improvement in the treatment, diagnosis or prevention of a disease compared to marketed products. The FDA will attempt to direct additional resources to the evaluation of an application for a new drug or biological product designated for priority review in an effort to facilitate the review. Additionally, a product may be eligible for accelerated approval. Drug or biological products studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit over existing treatments may receive accelerated approval, which means that they may be approved on the basis of adequate and well-controlled clinical studies establishing that the product has an effect on a surrogate endpoint that is reasonably likely to predict a clinical benefit, or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity. As a condition of approval, the FDA may require that a sponsor of a drug or biological product receiving accelerated approval perform adequate and well-controlled post-marketing clinical studies. In addition, the FDA currently requires as a condition for accelerated approval pre-approval of promotional materials, which could adversely impact the timing of the commercial launch of the product. Fast Track designation, Breakthrough Therapy designation, priority review and accelerated approval do not change the standards for approval but may expedite the development or approval process.

Regenerative medicine advanced therapies designation

As part of the 21st Century Cures Act, Congress amended the FD&C Act to facilitate an efficient development program for, and expedite review of regenerative medicine advanced therapies, which include cell and gene therapies, therapeutic tissue engineering products, human cell and tissue products, and combination products using any such therapies or products. Regenerative medicine advanced therapies do not include those human cells, tissues, and cellular and tissue based products regulated solely under section 361 of the Public Health Service Act and 21 CFR Part 1271. This program is intended to facilitate efficient development and expedite review of regenerative medicine therapies, which are intended to treat, modify, reverse, or cure a serious or life-threatening disease or condition and qualify for RMAT designation. A drug sponsor may request that FDA designate a drug as a RMAT concurrently with or at any time after submission of an IND. FDA has 60 calendar days to determine whether the drug meets the criteria, including whether there is preliminary clinical evidence indicating that the drug has the potential to address unmet medical needs for a serious or life-threatening disease or condition. A BLA for a regenerative medicine therapy that has received RMAT designation may be eligible for priority review or accelerated approval through use of surrogate or intermediate endpoints reasonably likely to predict long-term clinical benefit,

or reliance upon data obtained from a meaningful number of sites. Benefits of RMAT designation also include early interactions with FDA to discuss any potential surrogate or intermediate endpoint to be used to support accelerated approval. A regenerative medicine therapy with RMAT designation that is granted accelerated approval and is subject to post-approval requirements may fulfill such requirements through the submission of clinical evidence from clinical studies, patient registries, or other sources of real world evidence, such as electronic health records; the collection of larger confirmatory data sets; or post-approval monitoring of all patients treated with such therapy prior to its approval.

Post-approval requirements

Maintaining compliance with applicable federal, state, and local statutes and regulations requires the expenditure of substantial time and financial resources. Rigorous and extensive FDA regulation of biological products continues after approval, particularly with respect to GMP. We will rely, and expect to continue to rely, on third parties for the production of clinical and commercial quantities of any future products that we may commercialize. Manufacturers of our products are required to comply with applicable requirements in the GMP regulations, including quality control and quality assurance and maintenance of records and documentation. Other post-approval requirements applicable to biological products, include reporting of GMP deviations that may affect the identity, potency, purity and overall safety of a distributed product, record-keeping requirements, reporting of adverse effects, reporting updated safety and efficacy information, and complying with electronic record and signature requirements. After a BLA is approved, the product also may be subject to official lot release. 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 a summary of the history of manufacture of the lot and the results of all of the manufacturer's tests performed on the lot. The FDA also may perform certain confirmatory tests on lots of some products, such as viral vaccines, 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.

Biological product manufacturers and other entities involved in the manufacture and distribution of approved biological products are required to register their establishments with the FDA and certain state agencies, and are subject to periodic unannounced inspections by the FDA and certain state agencies for compliance with GMPs and other laws. Accordingly, manufacturers must continue to expend time, money, and effort in the area of production and quality control to maintain GMP compliance. Discovery of problems with a product after approval may result in restrictions on a product, manufacturer, or holder of an approved BLA, including withdrawal of the product from the market. In addition, changes to the manufacturing process or facility generally require prior FDA approval before being implemented and other types of changes to the approved product, such as adding new indications and additional labeling claims, are also subject to further FDA review and approval. In addition, companies that manufacture or distribute drug or biological products or that hold approved BLAs must comply with other regulatory requirements, including submitting annual reports, reporting information about adverse drug experiences, and maintaining certain records. Newly discovered or developed safety or effectiveness data may require changes to a drug's approved labeling, including the addition of new warnings and contraindications, and also may require the implementation of other risk management measures, including a REMS or the conduct of post-marketing studies to assess a newly-discovered safety issue.

We also must comply with the FDA's advertising and promotion requirements, such as those related to direct-to-consumer advertising and advertising to healthcare professionals, the prohibition on promoting products for uses or in patient populations that are not described in the product's approved labeling (known as "off-label use"), industry-sponsored scientific and educational activities, and promotional activities involving the internet. Discovery of previously unknown problems or the failure to comply with the applicable regulatory requirements may result in restrictions on the marketing of a product or withdrawal of the product from the market as well as possible civil or criminal sanctions. Failure to comply with the applicable U.S. requirements at any time during the product development process, approval process or after approval, may subject an applicant or manufacturer to administrative or judicial civil or criminal sanctions and adverse publicity. Consequences could include refusal to approve pending applications, withdrawal of an approval, clinical hold, warning or untitled letters, product recalls, product seizures, total or partial suspension of production or distribution, injunctions, fines, refusals of government contracts, mandated corrective advertising or communications with healthcare professionals, debarment, restitution, disgorgement of profits, or civil or criminal penalties. Any agency or judicial enforcement action could have a material adverse effect on us.

U.S. patent term restoration and marketing exclusivity

Depending upon the timing, duration and specifics of the FDA approval of the use of our product candidates, some of our U.S. patents may be eligible for limited patent term extension under the Drug Price Competition and Patent Term Restoration

Act of 1984, commonly referred to as the Hatch-Waxman Amendments. The Hatch-Waxman Amendments permit a patent restoration term of up to five years as compensation for patent term lost during product development and the FDA regulatory review process. However, patent term restoration cannot extend the remaining term of a patent beyond a total of 14 years from the product's approval date. The patent term restoration period is generally one-half the time between the effective date of an IND and the submission date of a BLA plus the time between the submission date of a BLA and the approval of that application. Only one patent applicable to an approved biological product is eligible for the extension and the application for the extension must be submitted prior to the expiration of the patent. The U.S. PTO, in consultation with the FDA, reviews and approves the application for any patent term extension or restoration. In the future, we may intend to apply for restoration of patent term for one of our currently owned or licensed patents to add patent life beyond its current expiration date, depending on the expected length of the clinical studies and other factors involved in the filing of the relevant BLA.

A biological product can obtain pediatric market exclusivity in the United States. Pediatric exclusivity, if granted, adds six months to existing exclusivity periods and patent terms. This six-month exclusivity, which runs from the end of other exclusivity protection or patent term, may be granted based on the voluntary completion of a pediatric study in accordance with an FDA-issued "Written Request" for such a study.

The Patient Protection and Affordable Care Act (the "Affordable Care Act") signed into law on March 23, 2010, includes a subtitle called the Biologics Price Competition and Innovation Act of 2009 which created an abbreviated approval pathway for biological products shown to be similar to, or interchangeable with, an FDA-licensed reference biological product. This amendment to the PHS Act attempts to minimize duplicative testing. Biosimilarity, which requires that there be no clinically meaningful differences between the biological product and the reference product in terms of safety, purity, and potency, can be shown through analytical studies, animal studies, and a clinical study or studies. Interchangeability requires that a product is biosimilar to the reference product and the product must demonstrate that it can be expected to produce the same clinical results as the reference product and, for products administered multiple times, 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. However, complexities associated with the larger, and often more complex, structure of biological products, as well as the process by which such products are manufactured, pose significant hurdles to implementation that are still being worked out by the FDA.

A reference biologic is granted twelve years of exclusivity from the time of first licensure of the reference product. The first biologic product submitted under the abbreviated approval pathway that is determined to be interchangeable with the reference product has exclusivity against other biologics submitting under the abbreviated approval pathway for the lesser of (i) one year after the first commercial marketing, (ii) 18 months after approval if there is no legal challenge, (iii) 18 months after the resolution in the applicant's favor of a lawsuit challenging the biologics' patents if an application has been submitted, or (iv) 42 months after the application has been approved if a lawsuit is ongoing within the 42-month period.

Healthcare and Privacy Laws

In addition to restrictions on marketing of pharmaceutical products, several other types of state/ federal laws and trade association membership codes of conduct have been applied to restrict certain marketing practices in the pharmaceutical industry in recent years. These laws include Anti-Kickback and false claims statutes. The U.S. federal healthcare program Anti-Kickback statute prohibits, among other things, knowingly and willfully offering, paying, soliciting or receiving remuneration, directly or indirectly, in cash or in kind, to induce or in return for purchasing, leasing, ordering or arranging for or recommending the purchase, lease or order of any healthcare item or service reimbursable, in whole or in part, under Medicare, Medicaid or other federally financed healthcare programs. This statute has been interpreted to apply to arrangements between pharmaceutical manufacturers on one hand and prescribers, purchasers, and formulary managers on the other. A person or entity need not have actual knowledge of the federal Anti-Kickback Statute or specific intent to violate it in order to have committed a violation. Violations are subject to civil and criminal fines and penalties for each violation, plus up to three times the remuneration involved, imprisonment, and exclusion from government healthcare programs. Although there are a number of statutory exemptions and regulatory safe harbors protecting certain common activities from prosecution, the exemptions and safe harbors are drawn narrowly and practices that involve remuneration to those who prescribe, purchase, or recommend pharmaceutical and biological products, including certain discounts, or engaging healthcare professionals or patients as speakers or consultants, may be subject to scrutiny if they do not fit squarely within the exemption or safe harbor. Our practices may not in all cases meet all of the criteria for safe harbor protection from anti-kickback liability. Moreover, there are no safe harbors for many common practices, such as educational and research grants or patient assistance programs.

The U.S. federal civil False Claims Act prohibits, among other things, any person from knowingly presenting, or causing to be presented, a false or fraudulent claim for payment of government funds, or knowingly making, using, or causing to be made or used, a false record or statement material to an obligation to pay money to the government or knowingly concealing or

knowingly and improperly avoiding, decreasing, or concealing an obligation to pay money to the federal government. Manufacturers can be held liable under the False Claims Act even when they do not submit claims directly to government payers if they are deemed to "cause" the submission of false or fraudulent claims. The False Claims Act also permits a private individual acting as a "whistleblower" to bring actions on behalf of the federal government alleging violations of the False Claims Act and to share in any monetary recovery. In recent years, several pharmaceutical and other healthcare companies have faced enforcement actions under the federal False Claims Act for, among other things, allegedly submitting false or misleading pricing information to government health care programs and providing free product to customers with the expectation that the customers would bill federal programs for the product. Other companies have faced enforcement actions for causing false claims to be submitted because of the company's marketing the product for unapproved, and thus non-reimbursable, uses. Federal enforcement agencies also have shown 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. In addition, the Affordable Care Act amended federal law to provide that the government may assert that a claim including items or services resulting from a violation of the federal Anti-Kickback statute constitutes a false or fraudulent claim for purposes of the federal civil False Claims Act. Criminal prosecution is possible for making or presenting a false or fictitious or fraudulent claim to the federal government.

The Health Insurance Portability and Accountability Act of 1996 ("HIPAA") also created several new federal crimes, including healthcare fraud and false statements relating to healthcare matters. The healthcare fraud statute prohibits knowingly and willfully executing a scheme to defraud any healthcare benefit program, including private third-party payers. The false statements statute prohibits knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false, fictitious or fraudulent statement in connection with the delivery of or payment for healthcare benefits, items or services. Similar to the federal Anti-Kickback Statute, a person or entity does not need to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation.

The U.S. federal Physician Payment Sunshine Act, being implemented as the Open Payments Program, requires certain manufacturers of drugs, devices, biologics and medical supplies to engage in extensive tracking of payments and other transfers of value to prescribers and teaching hospitals, including physician ownership and investment interests, and public reporting of such data. Effective January 1, 2022, these reporting obligations extend to include transfers of value made to certain non-physician providers such as physician assistants and nurse practitioners. Pharmaceutical and biological manufacturers with products for which payment is available under Medicare, Medicaid or the State Children's Health Insurance Program are required to track such payments, and must submit a report on or before the 90th day of each calendar year disclosing reportable payments made in the previous calendar year. A number of other countries, states and municipalities have also implemented additional payment tracking and reporting requirements, which if not done correctly may result in additional penalties.

In addition, the U.S. Foreign Corrupt Practices Act ("FCPA") prohibits corporations and individuals from engaging in certain activities to obtain or retain business or to influence a person working in an official capacity. It is illegal to pay, offer to pay or authorize the payment of anything of value to any official of another country, government staff member, political party or political candidate in an attempt to obtain or retain business or to otherwise influence a person working in that capacity. In many other countries, healthcare professionals who prescribe pharmaceuticals are employed by government entities, and the purchasers of pharmaceuticals are government entities. Our dealings with these prescribers and purchasers may be subject to the FCPA.

HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act of 2009 ("HITECH") and their respective implementing regulations, including the Final Omnibus Rule published in January 2013, impose requirements on certain covered healthcare providers, health plans, and healthcare clearinghouses as well as their respective business associates that perform services for them that involve the use, or disclosure of, individually identifiable health information, relating to the privacy, security and transmission of individually identifiable health information. HITECH also created new tiers of civil monetary penalties, amended HIPAA to make civil and criminal penalties directly applicable to business associates, and gave state attorneys general new authority to file civil actions for damages or injunctions in federal courts to enforce the federal HIPAA laws and seek attorneys' fees and costs associated with pursuing federal civil actions. In California the California Consumer Protection Act ("CCPA"), which went into effect on January 1, 2020, establishes a new privacy framework for covered businesses by creating an expanded definition of personal information, establishing new data privacy rights for consumers in the State of California, imposing special rules on the collection of consumer data from minors, and creating a new and potentially severe statutory damages framework for violations of the CCPA and for businesses that fail to implement reasonable security procedures and practices to prevent data breaches. While clinical trial data and information governed by HIPAA are currently exempt from the current version of the CCPA, other personal information may be applicable and possible changes to the CCPA may broaden its scope.

The majority of states also have statutes or regulations similar to the federal anti-kickback and false claims laws, which apply to items and services reimbursed under Medicaid and other state programs, or, in several states, apply regardless of the payer. Several states now require pharmaceutical companies to report expenses relating to the marketing and promotion of pharmaceutical products in those states and to report gifts and payments to individual health care providers in those states. Some of these states also prohibit certain marketing-related activities including the provision of gifts, meals, or other items to certain health care providers. In addition, some state laws require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government in addition to requiring manufacturers to report information related to payments to physicians and other healthcare providers, marketing expenditures, and drug pricing information. Certain state and local laws require the registration of pharmaceutical sales representatives. State and foreign laws, including for example the European Union General Data Protection Regulation, also govern the privacy and security of health information in some circumstances, many of which differ from each other in significant ways and often are not preempted by HIPAA, thus complicating compliance efforts.

Because of the breadth of these various healthcare and privacy laws, it is possible that some of our business activities could be subject to challenge under one or more of such laws. Such a challenge could have material adverse effects on our business, financial condition and results of operations. In the event governmental authorities conclude that our business practices do not comply with current or future statutes, regulations or case law involving applicable fraud and abuse or other healthcare and privacy laws and regulations, they may impose sanctions under these laws, which are potentially significant and may include civil monetary penalties, damages, exclusion of an entity or individual from participation in government healthcare programs, criminal fines and imprisonment, as well as the potential curtailment or restructuring of our operations. Even if we are 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 harm our financial condition and divert the attention of our management from operating our business.

Pricing, Coverage and Reimbursement

Significant uncertainty exists as to the coverage and reimbursement status of any drug products for which we obtain regulatory approval. In the United States, sales of any products for which we may receive regulatory approval for commercial sale will depend in part on the availability of reimbursement from third-party payers, including governments. In the United States, no uniform policy of coverage and reimbursement for drug products exists among third-party payers. Therefore, coverage and reimbursement for drug products can differ significantly from payer to payer. Third-party payers can include government healthcare systems, managed care providers, private health insurers and other organizations. The process for determining whether a payer will provide coverage for a drug product may be separate from the process for setting the price or reimbursement rate that the payer will pay for the drug product. Third-party payers may limit coverage to specific drug products on an approved list, or formulary, which might not include all of the FDA-approved drugs for a particular indication. Third-party payers may provide coverage, but place stringent limitations on such coverage, such as requiring alternative treatments to be tried first. These third-party payers are increasingly challenging the price and examining the medical necessity and cost-effectiveness of medical products and services, in addition to their safety, efficacy, and overall value. In addition, significant uncertainty exists as to the reimbursement status of newly approved healthcare products. We may need to conduct expensive pharmacoeconomic studies in order to demonstrate the medical necessity and cost-effectiveness of our products, in addition to incurring the costs required to obtain FDA approvals. Our product candidates may not be considered medically reasonable or necessary or cost-effective. Even if a drug product is covered, a payer's decision to provide coverage for a drug product does not imply that an adequate reimbursement rate will be approved. For products administered under the supervision of a physician, obtaining coverage and adequate reimbursement may be particularly difficult because of the higher prices often associated with such drugs. Additionally, separate reimbursement for the product itself or the treatment or procedure in which the product is used may not be available, which may impact physician utilization. Adequate third-party reimbursement may not be available to enable us to maintain price levels sufficient to realize an appropriate return on our investment in product development.

Federal, state and local governments in the United States continue to consider legislation to limit the growth of healthcare costs, including the cost of prescription drugs. Specifically, there have been several recent U.S. Congressional inquiries and proposed federal and state legislation designed to, among other things, bring more transparency to drug pricing, reduce the cost of prescription drugs under Medicare, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for drugs. On January 2, 2013, the American Taxpayer Relief Act of 2012 was signed into law, which, among other things, further reduced Medicare payments to several types of providers and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. Future legislation could limit payments for pharmaceuticals such as the drug candidates that we are developing.

The marketability of any products for which we receive regulatory approval for commercial sale may suffer if the government and third-party payers fail to provide adequate coverage and reimbursement. In addition, the emphasis on managed care in the United States has increased and we expect will continue to exert downward pressure on pharmaceutical pricing. Coverage policies, third-party reimbursement rates and pharmaceutical pricing regulations 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.

We have proposed novel payment models, including outcomes-based arrangements with payments over time, to assist with realizing the value and sharing the risk of a potential one-time treatment, such as for beti-cel. While we are engaged in discussions with potential payers, there is no assurance that these payment models will be widely adopted by payers. Even with these payment models, there may be substantial resistance to the cost of our products by payers and the public generally. These payment models may not be sufficient for payers to grant coverage, and if we are unable to obtain adequate coverage for our products, the adoption of our products and access for patients may be limited. In addition, to the extent reimbursement for our products is subject to outcomes-based arrangements, our future revenues from product sales will be more at risk. These factors could affect our ability to successfully commercialize our products and adversely impact our business, financial condition, results of operations and prospects.

COVID-19

Beginning in late 2019, the outbreak of a novel strain of coronavirus ("COVID-19") has evolved into a global pandemic. As a result, we continue to experience disruptions and increased risk in our operations and those of third parties upon whom we rely, which may materially and adversely affect our business. These include disruptions and risks related to the conduct of our clinical trials, manufacturing, and commercialization efforts, as policies at various clinical sites and federal, state, local and foreign laws, rules and regulations continue to evolve, including quarantines, travel restrictions, and direction of healthcare resources toward pandemic response efforts. We continue to evaluate the impact of the COVID-19 global pandemic on patients, healthcare providers and our employees, as well as our operations and the operations of our business partners and healthcare communities. In response to the COVID-19 pandemic, we have implemented policies at our location to mitigate the risk of exposure to COVID-19 by our personnel, including restrictions on the number of staff in any given research and development laboratory or manufacturing facility, a work-from-home policy applicable to the majority of our personnel, and a phased approach to bringing personnel back to our location over time. Further, we are working with our clinical study sites to understand the duration and scope of the impact on enrollment, develop protocols to help mitigate the impact of the COVID-19 pandemic, and other activities for our ongoing clinical studies. Refer to Management’s Discussion and Analysis of Financial Condition and Results of Operations (Part II, Item 7 of this Form 10-K) for further discussion regarding the impact of COVID-19 on our fiscal year 2021 financial results.

The extent to which the COVID-19 pandemic impacts our business going forward will depend on numerous evolving factors we cannot reliably predict, including the duration and scope of the pandemic; governmental, business, and individuals' actions in response to the pandemic; and the impact on economic activity including the possibility of recession or financial market instability. Refer to Risk Factors (Part I, Item 1A of this Form 10-K) for a discussion of these factors and other risks.

Human capital

As of January 31, 2022, we had 518 full-time employees, 80 of whom have Ph.D., M.D. or Pharm.D. degrees. Of these full-time employees, 330 employees are engaged in research and development activities and 188 employees are engaged in commercial, finance, legal, business development, human resources, information technology, facilities and other general administrative functions. We have no collective bargaining agreements with our employees and we have not experienced any work stoppages. We consider our relations with our employees to be good.

Compensation and benefits programs

Our compensation programs are designed to align our employees' interests with the drivers of growth and stockholder returns by supporting the Company's achievement of its primary business goals. The Company's goal is to attract and retain employees whose talents, expertise, leadership, and contributions are expected to sustain growth and drive long-term stockholder value. Consequently, we provide employee wages that are competitive within our industry, and we engage a nationally-recognized outside compensation and benefits consulting firm to independently evaluate the effectiveness of our compensation and benefit programs and to provide benchmarking against our peers within the industry. We seek to align our employees' interests with those of stockholders by linking annual changes in compensation to overall Company performance, as well as each individual’s contribution to the results achieved. The emphasis on overall Company performance is intended to align the employee’s financial interests with the interests of stockholders. We are also committed to providing comprehensive

benefit options and it is our intention to offer benefits that will allow our employees and their families to live healthier and more secure lives. All employees are eligible for medical, dental, and vision insurance, paid and unpaid leaves, employee stock purchase plan, 401(k) plan, and group life and disability coverage.

Employee development and training

The development, recruitment and retention of our employees is a critical success factor for our company. To ensure we provide a meaningful experience for our employees, we regularly measure organizational culture and engagement, to build on the competencies that are important for our future success. We have a robust talent and succession planning process and have established programs to support the talent pipeline for critical roles throughout our organization, to help us identify, foster, and retain high performing employees. To empower our employees to realize their potential at bluebird, we provide a range of development programs, opportunities and resources they need to be successful, including leveraging formal leadership training and coaching to improve performance and retention, increase our organizational learning and support the promotion of our current employees.

Diversity

We are committed to taking action to help address racial injustice and inequality. With significant input from employees and leaders at bluebird, we have adopted corporate goals to increase diversity and representation across our employee population.

Corporate Information

We were incorporated in Delaware in April 1992 under the name Genetix Pharmaceuticals, Inc., and subsequently changed our name to bluebird bio, Inc. in September 2010. In November 2021, we completed a tax-free spin-off of our oncology programs and portfolio, including idecabtagene vicleucel, a CAR-T cell therapy for the treatment of relapsed and refractory multiple myeloma marketed as ABECMA pursuant to a co-promotion and co-development agreement with Bristol-Myers Squibb Company, into a separate independent publicly traded company, 2seventy bio, Inc., or 2seventy. Our mailing address and executive offices are located at 60 Binney Street, Cambridge, Massachusetts and our telephone number at that address is (339) 499-9300. Following our move to our new corporate headquarters expected in the second quarter of 2022, our mailing address and executive offices will be 455 Grand Union Boulevard, Somerville, Massachusetts, and our telephone number at that address will be (339) 499-9300. We maintain an Internet website at the following address: www.bluebirdbio.com. The information on our website is not incorporated by reference in this annual report on Form 10-K or in any other filings we make with the Securities and Exchange Commission ("SEC").

We make available on or through our website certain reports and amendments to those reports that we file with or furnish to the SEC in accordance with the Securities Exchange Act of 1934, as amended. These include our annual reports on Form 10-K, our quarterly reports on Form 10-Q, and our current reports on Form 8-K, and amendments to those reports filed or furnished pursuant to Section 13(a) or 15(d) of the Exchange Act. We make this information available on or through our website free of charge as soon as reasonably practicable after we electronically file the information with, or furnish it to, the SEC.

Item 1A. Risk Factors

An investment in shares of our common stock involves a high degree of risk. You should carefully consider the following information about these risks, together with the other information appearing elsewhere in this Annual Report on Form 10-K, including our financial statements and related notes hereto, before deciding to invest in our common stock. The occurrence of any of the following risks could have a material adverse effect on our business, financial condition, results of operations and future growth prospects. In these circumstances, the market price of our common stock could decline, and you may lose all or part of your investment.

We have incurred significant losses since our inception and anticipate that we will continue to incur significant losses for the foreseeable future.

We have incurred net losses in each year since our inception in 1992, including net losses from continuing operations of $562.6 million for the year ended December 31, 2021. As of December 31, 2021, we had an accumulated deficit of $3.72 billion. The amount of our future net losses will depend, in part, on the rate of our future expenditures and our ability to generate revenues. We have devoted significant financial resources to research and development, including our clinical and

preclinical development activities, which we expect to continue for the foreseeable future. To date, we have financed our operations primarily through the sale of equity securities and, to a lesser extent, through collaboration agreements and grants from governmental agencies and charitable foundations. We have not generated material revenues from the sale of beti-cel in the European Union, and we do not expect to generate meaningful product revenues in the foreseeable future until we obtain marketing approval for products in the United States and following any potential commercial launch. Following marketing approval, our future revenues will depend upon the size of any markets in which our potential products have received approval, and our ability to achieve sufficient market acceptance, reimbursement from third-party payers and adequate market share for our potential products in those markets.

We expect to continue to incur significant expenses and operating losses for the foreseeable future. We anticipate that our expenses will increase substantially if and as we:

- continue our research and clinical development of our product candidates;
- establish capabilities to support our commercialization efforts, including establishing a sales, marketing and distribution infrastructure in the United States, and to commercialize products for which we may obtain marketing approval;
- obtain, build and expand manufacturing capacity, including capacity at third-party manufacturers;
- initiate additional research, preclinical, clinical or other programs as we seek to identify and validate additional product candidates;
- acquire or in-license other product candidates and technologies;
- maintain, protect and expand our intellectual property portfolio;
- attract and retain skilled personnel; and
- experience any delays or encounter issues with any of the above.

The net losses we incur may fluctuate significantly from quarter to quarter and year to year, such that a period-to-period comparison of our results of operations may not be a good indication of our future performance. In any particular quarter or quarters, our operating results could be below the expectations of securities analysts or investors, which could cause our stock price to decline.

There is substantial doubt regarding our ability to continue as a going concern. We will need to raise additional funding, which may not be available on acceptable terms, or at all. Failure to obtain this necessary capital when needed may force us to delay, limit or terminate our product development efforts or other operations.

We are currently advancing our late-stage programs in severe genetic diseases through clinical development. Developing and commercializing gene therapy products is expensive, and we do not expect to generate meaningful product revenues in the foreseeable future until we obtain marketing approval for products in the United States and following any potential commercial launch.

As of December 31, 2021, our cash, cash equivalents and marketable securities were $396.6 million. As of completion of the separation, we had restricted cash, cash and cash equivalents, and marketable securities of approximately $507.2 million. Based on our current business plan, there is substantial doubt regarding our ability to continue as a going concern for a period of one year after the date that our financial statements for the year ended December 31, 2021 are issued. Our fundraising efforts to raise additional funding may divert our management from their day-to-day activities, which may adversely affect our ability to develop and commercialize our potential products following marketing approval if and when obtained. In addition, we cannot guarantee that financing will be available in sufficient amounts or on terms acceptable to us, if at all. Moreover, the terms of any financing may adversely affect the holdings or the rights of our stockholders and the issuance of additional securities, whether equity or debt, by us, or the possibility of such issuance, may cause the market price of our shares to decline. The sale of additional equity or convertible securities would dilute all of our stockholders. The incurrence of indebtedness would result in increased fixed payment obligations and we may be required to agree to certain restrictive covenants, such as limitations on our ability to incur additional debt, limitations on our ability to acquire, sell or license intellectual property rights and other operating restrictions that could adversely impact our ability to conduct our business. We could also be required to seek funds through arrangements with collaborative partners or otherwise at an earlier stage than otherwise would be desirable and we may be required to relinquish rights to some of our technologies or product candidates or otherwise agree to terms unfavorable to us, any of which may have a material adverse effect on our business, operating results and prospects.

If we are unable to obtain funding on a timely basis, or if revenues from collaboration arrangements or product sales are less than we have projected, we may be required to further revise our business plan and strategy, which may result in us significantly curtailing, delaying or discontinuing one or more of our research or development programs or the commercialization of any product candidates or may result in our being unable to expand our operations or otherwise capitalize on our business opportunities. As a result, our business, financial condition and results of operations could be materially affected.

Our future success depends on our ability to retain key employees and to attract, retain and motivate qualified personnel.

We are highly dependent on our executive team and key employees, the loss of whose services may adversely impact the achievement of our objectives. While we have entered into employment agreements with each of our executive officers, any of them could leave our employment at any time, as all of our employees are "at will" employees. Recruiting and retaining other qualified employees, consultants and advisors for our business, including scientific and technical personnel, will also be critical to our success. There is currently a shortage of skilled executives in our industry, which is likely to continue. As a result, competition for skilled personnel is intense and our turnover rate has been high. We may not be able to attract and retain personnel on acceptable terms given the competition among numerous pharmaceutical and biotechnology companies for individuals with similar skill sets. In addition, our financial condition and recent delays in our late-stage programs have made it more challenging to recruit and retain qualified personnel. The inability to recruit or loss of the services of any executive, key employee, consultant or advisor may impede the progress of our research, development and commercialization objectives.

Insertional oncogenesis is a risk of gene therapies using viral vectors that can integrate into the genome, and several patients with CALD treated with eli-cel in our clinical studies have been diagnosed with MDS likely mediated by Lenti-D LVV insertion. These events may require us to halt or delay further clinical development of our product candidates, such as eli-cel, or to suspend or cease commercialization following marketing approval, and the commercial potential of our product candidates may be materially and negatively impacted.

A potentially significant risk in any gene therapy product using viral vectors that can integrate into the genome is that the vector will insert in or near cancer-causing genes, leading to the proliferation of certain cellular clones that can cause cancer in the patient, known as insertional oncogenesis. Several patients with CALD treated with eli-cel in our clinical studies have been diagnosed with MDS likely mediated by Lenti-D LVV insertion, and as a result, the FDA placed our clinical studies of eli-cel on clinical hold. On February 23, 2022, the FDA notified us that the clinical hold on the eli-cel program would remain in place, and requested additional information about safety events and monitoring in the eli-cel clinical program. We have no assurances as to whether we will successfully resolve the clinical hold. In addition, we cannot make assurances that additional patients treated with eli-cel, beti-cel or lovo-cel in the clinical or commercial setting will not exhibit clonal predominance in the future, or that additional patients will not be diagnosed with MDS, leukemia or lymphoma. There is also the potential risk of delayed adverse events following exposure to gene therapy products due to persistent biological activity of the genetic material or other components of products used to carry the genetic material. The FDA has stated that LVV possess characteristics that may pose high risks of delayed adverse events. If any such adverse events occur, further advancement of our clinical studies could be halted or delayed, we may not receive marketing approval for our product candidates, and we may be unable to commercialize any approved product. It is possible that upon occurrence or recurrence of any of these events, the FDA may place one or more of our programs on hold, impose requirements that result in delays for regulatory approval for one or more of our programs, require risk evaluation or mitigation strategies as a condition for regulatory approval, or may cause us to cease commercialization following the receipt of any marketing approval. If any of these were to occur, the commercial potential of our programs may be materially and negatively impacted.

Furthermore, treatment with our potential products involve chemotherapy or myeloablative treatments which can cause side effects or adverse events that may impact the perception of the potential benefits of our potential products. For instance, MDS leading to acute myeloid leukemia is a known risk of certain myeloablative regimens. Additionally, beti-cel, eli-cel, or lovo-cel, the procedures associated with their administration, or with the collection of patients' cells, could potentially cause other adverse events that have not yet been predicted. The inclusion of patients with significant underlying medical problems in our clinical studies may result in deaths, or other adverse medical events, due to other therapies or medications that such patients may be using, or the progression of their disease. For instance, it is possible that the events of MDS and acute myeloid leukemia previously reported in our HGB-206 clinical study were caused by lovo-cel, in combination with underlying SCD, transplant procedure, and stress on the bone marrow following drug product infusion. Even if a product such as lovo-cel, eli-cel or beti-cel is ultimately approved, such safety events may result in the product being removed from the market or its market opportunity being significantly reduced. Other patients receiving our product candidates may develop leukemia, lymphoma, or MDS in the future, which may negatively impact the commercial prospects of our product candidates. Any of these events could impair our ability to develop or commercialize our product candidates, and their commercial potential may be materially and negatively impacted.

Risks related to commercialization

We have limited experience as a commercial company and the marketing and sale of beti-cel, eli-cel, and lovo-cel following marketing approval, if and when obtained, may be unsuccessful or less successful than anticipated.

We have limited experience as a commercial company. To-date, our experience as a commercial company has been limited to commercializing beti-cel in Europe. In August 2021, we announced that we are focusing our efforts in the near-term on the U.S. market and plan to execute an orderly wind down of our European operations. Consequently, there is limited information about our ability to overcome many of the risks and uncertainties encountered by companies commercializing products in the biopharmaceutical industry. To execute our business plan, we will need to successfully:

- gain regulatory approval to commercialize beti-cel, eli-cel, and lovo-cel in the United States;
- obtain adequate pricing and reimbursement for beti-cel, eli-cel, and lovo-cel across payers in the United States;
- establish and maintain, in the regions where we hope to treat patients, relationships with qualified treatment centers who will be treating the patients who receive beti-cel, eli-cel, and lovo-cel;
- manage our spending in the conduct of our clinical trials, seek marketing approvals, and engage in commercialization efforts, including for any extension of marketing approval of beti-cel, eli-cel, and lovo-cel; and
- initiate, develop and maintain successful strategic alliances.

If we are not successful in accomplishing these objectives, we may not be able to develop and commercialize beti-cel, eli-cel, or lovo-cel, raise capital, expand our business, or continue our operations.

The commercial success of beti-cel, eli-cel, and lovo-cel following marketing approval, if and when obtained, will depend upon the degree of market acceptance by physicians, patients, payers and others in the medical community.

The commercial success of beti-cel, eli-cel, and lovo-cel following marketing approval, if and when obtained, will depend in part on the medical community, patients, and third-party or governmental payers accepting gene therapy products in general, and beti-cel, eli-cel, and lovo-cel, in particular, as medically useful, cost-effective, and safe. Beti-cel, eli-cel, and lovo-cel that we may bring to the market may not gain market acceptance by physicians, patients, payers and others in the medical community. If these products do not achieve an adequate level of acceptance, we may not generate significant product revenue and may not become profitable. The degree of market acceptance of beti-cel, eli-cel, and lovo-cel following marketing approval, if and when obtained, will depend on a number of factors, including:

- the potential efficacy and potential advantages over alternative treatments;
- the prevalence and severity of any side effects, including any limitations or warnings contained in a product's approved labeling;
- the prevalence and severity of any side effects resulting from the chemotherapy and myeloablative treatments associated with the procedure by which our potential products are administered;
- relative convenience and ease of administration;
- 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 and timing of market introduction of competitive products;
- the pricing of our potential products;
- publicity concerning our potential products, or competing products and treatments; and
- sufficient insurance coverage or reimbursement.

Even if a potential product displays a favorable efficacy and safety profile in preclinical and clinical studies, market acceptance of the product will not be known until after it is launched. Our efforts to educate the medical community and payers on the benefits of our potential products may require significant resources and may never be successful. For instance, following marketing approval of beti-cel in the European Union, we did not reach agreement with payers on an acceptable price for reimbursement in our priority markets in Europe, and we are no longer seeking to commercialize our product candidates in

Europe for the foreseeable future. Our efforts to educate the marketplace may require more resources than are required by the conventional technologies marketed by our competitors. Any of these factors may cause beti-cel, eli-cel, or lovo-cel, to be unsuccessful or less successful than anticipated.

If the market opportunities for our potential products are smaller than we believe they are, and if we are not able to successfully identify patients and achieve significant market share, our revenues may be adversely affected and our business may suffer.

We focus our research and product development on treatments for severe genetic diseases. Our projections of both the number of people who have these diseases, as well as the subset of people with these diseases who have the potential to benefit from treatment with our potential products, are based on estimates. These estimates have been derived from a variety of sources, including scientific literature, surveys of clinics, patient foundations, or market research, and may prove to be incorrect. Further, new studies may change the estimated incidence or prevalence of these diseases. The number of patients may turn out to be lower or more difficult to identify than expected. Additionally, the potentially addressable patient population for our potential products may be limited or may not be amenable to treatment with our potential products. For instance, in our lovo-cel and eli-cel programs, we have received notice of safety events of acute myeloid leukemia or myelodysplastic syndrome, and additional such events may be reported in the future. The market opportunity for our gene therapies may be negatively impacted even if our gene therapies ultimately receive marketing approval.

Even if we obtain significant market share for a product within an approved indication, because the potential target populations for our potential products are small, we may never achieve profitability without obtaining marketing approval for additional indications.

Any of these factors may negatively affect our ability to generate revenues from sales of our potential products and our ability to achieve and maintain profitability and, as a consequence, our business may suffer.

We rely on a complex supply chain for beti-cel, eli-cel, and lovo-cel. The manufacture and delivery of LVV and drug products present significant challenges for us, and we may not be able to produce our vector and drug products at the quality, quantities, locations or timing needed to support our clinical programs and commercialization following marketing approval if and when obtained. In addition, we may encounter challenges with engaging or coordinating with qualified treatment centers needed to support commercialization following marketing approval if and when obtained.

We rely on third parties to manufacture the LVV and the drug product for any clinical trials that we conduct, and we intend to rely on third parties for the supply of LVV and drug product for commercialization following any marketing approval, if and when obtained. We have not secured all of the commercial-scale manufacturing capacity that we anticipate requiring for the commercialization of our therapies to meet our forecasts beyond the potential launch, if they should receive marketing approval. If we fail to secure adequate capacity to manufacture our drug products or LVV used in the manufacture of our drug products in accordance with our forecasts beyond the potential launch of our therapies, we may be unable to execute on our development and commercialization plans on the timing that we expect, or at all.

The manufacture of LVV and drug products is complex and requires significant expertise. Even with the relevant experience and expertise, manufacturers of cell therapy products often encounter difficulties in production, particularly in scaling out and validating initial production, managing the transition from clinical manufacturing to manufacturing in the commercial setting, and ensuring that the product meets required specifications. These problems include difficulties with production costs and yields, quality control, including stability of the product, quality assurance testing, operator error, shortages of qualified personnel, as well as compliance with strictly enforced federal, state and foreign regulations. We cannot make any assurances that these problems will not occur in the future, or that we will be able to resolve or address in a timely manner or with available funds problems that occur. Because of this complexity, transitioning production of either LVV or drug products to backup or second source manufacturing, or to internal manufacturing capacity, requires a lengthy technology transfer process and may require additional significant financial expenditures. Furthermore, our cost of goods development is at an early stage. The actual cost to manufacture our LVV and drug products could be greater than we expect and could materially and adversely affect the commercial viability of beti-cel, eli-cel, or lovo-cel. If we or such third-party manufacturers are unable to produce the necessary quantities of LVV and our drug products, or in compliance with GMP or other pertinent regulatory requirements, and within our planned time frame and cost parameters, the development and commercialization of our potential products may be materially harmed, result in delays in our plans or increased capital expenditures.

In addition, any significant disruption in our supplier relationships could harm our business. We source key materials from third parties, either directly through agreements with suppliers or indirectly through our manufacturers who have agreements with suppliers. There are a small number of suppliers for certain key materials that are used to manufacture beti-cel, eli-cel, and

lovo-cel. Such suppliers may not sell these key materials to us or to our manufacturers at the times we need them or on commercially reasonable terms. We do not have any control over the process or timing of the acquisition of these key materials by our manufacturers, and we currently do not have agreements for the commercial supply for all of these key materials.

Additionally, since the HSCs used as starting material for drug products have a limited window of stability following procurement from a patient, we must establish transduction facilities in the regions where we wish to commercialize beti-cel, eli-cel, and lovo-cel following marketing approval, if and when obtained. Establishment of such facilities may be financially impractical or impeded by technical, quality, or regulatory issues related to these new sites and we may also run into technical or scientific issues related to transfer of our transduction process or other developmental issues that we may be unable to resolve in a timely manner or with available funds. We have no assurance as to when drug product manufacturing using cryopreserved apheresis starting material will be available, if ever.

Our commercial strategy is to engage apheresis and transplant centers as qualified treatment centers for the collection of patient HSCs and infusion of the drug product once manufactured. To ensure that the qualified treatment centers are prepared to collect patient HSCs and to ship them to our transduction facilities in accordance with our specifications and regulatory requirements, we train and conduct quality assessments of each center as part of engagement. These qualified treatment centers are the first and last points on our complex supply chain to reach patients in the commercial setting. We may not be able to engage qualified treatment centers in all of the regions in our commercial launch strategy, or we may encounter other challenges or delays in engaging qualified treatment centers. We may fail to manage the logistics of collecting and shipping patient material to the manufacturing site and shipping the drug product back to the patient. Logistical and shipment delays and problems caused by us, our third-party vendors, and other factors not in our control, such as weather, could prevent or delay the manufacture of or delivery of drug product to patients. If our qualified treatment centers fail to perform satisfactorily, we may suffer reputational, operational, and business harm. We are required to maintain a complex chain of identity and chain of custody with respect to patient material as it moves through the manufacturing process, from the qualified treatment center to the transduction facility, and back to the patient. Failure to maintain chain of identity and chain of custody could result in adverse patient outcomes, loss of product or regulatory action.

We have limited sales and distribution experience and limited capabilities for marketing and market access. We expect to invest significant financial and management resources to establish these capabilities and infrastructure to support commercial operations following marketing approval if and when obtained. If we are unable to establish these commercial capabilities and infrastructure or to enter into agreements with third parties to market and sell our potential products, we may be unable to generate sufficient revenue to sustain our business.

We have limited prior sales or distribution experience and limited capabilities for marketing and market access, and we did not generate meaningful product sales following the commercial launch of beti-cel following marketing approval in Europe. To successfully commercialize beti-cel, eli-cel, and lovo-cel following marketing approval in the United States, if and when obtained, we will need to further develop these capabilities. We may need to expand our infrastructure to support commercial operations in the United States, either on our own or with others. Commercializing an autologous gene therapy is resource-intensive and has required, and will continue to require, substantial investment in commercial capabilities. We are competing with companies that currently have extensive and well-funded marketing and sales operations. Without significant commercial experience as a company or the support of a third-party to perform these functions, including marketing and sales functions, we may be unable to compete successfully against these more established companies. Furthermore, a significant proportion of the patient populations for beti-cel, eli-cel, and lovo-cel lies outside of the United States. We currently expect to focus our operations and efforts on markets in the United States and intend to rely heavily on third parties for geographies outside of the United States. We may enter into collaborations with third parties to utilize their mature marketing and distribution capabilities, but we may be unable to enter into agreements on favorable terms, if at all. If we do not enter into collaboration arrangements with third parties to pursue regulatory authorization or commercialization of our programs for markets outside of the United States, or if our future collaborative partners do not commit sufficient resources to such efforts, we may be unable to generate sufficient revenue to sustain our business.

The insurance coverage and reimbursement status of newly-approved products in the United States is uncertain. Due to the novel nature of our technology and the potential for our product to offer lifetime therapeutic benefit in a single administration, we face additional challenges in obtaining adequate pricing and reimbursement for our product. Failure to obtain or maintain adequate coverage and reimbursement for any new or current product could limit our ability to market those products and decrease our ability to generate revenue.

The availability and extent of reimbursement by governmental and private payers is essential for most patients to be able to afford expensive treatments, such as gene therapy products. Sales of our potential products will depend substantially, both domestically and abroad, on the extent to which the costs of our potential products will be paid by health maintenance, managed

care, pharmacy benefit and similar healthcare management organizations, or reimbursed by government health administration authorities, private health coverage insurers and other payers. There is no assurance that the approved prices or reimbursement levels that payers will be willing to pay will be acceptable to us. In addition, because our therapies represent new treatment approaches, the estimation of potential revenues will be complex. For products administered under the supervision of a physician, obtaining reimbursement may be particularly difficult because of the higher prices often associated with such drugs. Additionally, separate reimbursement for the product itself or the treatment or procedure in which the product is used may not be available, which may impact physician utilization.

There is significant uncertainty related to the insurance coverage and reimbursement of newly approved products, including gene therapies that are potential one-time treatments. In the United States, the principal decisions about reimbursement for new medicines are typically made by the Centers for Medicare & Medicaid Services ("CMS") an agency within the U.S. Department of Health and Human Services ("HHS"), as CMS decides whether and to what extent a new medicine will be covered and reimbursed under Medicare. Private payers tend to follow CMS to a substantial degree. It is difficult to predict what CMS will decide with respect to reimbursement for fundamentally novel products such as ours, as there is no body of established practices and precedents for these new products.

Moreover, increasing efforts by governmental and third-party payers to cap or reduce healthcare costs may cause such organizations to limit both coverage and level of reimbursement for new products approved and, as a result, they may not cover or provide adequate payment for beti-cel, eli-cel, or lovo-cel following marketing approval, if and when obtained. We expect to experience pricing pressures in connection with the sale of our potential products, due to the trend toward managed healthcare, the increasing influence of health maintenance organizations and additional legislative changes. Net prices for drugs may be reduced by mandatory discounts or rebates required by government or private payers and by any future relaxation of laws that presently restrict imports of drugs from countries where they may be sold at lower prices than in the United States. The downward pressure on healthcare costs in general, particularly prescription drugs and surgical procedures and other treatments, has become very intense. As a result, increasingly high barriers are being erected to the entry of new products.

Furthermore, because our target patient populations are relatively small, the pricing and reimbursement of our potential products must be adequate to cover the costs to treat and support the treatment of patients. If we are unable to obtain adequate levels of reimbursement, our ability to successfully market and sell our potential products will be adversely affected. Even if coverage is provided, the approved reimbursement amount may not be high enough to allow us to establish or maintain pricing sufficient to realize a sufficient return on our investment.

In addition, the administration of autologous drug products requires procedures for the collection of HSCs from the patient, followed by chemotherapy and myeloablative treatments, before infusion of the engineered cell therapy product. The manner and level at which reimbursement is provided for these services is also important. Inadequate reimbursement for such services may lead to physician resistance and adversely affect our ability to market or sell our product.

Although we have proposed novel payment models, including outcomes-based arrangements with payments over time, to assist with realizing the value and sharing the risk of a potential one-time treatment, we did not reach agreement with payers on an acceptable price for reimbursement in our priority markets in Europe. In addition, to the extent reimbursement for our product is subject to outcomes-based arrangements, the total payments received from product sales may vary, our cash collection of future payments and revenue assumptions from product sales will be at risk, and the timing of revenue recognition may not correspond to the timing of cash collection. We plan on commercializing our product candidates in the United States once approved, and will be subject to price reporting obligations set forth by CMS. To the extent reimbursement for our potential products in the United States by U.S. governmental payers is subject to outcomes-based arrangements, the increased complexity increases the risk that CMS may disagree with the assumptions and judgments that we use in our price reporting calculations, which may result in significant fines and liability.

Collectively, these factors could affect our ability to successfully commercialize our potential products and generate or recognize revenues, which would adversely impact our business, financial condition, results of operations and prospects.

Risks related to the research and development of our product candidates

We cannot predict when or if we will obtain marketing approval to commercialize beti-cel, eli-cel, or lovo-cel, and the marketing approval of our product candidates may ultimately be for more narrow indications than we expect. If our product candidates are not approved in a timely manner or at all for any reason, our business prospects, results of operations, and financial condition would be adversely affected.

Before obtaining marketing approval from regulatory authorities for the commercialization of our product candidates, we must conduct extensive clinical studies to demonstrate the safety, purity and potency, and efficacy, of the product candidates in humans. Clinical testing is expensive, time-consuming and uncertain as to outcome. There is a high failure rate for therapies proceeding through clinical studies. A number of companies in the pharmaceutical and biotechnology industries have suffered significant setbacks in later stage clinical studies even after achieving promising results in earlier stage clinical studies. We cannot guarantee that any clinical studies will be conducted as planned or completed on schedule, if at all. A failure of one or more clinical studies can occur at any stage of testing. Events that may prevent successful or timely completion of clinical development include:

- delays in reaching a consensus with regulatory agencies on study design;
- imposition of a clinical hold by regulatory agencies, after an inspection of our clinical study operations or study sites or due to unforeseen safety issues;
- delays in the testing, validation, manufacturing and delivery of our product candidates to the clinical sites;
- failure to obtain sufficient cells from patients to manufacture enough drug product or achieve target cell doses;
- delays patient enrollment, or in having patients complete participation in a study or return for post-treatment follow-up;
- occurrence of serious adverse events associated with the product candidate that are viewed to outweigh its potential benefits; or
- changes in regulatory requirements and guidance that require amending or submitting new clinical protocols.

We have experienced delays in some of our clinical studies in the past, and we may experience similar delays in the future.

Results from previous or ongoing studies are not necessarily predictive of our future clinical study results, and initial or interim results may not continue or be confirmed upon completion of the study. There is limited data concerning long-term safety and efficacy following treatment with our product candidates. These data, or other positive data, may not continue or occur for these patients or for any future patients in our ongoing or future clinical studies, and may not be repeated or observed in ongoing or future studies involving our product candidates. Furthermore, our product candidates may also fail to show the desired safety and efficacy in later stages of clinical development despite having successfully advanced through initial clinical studies. There can be no assurance that any of these studies will ultimately be successful or support further clinical advancement or marketing approval of our product candidates. For instance, while patients with SCD who have been treated with lovo-cel may experience a reduction of vaso-occlusive events following successful engraftment, there can be no assurance that they will not experience vaso-occlusive events in the future. We have experienced unexpected results in the past, and we may experience unexpected results in the future.

Even if our product candidates demonstrate safety and efficacy in clinical studies, regulatory delays or rejections may be encountered as a result of many factors, including changes in regulatory policy during the period of product development. We may experience delays or rejections based upon additional government regulation from future legislation or administrative action, changes in regulatory agency policy, or additional regulatory feedback or guidance during the period of product development, clinical studies and the review process. The field of cell and gene therapy is evolving, and as more products are reviewed by regulatory authorities, they may impose additional requirements that were not previously anticipated. Regulatory agencies also may approve a treatment candidate for fewer or more limited indications than requested or may grant approval subject to the performance of post-marketing studies. In addition, regulatory agencies may not approve the labeling claims that are necessary or desirable for the successful commercialization of our treatment candidates. For example, the development of our product candidates for pediatric use is an important part of our current business strategy, and if we are unable to obtain marketing approval for the desired age ranges, our business may suffer.

The BLA submission for beti-cel is based on data from patients treated in our studies, including the Phase 3 HGB-207 (Northstar-2) and HGB-212 (Northstar-3) studies, and the Phase 1/2 HGB-204 (Northstar) and HGB-205 studies, and has been accepted for filing by the FDA with priority review and a PDUFA goal date of August 19, 2022. However, it should be noted that our ability to obtain approval of a BLA is ultimately an FDA review decision, which will be dependent upon the data and information submitted in the original BLA and during review, and the data submitted may not be sufficiently robust from a safety and/or efficacy perspective, or from a manufacturing and/or quality perspective, to support the approval of the BLA. Based on the available data from these clinical studies and the information submitted, the FDA may require that we conduct additional or larger pivotal trials before we can obtain approval of the BLA for beti-cel for the treatment of patients with β-thalassemia who require regular transfusions.

The BLA submission for eli-cel is based on the safety and efficacy data from our completed Starbeam study, our ongoing ALD-104 study, and the completed ALD-103 observational study, and has been accepted for filing by the FDA for filing and and granted priority review, with a PDUFA goal date of September 16, 2022. Whether eli-cel is eligible for approval will ultimately be determined at the discretion of the FDA, and is dependent upon the data and information submitted in the BLA and during review, and the data submitted may not be sufficiently robust from a safety and/or efficacy perspective, or from a manufacturing and/or quality perspective, to support approval of the BLA. Moreover, several patients with CALD treated with eli-cel in our clinical studies have been diagnosed with MDS likely mediated by Lenti-D LVV insertion, and as a result, our clinical studies of eli-cel have been subject to a clinical hold. On February 23, 2022, the FDA notified us that the clinical hold on the eli-cel program would remain in place, and requested additional information about safety events and monitoring in the eli-cel clinical program. We have no assurances as to whether we will successfully resolve the clinical hold. Based on the available data submitted from our clinical studies, and pending the resolution of the clinical hold, the FDA may determine that eli-cel cannot be approved or it may require that we conduct additional follow-up or larger clinical trials before we can obtain approval of the BLA for eli-cel for the treatment of patients with CALD, if ever.

Based on our discussions with the FDA, we believe that we may be able to seek approval for lovo-cel in the United States on the basis of clinical data from Group C of our ongoing HGB-206 clinical study, and supporting data from our ongoing HGB-210 clinical study. However, in December 2021, we announced that the FDA has placed our clinical program for lovo-cel on partial clinical hold for patients under the age of 18, which relates to our ongoing investigation into an adolescent patient with persistent, non-transfusion-dependent anemia following treatment with lovo-cel, who was 18 months post-treatment. We do not have any assurance as to when, if ever, we may resume enrolling patients under the age of 18 in our lovo-cel studies. The partial clinical hold has the potential to negatively impact our ability to generate the analytical comparability and validation data for our commercial manufacturing process needed to support our planned BLA submission for lovo-cel.

If our product candidates are ultimately not approved for any reason, our business, prospects, results of operations and financial condition would be adversely affected.

Changes in our manufacturing processes may cause delays in our clinical development and commercialization plans.

The manufacturing processes for our LVV and our drug products are complex. We explore improvements to our manufacturing processes on a continual basis, as we evaluate clinical and manufacturing data and based on discussions with regulatory authorities. In some circumstances, changes in the manufacturing process may require us to perform additional comparability studies, collect additional data from patients, submit additional regulatory filings, or comply with additional requirements, which may lead to delays in our clinical development and commercialization plans. For instance, following the conditional approval of beti-cel by the European Commission, we continued to refine our commercial drug product manufacturing process to narrow some of the manufacturing process parameters and to tighten the range of commercial drug product release specifications, based on discussions with the European Medicines Agency and evolving clinical data. Implementing these changes to the beti-cel commercial manufacturing process had the effect of delaying our ability to treat the first patient in the commercial context in Europe. In lovo-cel, we plan to seek regulatory approval for drug product utilizing LVV manufactured using a scalable suspension manufacturing process using bioreactors, rather than an adherent cell tray manufacturing process, and we will need to generate analytical comparability and validation data that is acceptable to the FDA in support of such process change. Over time, we also intend to transition the LVV manufacturing process for beti-cel in the United States to the suspension manufacturing process, and the timing in which we are able to make the transition will be dependent upon reaching agreement with the FDA, which may require us to conduct additional studies, collect additional data, develop additional assays, or modify release specifications. Following potential marketing approval if and when received, we also intend to transition our drug product manufacturing process in lovo-cel to utilize cryopreserved apheresis patient starting material in order to expand the potential reach of our therapy, which would similarly require comparability and process validation data to support such transition.

We face intense competition and rapid technological change and the possibility that our competitors may develop therapies that are more advanced, safer or more effective than ours, which may adversely affect our financial condition and our ability to successfully develop and commercialize beti-cel, eli-cel, and lovo-cel. If our competitors obtain orphan drug exclusivity for products that regulatory authorities determine constitute the same drug and treat the same indications as our product candidates, and they obtain marketing authorization, we may not be able to have competing products approved by the applicable regulatory authority for a significant period of time.

We are engaged in the development of gene therapies for severe genetic diseases, which is a competitive and rapidly-changing field. We have competitors both in the United States and internationally, including major multinational pharmaceutical companies, biotechnology companies and universities and other research institutions. Many of our competitors have substantially greater financial, technical and other resources, such as larger research and development staff, more experienced manufacturing capabilities, or more established commercial infrastructure. Competition may increase further as a result of advances in the commercial applicability of technologies and greater availability of capital for investment in these industries. Our competitors may succeed in developing, acquiring or licensing on an exclusive basis, products that are more effective, safer, or less costly than any products that we may develop, or achieve patent protection, marketing approval, product commercialization and market penetration earlier than us. Additionally, technologies developed by our competitors may render our potential products uneconomical or obsolete, and we may not be successful in marketing our product candidates against competitors. For additional information regarding our competition, see "Item 1. Business—Competition" in our Annual Report on Form 10-K.

Even if we are successful in achieving marketing approval to commercialize a product candidate faster than our competitors, we may face competition from biosimilars due to the changing regulatory environment. In the United States, the Biologics Price Competition and Innovation Act of 2009 created an abbreviated approval pathway for biological products that are demonstrated to be "highly similar," or biosimilar, to or "interchangeable" with an FDA-approved biological product. This pathway could allow competitors to reference data from biological products already approved after 12 years from the time of approval. In Europe, the European Commission has granted marketing authorizations for several biosimilars pursuant to a set of general and product class-specific guidelines for biosimilar approvals issued over the past few years. In Europe, a competitor may reference data from biological products already approved, but will not be able to get on the market until 10 years after the time of approval. This 10-year period will be extended to 11 years if, during the first eight of those 10 years, the marketing authorization holder obtains an approval for one or more new therapeutic indications that bring significant clinical benefits compared with existing therapies. In addition, companies may be developing biosimilars in other countries that could compete with our potential products. If competitors are able to obtain marketing approval for biosimilars referencing our potential products, our potential products may become subject to competition from such biosimilars, with the attendant competitive pressure and consequences. Expiration or successful challenge of our applicable patent rights could also trigger competition from other products, assuming any relevant exclusivity period has expired.

In addition, although beti-cel, eli-cel, and lovo-cel have been granted orphan drug status by the FDA there are limitations to the exclusivity. In the United States, the exclusivity period for orphan drugs is seven years, while pediatric exclusivity adds six months to any existing patents or exclusivity periods. Generally, if a product with an orphan drug designation receives the first marketing approval for the indication for which it has such designation, the product is entitled to a period of marketing exclusivity, which precludes the FDA from approving another marketing application for a product that constitutes the same drug treating the same indication for that marketing exclusivity period, except in limited circumstances. If another sponsor receives such approval before we do (regardless of our orphan drug designation), we will be precluded from receiving marketing approval for our potential products for the exclusivity period for the applicable indication.

Finally, as a result of the expiration or successful challenge of our patent rights, we could face more litigation with respect to the validity and/or scope of patents relating to our competitors' products. The availability of our competitors' products could limit the demand, and the price we are able to charge, for any products that we may develop and commercialize.

We may not be successful in our efforts to expand applications of our platform technologies through the discovery of additional product candidates or complementary technologies such as reduced toxicity conditioning.

The success of our business depends primarily upon our ability to identify, develop and commercialize products based on our platform technologies, such as *in vivo* product candidates. Our growth strategy also depends upon our ability to leverage advancements in complementary technologies such as in reduced toxicity conditioning or in stem cell mobilization. Our research programs may fail to identify other potential product candidates for clinical development or advance such complementary technologies for a number of reasons. We may be unsuccessful in identifying potential product candidates or our potential product candidates may be shown to have harmful side effects or may have other characteristics that may make the products unmarketable or unlikely to receive marketing approval. Research programs to identify new product candidates and

new technologies require substantial technical, financial and human resources. We may focus our efforts and resources on potential programs or product candidates that ultimately prove to be unsuccessful. If any of these events occur, we may be forced to abandon our research, development or commercialization efforts for a program or programs, which would have a material adverse effect on our business and could potentially cause us to cease operations.

Negative public opinion and increased regulatory scrutiny of gene therapy and genetic research may damage public perception of our potential products or adversely affect our ability to conduct our business or obtain and maintain marketing approvals for our product candidates.

Public perception may be influenced by claims that gene therapy, including gene editing technologies, is unsafe or unethical, and research activities and adverse events in the field, even if not ultimately attributable to us or our product candidates, could result in increased governmental regulation, unfavorable public perception, challenges in recruiting patients to participate in our clinical studies, potential regulatory delays in the testing or approval of our potential products, stricter labeling requirements for those product candidates that are approved, and a decrease in demand for any such product. More restrictive government regulations or negative public opinion would have a negative effect on our business or financial condition and may delay or impair the development and commercialization of our product candidates or demand for any approved products.

Risks related to our reliance on third parties

We rely on third parties to conduct some or all aspects of our LVV production, drug product manufacturing, and testing, and these third parties may not perform satisfactorily.

We do not independently conduct all aspects of our LVV production, drug product manufacturing, and testing. We currently rely, and expect to continue to rely, on third parties with respect to these items, including manufacturing and testing in the commercial context.

Our reliance on these third parties for manufacturing, testing, research and development activities reduce our control over these activities but will not relieve us of our responsibility to ensure compliance with all required regulations and study protocols. For example, for products that we develop and commercialize on our own, we will remain responsible for ensuring that each of our IND-enabling studies and clinical studies are conducted in accordance with the study plan and protocols, and that our LVV and drug products are manufactured in accordance with GMP as applied in the relevant jurisdictions.

If these third parties do not successfully carry out their contractual duties, meet expected deadlines, conduct our studies in accordance with regulatory requirements or our stated study plans and protocols, or manufacture our LVV and drug products in accordance with GMP, whether due to the impacts of COVID-19 or otherwise, we will not be able to complete, or may be delayed in completing, the preclinical and clinical studies and manufacturing process validation activities required to support future IND and BLA submissions and approval of our product candidates, or to support commercialization of our products, if approved. Many of our agreements with these third parties contain termination provisions that allow these third parties to terminate their relationships with us at any time. If we need to enter into alternative arrangements, our product development and commercialization activities could be delayed.

Reliance on third-party manufacturers entails risks to which we would not be subject if we manufactured the products ourselves, including:

- the inability to negotiate manufacturing agreements with third parties under commercially reasonable terms;
- reduced control as a result of using third-party manufacturers for all aspects of manufacturing activities;
- the risk that these activities are not conducted in accordance with our study plans and protocols;
- termination or nonrenewal of manufacturing agreements with third parties in a manner or at a time that is costly or damaging to us; and
- disruptions to the operations of our third-party manufacturers or suppliers caused by conditions unrelated to our business or operations, including the bankruptcy of the manufacturer or supplier.

We may be forced to manufacture LVV and drug product ourselves, for which we may not have the capabilities or resources, or enter into an agreement with a different manufacturer, which we may not be able to do on reasonable terms, if at all. In some cases, the technical skills required to manufacture our LVV or drug product candidates may be unique or proprietary to the original manufacturer, and we may have difficulty or there may be contractual restrictions prohibiting us

from, transferring such skills to a back-up or alternate supplier, or we may be unable to transfer such skills at all. Any of these events could lead to clinical study delays or failure to obtain marketing approval, or impact our ability to successfully commercialize our potential products. Some of these events could be the basis for FDA action, including injunction, recall, seizure or total or partial suspension of production.

We and our contract manufacturers are subject to significant regulation with respect to manufacturing our product candidates. The manufacturing facilities on which we rely may not continue to meet regulatory requirements and have limited capacity.

All entities involved in the preparation of therapeutics for clinical studies or commercial sale, including our existing contract manufacturers for our product candidates, are subject to extensive regulation. Some components of a finished therapeutic product approved for commercial sale or used in late-stage clinical studies must be manufactured in accordance with GMP. These regulations govern manufacturing processes and procedures (including record keeping) and the implementation and operation of quality systems to control and assure the quality of investigational products and products approved for sale. Poor control of production processes can lead to the introduction of adventitious agents or other contaminants, or to inadvertent changes in the properties or stability of our product candidates that may not be detectable in final product testing. We or our contract manufacturers must supply all necessary documentation in support of a BLA on a timely basis and where required, must adhere to the FDA's or other regulator's good laboratory practices ("GLP"), and GMP regulations enforced by the FDA or other regulator through facilities inspection programs. Some of our contract manufacturers have not produced a commercially-approved product and therefore have not obtained the requisite FDA or other marketing approvals to do so. Our facilities and quality systems and the facilities and quality systems of some or all of our third-party contractors must pass a pre-approval inspection for compliance with the applicable regulations as a condition of marketing approval of our potential products. In addition, the regulatory authorities may, at any time, audit or inspect a manufacturing facility involved with the preparation of our potential products or the associated quality systems for compliance with the regulations applicable to the activities being conducted. If these facilities do not pass a pre-approval plant inspection, FDA or other marketing approval of the products will not be granted.

The regulatory authorities also may, at any time following approval of a product for sale, audit the manufacturing facilities of our third-party contractors. If any such inspection or audit identifies a failure to comply with applicable regulations or if a violation of our product specifications or applicable regulations occurs independent of such an inspection or audit, we or the relevant regulatory authority may require remedial measures that may be costly and/or time-consuming for us or a third-party to implement and that may include the temporary or permanent suspension of a clinical study or commercial sales or the temporary or permanent closure of a facility. Any such remedial measures imposed upon us or third parties with whom we contract could materially harm our business.

If we or any of our third-party manufacturers fail to maintain regulatory compliance, the FDA or other regulators can impose regulatory sanctions including, among other things, refusal to approve a pending application for a biologic product, or revocation of a pre-existing approval. As a result, our business, financial condition and results of operations may be materially harmed.

Additionally, if supply from one approved manufacturer is interrupted, there could be a significant disruption in commercial supply. The number of manufacturers with the necessary manufacturing capabilities is limited. In addition, an alternative manufacturer would need to be qualified through a BLA supplement or similar regulatory submission which could result in further delay. The regulatory agencies may also require additional studies if a new manufacturer is relied upon for commercial production. Switching manufacturers may involve substantial costs and is likely to result in a delay in our desired clinical and commercial timelines.

These factors could cause the delay of clinical studies, regulatory submissions, required approvals or commercialization of our potential products, cause us to incur higher costs and prevent us from commercializing our potential products successfully. Furthermore, if our suppliers fail to meet contractual requirements, and we are unable to secure one or more replacement suppliers capable of production at a substantially equivalent cost, our clinical studies may be delayed or we could lose potential revenues.

We expect to rely on third parties to conduct, supervise and monitor our clinical studies, and if these third parties perform in an unsatisfactory manner, it may harm our business.

We expect to rely on CROs and clinical study sites to ensure our clinical studies are conducted properly and on time. While we will have agreements governing their activities, we will have limited influence over their actual performance. We will control only certain aspects of our CROs' activities. Nevertheless, we will be responsible for ensuring that each of our clinical

studies is conducted in accordance with the applicable protocol, legal, regulatory and scientific standards, and our reliance on the CROs does not relieve us of our regulatory responsibilities.

We and our CROs are required to comply with the FDA's and other regulatory authorities' GCPs for conducting, recording and reporting the results of clinical studies to assure that the data and reported results are credible and accurate and that the rights, integrity and confidentiality of clinical study participants are protected. If we or our CROs fail to comply with applicable GCPs, the clinical data generated in our future clinical studies may be deemed unreliable and the FDA and other regulatory authorities may require us to perform additional clinical studies before approving any marketing applications.

If our CROs do not successfully carry out their contractual duties or obligations, fail to meet expected deadlines, or if the quality or accuracy of the clinical data they obtain is compromised due to the failure to adhere to our clinical protocols or regulatory requirements, or for any other reasons, our clinical studies may be extended, delayed or terminated, and we may not be able to obtain marketing approval for, or successfully commercialize our product candidates. As a result, our financial results and the commercial prospects for our product candidates would be harmed, our costs could increase, and our ability to generate revenues could be delayed.

Our reliance on third parties requires us to share our trade secrets, which increases the possibility that a competitor will discover them or that our trade secrets will be misappropriated or disclosed.

Because we rely on third parties to manufacture our vectors and our drug products, and because we collaborate with various organizations and academic institutions on the advancement of our gene therapy platform, we must, at times, share trade secrets with them. We seek to protect our proprietary technology in part by entering into confidentiality agreements and, if applicable, material transfer agreements, collaborative research agreements, consulting agreements or other similar agreements with our collaborators, advisors, employees and consultants prior to beginning research or disclosing proprietary information. These agreements typically limit the rights of the third parties to use or disclose our confidential information, such as trade secrets. Despite the contractual provisions employed when working with third parties, the need to share trade secrets and other confidential information increases the risk that such trade secrets become known by our competitors, are inadvertently incorporated into the technology of others, or are disclosed or used in violation of these agreements. Given that our proprietary position is based, in part, on our know-how and trade secrets, a competitor's discovery of our trade secrets or other unauthorized use or disclosure would impair our competitive position and may have a material adverse effect on our business.

In addition, these agreements typically restrict the ability of our collaborators, advisors, employees and consultants to publish data potentially relating to our trade secrets. Our academic collaborators typically have rights to publish data, provided that we are notified in advance and may delay publication for a specified time in order to secure our intellectual property rights arising from the collaboration. In other cases, publication rights are controlled exclusively by us, although in some cases we may share these rights with other parties. We also conduct joint research and development programs that may require us to share trade secrets under the terms of our research and development partnerships or similar agreements. Despite our efforts to protect our trade secrets, our competitors may discover our trade secrets, either through breach of these agreements, independent development or publication of information including our trade secrets in cases where we do not have proprietary or otherwise protected rights at the time of publication. A competitor's discovery of our trade secrets would impair our competitive position and have an adverse impact on our business.

Risks related to our financial condition and capital requirements

We have not generated material revenue from product sales and may never be profitable.

Our ability to generate revenues and achieve profitability depends on our ability, alone or with strategic collaboration partners, to successfully complete the development of, and obtain the regulatory, pricing and reimbursement approvals necessary to commercialize beti-cel, eli-cel, or lovo-cel. Our ability to generate revenues from product sales depends heavily on our success in:

- completing research and preclinical and clinical development of our product candidates;
- seeking and obtaining regulatory and marketing approvals for product candidates for which we complete clinical studies;
- developing a sustainable, commercial-scale, reproducible, and transferable manufacturing process for our vectors and drug products;

- establishing and maintaining supply and manufacturing relationships with third parties that can provide adequate (in amount and quality) products and services to support clinical development for our product candidates and commercial demand for any approved product;
- launching and commercializing any approved product, either by collaborating with a partner or, if launched independently, by establishing a field-based team, marketing and distribution infrastructure;
- obtaining sufficient pricing and reimbursement for any approved product from private and governmental payers;
- obtaining market acceptance and adoption of any approved product and gene therapy as a viable treatment option;
- addressing any competing technological and market developments;
- negotiating favorable terms in any collaboration, licensing or other arrangements into which we may enter; and
- maintaining, protecting and expanding our portfolio of intellectual property rights, including patents, trade secrets and know-how.

We expect to continue to incur significant expenditures for the foreseeable future, and we expect these expenditures to increase, which costs may increase further as competitors enter the market. Our expenses could increase beyond expectations if we are required by the FDA or other regulatory agencies, domestic or foreign, to perform clinical and other studies in addition to those that we currently anticipate. Even if we are able to generate material product revenues, we may not become profitable and may need to obtain additional funding to continue operations.

If the estimates we make, or the assumptions on which we rely, in preparing our consolidated financial statements are incorrect, our actual results may vary from those reflected in our projections and accruals.

Our consolidated financial statements have been prepared in accordance with accounting principles generally accepted in the United States of America ("GAAP"). The preparation of these consolidated financial statements requires us to make estimates and judgments that affect the reported amounts of our assets, liabilities, revenues and expenses, and related disclosure of contingent assets and liabilities. We base our estimates on historical experience and on various other assumptions that we believe to be reasonable under the circumstances. We cannot assure you, however, that our estimates, or the assumptions underlying them, will be correct. We may be incorrect in our assumptions regarding the applicability of drug pricing programs and rebates that may be applicable to our potential products, which may result in our under- or over-estimating our anticipated product revenues especially as applicable laws and regulations governing pricing evolve over time. In addition, to the extent payment for our potential products is subject to outcomes-based arrangements over time, the total payments received from product sales may vary, our cash collection of future payments and revenue assumptions from product sales will be at risk, and the timing of revenue recognition may not correspond to the timing of cash collection.

Further, from time to time we issue financial guidance relating to our expectations for our cash, cash equivalents, and marketable securities available for operations, which guidance is based on estimates and the judgment of management. If, for any reason, our expenses differ materially from our guidance or we utilize our cash more quickly than anticipated, we may have to adjust our publicly announced financial guidance. If we fail to meet, or if we are required to change or update any element of, our publicly disclosed financial guidance or other expectations about our business, our stock price could decline.

Our operating results may fluctuate significantly, which makes our future operating results difficult to predict and could cause our operating results to fall below expectations or our guidance.

Our operating results are difficult to predict and will likely fluctuate from quarter to quarter and year to year. We expect that following marketing approval, if and when obtained, revenues from product sales will be difficult to predict from period to period, given the absence of historical sales data for beti-cel, eli-cel and lovo-cel.

Further, changes in our operations, such as increased development, manufacturing and clinical trial expenses in connection with expanding our pipeline programs, or our undertaking of additional programs, or business activities, or entry into strategic transactions, including potential future acquisitions of products, technologies or businesses may also cause significant fluctuations in our expenses.

The cumulative effects of these factors, further exacerbated by the impacts of the ongoing COVID-19 pandemic on healthcare systems and economic conditions, will likely result in large fluctuations and unpredictability in our quarterly and annual operating results. As a result, comparing our operating results on a period-to-period basis may not be meaningful.

Investors should not rely on our past results as an indication of our future performance. This variability and unpredictability could also result in our failing to meet the expectations of industry or financial analysts or investors for any period. If our revenue or operating results fall below the expectations of analysts or investors or below any forecasts we may provide to the market, or if the forecasts we provide to the market are below the expectations of analysts or investors, the price of our common stock could decline substantially. Such a stock price decline could occur even when we have met any previously publicly stated revenue or earnings guidance we may provide.

Risks related to our business operations

Our business may be materially and adversely affected by the ongoing COVID-19 pandemic. The COVID-19 pandemic has had, and may continue to have, an impact on various aspects of our business and that of third parties on which we rely. The extent to which the COVID-19 pandemic impacts our business will depend in part on future developments, which are uncertain and unpredictable in nature.

Since March 2020, when the World Health Organization characterized COVID-19 as a pandemic, the related adverse public health developments, including orders to shelter-in-place, travel restrictions, and the imposition of additional requirements on businesses, have adversely affected workforces, organizations, healthcare communities, economies, and financial markets globally, leading to economic uncertainty and increased market volatility. It has also disrupted the normal operations of businesses across industries, including ours. As a result of the COVID-19 pandemic, we have experienced and expect to experience disruptions in our operations and business, and those of third parties upon whom we rely. For instance, we have experienced disruptions in the conduct of our clinical trials, manufacturing and commercialization efforts, including the commercial launch of beti-cel in Germany and the treatment of patients in the commercial context. We cannot reasonably assess or predict at this time the full extent of the negative impact that the COVID-19 pandemic and related effects may have on our business, financial condition, results of operations and cash flows. We expect to continue experiencing these disruptions in our operations and those of our third parties for an unknown period of time, as the trajectory of the COVID-19 pandemic remains uncertain and continues to evolve in the United States. These impacts, which may materially and adversely affect our business, include the following:

- We are conducting a number of clinical studies across our programs in geographies which are affected by the COVID-19 pandemic. The COVID-19 pandemic has had, and will likely continue to have, an impact on various aspects of our clinical studies. Policies at various clinical sites and federal, state, local and foreign laws, rules and regulations are continuing to evolve, including through the implementation of quarantines and travel restrictions, and direction of healthcare resources toward pandemic response efforts. For instance, the availability of intensive care unit beds and related healthcare resources available to support activities unrelated to COVID-19 response have fluctuated with the incidence of severe cases of COVID-19 in the surrounding communities, and we anticipate that the availability of healthcare resources will continue to fluctuate and may become significantly constrained, with variability across geographies. The COVID-19 pandemic has disrupted the conduct of our ongoing clinical studies, with the result of slower patient enrollment and treatment as well as delays in post-treatment patient follow-up visits. These impacts have varied by clinical study, with the most significant impacts being on our ongoing HGB-210 study for lovo-cel. It is possible that these delays may impact the timing of our regulatory submissions. It is unknown how long these disruptions could continue.

- We currently rely on third parties to manufacture, perform quality testing, and ship LVV and drug product for our clinical studies and, if and when we receive marketing approval for our therapies, expect to rely on such third parties to support commercialization efforts. The third parties in our supply chain have been and may continue to be subject to restrictions in operations arising from the COVID-19 pandemic, and in addition, a number of these third parties have experienced operational disruptions, which have affected activities necessary for our research and development efforts, as well as our commercialization efforts in the United States. These restrictions and disruptions in operations have also given rise to staffing shortages from time to time, which may result in production slowdowns and/or disruptions in delivery systems, potentially interrupting our supply chain and limiting our ability to manufacture LVV and drug product for our clinical studies and for commercial use. At this time, it is unknown how long these disruptions may continue, or the full extent of their impacts.

- The operations of health regulatory agencies globally have been impacted as a result of the COVID-19 pandemic. They have communicated slower response times to regulatory interactions and submissions and, in the future, may lack resources to continue to monitor our clinical studies or to engage in other activities related to review of regulatory submissions in drug development. As a result, timelines for the review of regulatory submissions for our programs have been impacted, and we may experience other delays of unknown duration in the review, inspection, and other regulatory interactions. Any de-prioritization of our clinical studies or delay in regulatory review or interaction

resulting from such disruptions could materially affect the development of our product candidates. In addition, we have been engaging in reimbursement discussions with governmental health programs as part of our commercial preparation activities.

- The trading prices for our shares of common stock and other biopharmaceutical companies have been highly volatile as a result of the economic volatility and uncertainty caused by the COVID-19 pandemic. As a result, we may face difficulties raising capital through sales of shares of our common stock or such sales may be on unfavorable terms. In addition, a recession, depression or other sustained adverse market event resulting from the spread of, or failure to manage or contain, the COVID-19 pandemic will materially and adversely affect our business, the value of our common stock, and our ability to operate under our operating plan and execute our strategy. Our business and operating plan have already been impacted by the COVID-19 pandemic, the associated governmental restrictions, and the resulting economic conditions, leading us to reduce and defer costs, adjust our priorities, timelines and expectations, and review and revise our operating plans with the intention that it would enable us to advance our corporate strategy and pipeline during an extended period of uncertainty.

The extent of the impacts described above will depend on numerous evolving factors that we may not be able to accurately predict, including:

- the duration, severity, and scope of the pandemic in the United States and globally;
- the effectiveness of governmental, business and individuals' protocols and actions that have been and continue to be taken in response to the pandemic;
- the impact of the pandemic on economic activity and actions taken in response;
- the effect on patients, healthcare providers and business partners;
- uncertainty as to when we will be able to resume normal clinical study enrollment and patient treatment or follow up activities, particularly at clinical study sites located in highly impacted geographies as a result of disruptions at these sites;
- the ability to obtain or deliver sufficient and timely supplies, given the disruptions to the production capabilities of our manufacturers and suppliers, particularly with respect to the priority given to the development, regulatory approval, and manufacture of COVID-19 vaccines and diagnostic tests;
- our access to the debt and equity markets on satisfactory terms, or at all;
- disruptions in regulatory oversight and actions, as a result of significant and unexpected resources expended to address the COVID-19 by regulators and industry professionals; and
- any impacts on our and our partners' offices, operations and facilities.

The ultimate impact of the COVID-19 pandemic on our business operations is highly uncertain and subject to change and will depend on future developments which are difficult to predict, including the duration of the pandemic, the ultimate geographic spread of the disease, additional or modified government actions, new information that will emerge concerning the severity and impact of COVID-19 and other actions taken to contain or address its impact in the short and long term, among others. We do not yet know the full extent of potential delays or impacts on our business, our clinical studies, our research programs, our commercial-readiness activities in the United States, healthcare systems or the global economy. If the ultimate impact of the COVID-19 pandemic and the resulting uncertain economic and healthcare environment is more severe than we anticipated, we may not be able to execute on our current operating plan or on our strategy. If the duration of the COVID-19 pandemic and the associated period of business and social restrictions and economic uncertainty is longer than we anticipated, our cash, cash equivalents, and marketable securities may not be sufficient to fund the activities under our operating plan for the time period that we anticipated, and we may be required to revise our operating plan further. To the extent the COVID-19 pandemic adversely affects our business and financial results, it may also have the effect of heightening many of the other risks described in this "Risk Factors" section.

Even if we receive marketing approval for a product candidate, any approved product will remain subject to regulatory scrutiny.

Even if we obtain marketing approval in a jurisdiction, regulatory authorities may still impose significant restrictions on the indicated uses or marketing of any approved products, or impose ongoing requirements for potentially costly post-approval

studies, post-market surveillance or patient or drug restrictions. For example, the FDA typically advises that patients treated with gene therapy undergo follow-up observations for potential adverse events for a 15-year period. Additionally, the holder of an approved BLA is obligated to monitor and report adverse events and any failure of a product to meet the specifications in the BLA. The holder of an approved BLA must also submit new or supplemental applications and obtain FDA approval for certain changes to the approved product, product labeling or manufacturing process. Advertising and promotional materials must comply with FDA rules and are subject to FDA review, in addition to other potentially applicable federal and state laws. We have experienced interruptions in our marketing of beti-cel in Europe due to safety concerns arising from our lovo-cel program, and we can make no assurance that we will not experience interruptions in any marketing or other commercialization activities in the future, whether due to safety concerns in any approved products, or due to events arising from programs that utilize technologies similar to or related to ours.

In addition, product manufacturers and their facilities are subject to payment of user fees and continual review and periodic inspections by the FDA and other regulatory authorities for compliance with good manufacturing practices ("GMP") and adherence to commitments made in the BLA. If we or a regulatory agency discovers previously unknown problems with a product such as adverse events of unanticipated severity or frequency, or problems with the facility where the product is manufactured, a regulatory agency may impose restrictions relative to that product or the manufacturing facility, including requiring recall or withdrawal of the product from the market or suspension of manufacturing.

If we fail to comply with applicable regulatory requirements following marketing approval for a product, a regulatory agency may:

- issue a warning letter asserting that we are in violation of the law;
- seek an injunction or impose civil or criminal penalties or monetary fines;
- suspend or withdraw marketing approval;
- suspend any ongoing clinical studies;
- refuse to approve a pending marketing application, such as a BLA or supplements to a BLA submitted by us;
- seize product; or
- refuse to allow us to enter into supply contracts, including government contracts.

Any government investigation of alleged violations of law could require us to expend significant time and resources in response and could generate negative publicity. The occurrence of any event or penalty described above may inhibit our ability to commercialize any approved product and generate revenues.

We are subject, directly or indirectly, to federal and state healthcare fraud and abuse laws, false claims laws and health information privacy and security laws. If we are unable to comply, or have not fully complied, with such laws, we could face substantial penalties, reputational harm, and diminished profits and future earnings.

In the United States, the research, manufacturing, distribution, sale, and promotion of drugs and biologic products are subject to regulation by various federal, state, and local authorities in addition to FDA, including CMS, other divisions of the HHS, (e.g., the Office of Inspector General), the United States Department of Justice offices of the United States Attorney, the Federal Trade Commission and state and local governments. Our operations are directly, or indirectly through our prescribers, customers and purchasers, subject to various federal and state fraud and abuse laws and regulations described in more detail under *"Item 1. Business--Government regulation"* in our Annual Report. These include the federal Anti-Kickback Statute, federal civil and criminal false claims laws and civil monetary penalty laws (including False Claims Laws), HIPAA, transparency requirements created under the Affordable Care Act, as well as analogous state and foreign laws.

These laws apply to, among other things, our sales, marketing and educational programs. State and federal regulatory and enforcement agencies continue actively to investigate violations of health care laws and regulations, and the United States Congress continues to strengthen the arsenal of enforcement tools. Most recently, the Bipartisan Budget Act of 2018 increased the criminal and civil penalties that can be imposed for violating certain federal health care laws, including the Anti-Kickback Statute. Enforcement agencies also continue to pursue novel theories of liability under these laws. In particular, government agencies have recently increased regulatory scrutiny and enforcement activity with respect to programs supported or sponsored by pharmaceutical companies, including reimbursement and co-pay support, funding of independent charitable foundations and

other programs that offer benefits for patients. Several investigations into these programs have resulted in significant civil and criminal settlements.

Because of the breadth of these laws and the narrowness of the statutory exceptions and safe harbors available, it is possible that some of our business activities could be subject to challenge under one or more of such laws. If our operations are found to be in violation of any of the laws described above or any other government regulations that apply to us, we may be subject to penalties, including civil and criminal penalties, damages, fines, exclusion from participation in government health care programs, such as Medicare and Medicaid, imprisonment and the curtailment or restructuring of our operations, any of which could adversely affect our ability to operate our business and our results of operations. Even if we are 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 harm our financial condition and divert the attention of our management from operating our business.

In addition, we may be subject to patient privacy laws by both the federal government and the states in which we conduct our business. For example, HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act of 2009 ("HITECH") and their respective implementing regulations, imposes requirements on certain covered healthcare providers, health plans, and healthcare clearinghouses as well as their respective business associates that perform services for them that involve the use, or disclosure of, individually identifiable health information, relating to the privacy, security and transmission of individually identifiable health information. HITECH also created new tiers of civil monetary penalties, amended HIPAA to make civil and criminal penalties directly applicable to business associates, and gave state attorneys general new authority to file civil actions for damages or injunctions in federal courts to enforce the federal HIPAA laws and seek attorneys' fees and costs associated with pursuing federal civil actions In addition to HIPAA, as amended by HITECH, and their respective implementing regulations, California recently enacted the California Consumer Privacy Act ("CCPA") which creates new individual privacy rights for California consumers (as defined in the law) and places increased privacy and security obligations on entities handling personal data of consumers or households. The CCPA requires covered companies to provide certain disclosures to consumers about its data collection, use and sharing practices, and to provide affected California residents with ways to opt-out of certain sales or transfers of personal information. While there is currently an exception for protected health information that is subject to HIPAA, as currently written, the CCPA may impact our business activities. The California Attorney General has proposed draft regulations, which have not been finalized to date, that may further impact our business activities if they are adopted. The uncertainty surrounding the implementation of CCPA exemplifies the vulnerability of our business to the evolving regulatory environment related to personal data and protected health information.

EU member states, Switzerland and other countries have also adopted data protection laws and regulations, which impose significant compliance obligations. In the European Union, the collection and use of personal health data is currently governed by the provisions of the General Data Protection Regulation ("GDPR"). The GDPR, together with the national legislation of the individual EU member states governing the processing of personal data, impose strict obligations and restrictions on the ability to collect, analyze and transfer personal data, including health data from clinical trials and adverse event reporting. In particular, these obligations and restrictions concern the consent of the individuals to whom the personal data relates, the information provided to the individuals for the consent to be considered valid, the transfer of personal data out of the European Economic Area, security breach notifications, the use of third-party processors in connection with the processing of the personal data, confidentiality of the personal data, as well as substantial potential fines for breaches of the data protection obligations. Data protection authorities from the different EU member states may interpret the GDPR and national laws differently and impose additional requirements, which add to the complexity of processing personal data in the European Union. The GDPR also imposes strict rules on the transfer of personal data to countries outside the European Union, including the United States, and permits data protection authorities to impose large penalties for violations of the GDPR, including potential fines of up to €20 million or 4% of annual global revenues, whichever is greater. The GDPR also confers a private right of action on data subjects and consumer associations to lodge complaints with supervisory authorities, seek judicial remedies, and obtain compensation for damages resulting from violations of the GDPR. Compliance with the GDPR is a rigorous and time-intensive process that may increase our cost of doing business or require us to change our business practices, and despite those efforts, there is a risk that we may be subject to fines and penalties, litigation, and reputational harm in connection with any activities falling within the scope of the GDPR. Further, Brexit has created uncertainty with regard to data protection regulation in the United Kingdom. In particular, it is unclear how data transfers to and from the United Kingdom will be regulated.

We face potential product liability, and, if successful claims are brought against us, we may incur substantial liability and costs. If the use of our product candidates harms patients, or is perceived to harm patients even when such harm is unrelated to our product candidates, our marketing approvals could be revoked or otherwise negatively impacted and we could be subject to costly and damaging product liability claims.

The use of our product candidates in clinical studies and the sale of any products for which we obtain marketing approval exposes us to the risk of product liability claims. Product liability claims might be brought against us by patients participating in clinical trials, consumers, healthcare providers, pharmaceutical companies or others selling or otherwise coming into contact with our product candidates. There is a risk that our product candidates may induce adverse events. If we cannot successfully defend against product liability claims, we could incur substantial liability and costs. In addition, regardless of merit or eventual outcome, product liability claims may result in:

- impairment of our business reputation;
- withdrawal of clinical study participants;
- costs due to related litigation;
- distraction of management's attention from our primary business;
- substantial monetary awards to patients or other claimants;
- the inability to develop our product candidates or commercialize any approved product; and
- decreased demand for any approved product.

We carry product liability insurance and we believe our product liability insurance coverage is sufficient in light of our current clinical programs and approved product; however, we may not be able to maintain insurance coverage at commercially reasonable cost or in sufficient amounts to protect us against losses due to liability. On occasion, large judgments have been awarded in class action lawsuits based on drugs or medical treatments that had unanticipated adverse effects. A successful product liability claim or series of claims brought against us could cause our stock price to decline and, if judgments exceed our insurance coverage, could adversely affect our results of operations and business.

Patients with the diseases targeted by our product candidates are often already in severe and advanced stages of disease and have both known and unknown significant pre-existing and potentially life-threatening health risks. During the course of treatment, patients may suffer adverse events, including death, for reasons that may be related to our product candidates. Such events could subject us to costly litigation, require us to pay substantial amounts of money to injured patients, delay, negatively impact or end our opportunity to receive or maintain marketing approval for any approved product, or require us to suspend or abandon our commercialization efforts. Even in a circumstance in which we do not believe that an adverse event is related to our product candidates the investigation into the circumstance may be time-consuming or inconclusive. These investigations may interrupt our sales efforts, delay our marketing approval process in other countries, or impact and limit the type of marketing approval our product candidates may receive or any approved product maintains. As a result of these factors, a product liability claim, even if successfully defended, could have a material adverse effect on our business, financial condition or results of operations.

Healthcare legislative reform measures may have a material adverse effect on our business and results of operations.

The United States and many foreign jurisdictions have enacted or proposed legislative and regulatory changes affecting the healthcare system that could prevent or delay marketing approval of our potential products, restrict or regulate post-approval activities and affect our ability to profitably sell any product for which we obtain marketing approval. Changes in regulations, statutes or the interpretation of existing regulations could impact our business in the future by requiring, for example: (i) changes to our manufacturing arrangements; (ii) additions or modifications to product labeling; (iii) the recall or discontinuation of our products; or (iv) additional record-keeping requirements. If any such changes were to be imposed, they could adversely affect the operation of our business.

In the United States, there have been and continue to be a number of legislative initiatives to contain healthcare costs. For example, in March 2010, the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act of 2010 ("Affordable Care Act"), was passed, which substantially changed the way health care is financed by both governmental and private insurers, and significantly impacts the U.S. pharmaceutical industry. The Affordable Care Act, among other things, addressed a new methodology by which rebates owed by manufacturers under the Medicaid Drug

Rebate Program are calculated for drugs that are inhaled, infused, instilled, implanted or injected, increased the minimum Medicaid rebates owed by manufacturers under the Medicaid Drug Rebate Program and extended the rebate program to individuals enrolled in Medicaid managed care organizations, established annual fees and taxes on manufacturers of certain branded prescription drugs, expanded the types of entities eligible for the 340B drug discount program, and a new Medicare Part D coverage gap discount program, in which manufacturers must agree to offer 70% (increased pursuant to the Bipartisan Budget Act of 2018, effective as of 2019) point-of-sale discounts off negotiated prices of applicable brand drugs to eligible beneficiaries during their coverage gap period, as a condition for the manufacturer's outpatient drugs to be covered under Medicare Part D.

Since its enactment, there have been numerous judicial, administrative, executive, and legislative challenges to certain aspects of the Affordable Care Act, and we expect there will be additional challenges and amendments to the Affordable Care Act in the future. Various portions of the Affordable Care Act are currently undergoing legal and constitutional challenges in the Fifth Circuit Court and the United States Supreme Court. It is unclear whether the Affordable Care Act will be overturned, repealed, replaced, or further amended. We cannot predict what effect further changes to the Affordable Care Act would have on our business.

In addition, other legislative changes have been proposed and adopted since the Affordable Care Act was enacted. In August 2011, President Obama signed into law the Budget Control Act of 2011, which, among other things, created the Joint Select Committee on Deficit Reduction to recommend to Congress proposals in spending reductions. The Joint Select Committee on Deficit Reduction did not achieve a targeted deficit reduction, which triggered the legislation's automatic reduction to several government programs. This includes aggregate reductions to Medicare payments to providers of, on average, 2% per fiscal year through 2025 unless Congress takes additional action. These reductions were extended through 2029 through subsequent legislative amendments. In January 2013, the American Taxpayer Relief Act of 2012, among other things, further reduced Medicare payments to several providers, including hospitals and cancer treatment centers, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years.

There has been increasing legislative and enforcement interest in the United States with respect to specialty drug pricing practices. Specifically, there have been several recent U.S. Congressional inquiries and proposed federal and state legislation designed to, among other things, bring more transparency to drug pricing, reduce the cost of prescription drugs under Medicare, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for drugs. At the federal level, the Trump administration's budget proposal for fiscal years 2019 and 2020 contain further drug price control measures that could be enacted during the budget process or in other future legislation, including, for example, measures to permit Medicare Part D plans to negotiate the price of certain drugs under Medicare Part B, to allow some states to negotiate drug prices under Medicaid, and to eliminate cost sharing for generic drugs for low-income patients. At the state level, legislatures have increasingly passed legislation and implemented regulations designed to control pharmaceutical and biological product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing.

We expect that the healthcare reform measures that have been adopted and may be adopted in the future, may result in more rigorous coverage criteria and in additional downward pressure on the price that we receive for any approved product and could seriously harm our future revenues. Any reduction in reimbursement from Medicare or other government programs may result in a similar reduction in payments from private third-party payers.

The delivery of healthcare in the European Union, including the establishment and operation of health services and the pricing and reimbursement of medicines, is almost exclusively a matter for national, rather than EU, law and policy. National governments and health service providers have different priorities and approaches to the delivery of health care and the pricing and reimbursement of products in that context. In general, however, the healthcare budgetary constraints in most EU member states have resulted in restrictions on the pricing and reimbursement of medicines by relevant health service providers. Coupled with ever-increasing EU and national regulatory burdens on those wishing to develop and market products, this could prevent or delay marketing approval of our product candidates, restrict or regulate post-approval activities and affect our ability to commercialize any products for which we obtain marketing approval.

There have been, and likely will continue to be, legislative and regulatory proposals at the foreign, federal and state levels directed at broadening the availability of healthcare and containing or lowering the cost of healthcare. The implementation of cost containment measures or other healthcare reforms may prevent us from being able to generate revenue, attain profitability, or commercialize our potential products. Such reforms could have an adverse effect on anticipated revenue from product candidates that we may successfully develop and for which we may obtain marketing approval and may affect our overall financial condition and ability to develop product candidates.

Our computer systems, or those of our third-party collaborators, service providers, contractors or consultants, may fail or suffer security breaches, which could result in a material disruption of our product candidates' development programs and have a material adverse effect on our reputation, business, financial condition or results of operations.

Our computer systems and those of our current or future third-party collaborators, service providers, contractors and consultants may fail and are vulnerable to damage from computer viruses, unauthorized access, natural disasters, terrorism, war and telecommunication and electrical failures. The size and complexity of our information technology systems, and those of our collaborators, service providers, contractors and consultants, and the large amounts of information stored on those systems make those systems vulnerable to service interruptions, security breaches, or other failures, resulting from inadvertent or intentional actions by our employees or those of third-party business partners, or from cyber-attacks by malicious third parties. Attacks on information technology systems are increasing in their frequency, levels of persistence, sophistication and intensity, and they are being conducted by increasingly sophisticated and organized groups and individuals with a wide range of motives and expertise. In addition to extracting sensitive information, such attacks could include the deployment of harmful malware, ransomware, denial-of-service attacks, social engineering and other means to affect service reliability and threaten the confidentiality, integrity and availability of information. The prevalent use of mobile devices also increases the risk of data security incidents. If we experience a material system failure, accident or security breach that causes interruptions in our operations or the operations of third-party collaborators, service providers, contractors and consultants, it could result in significant reputational, financial, legal, regulatory, business or operational harm. For example, the loss of clinical trial data for our product candidates could result in delays in our marketing approval efforts and significantly increase our costs to recover or reproduce the data. To the extent that any disruption or security breach results in a loss of or damage to our data or applications or other data or applications relating to our technology or product candidates, or inappropriate disclosure of confidential or proprietary information, we could incur liabilities and the further development of our product candidates could be delayed. In addition, we rely on third-party service providers for management of the manufacture and delivery of drug product to patients in the commercial context, including for chain of identity and chain of custody. We also rely on third-party service providers for aspects of our internal control over financial reporting and such service providers may experience a material system failure or fail to carry out their obligations in other respects, which may impact our ability to produce accurate and timely financial statements, thus harming our operating results, our ability to operate our business, and our investors' view of us. In addition, our liability insurance may not be sufficient in type or amount to cover us against claims related to material failures, security breaches, cyberattacks and other related breaches.

Any failure or perceived failure by us or any third-party collaborators, service providers, contractors or consultants to comply with our privacy, confidentiality, data security or similar obligations to third parties, or any data security incidents or other security breaches that result in the unauthorized access, release or transfer of sensitive information, including personally identifiable information, may result in governmental investigations, enforcement actions, regulatory fines, litigation or public statements against us. These events could cause third parties to lose trust in us or could result in claims by third parties asserting that we have breached our privacy, confidentiality, data security or similar obligations, any of which could have a material adverse effect on our reputation, business, financial condition or results of operations. Moreover, data security incidents and other security breaches can be difficult to detect, and any delay in identifying them may lead to increased harm. While we have implemented data security measures intended to protect our information technology systems and infrastructure, there can be no assurance that such measures will successfully prevent service interruptions or data security incidents.

Risks related to the separation of our oncology programs and portfolio

We may incur operational difficulties or be exposed to claims and liabilities as a result of the separation of 2seventy bio.

On November 4, 2021, we distributed all of the outstanding shares of 2seventy bio, Inc. ("2seventy") common stock to our stockholders in connection with the separation of our oncology programs and portfolio. In connection with the distribution, we entered into a separation agreement and various other agreements (including a tax matters agreement, an employee matters agreement, transition services agreements and an intellectual property license agreement). These agreements govern the separation and distribution and the relationship between us and 2seventy going forward, including with respect to potential tax-related losses associated with the separation and distribution. They also provide for the performance of services by each company for the benefit of the other for a period of time.

The separation agreement provides for indemnification obligations designed to make 2seventy financially responsible for many liabilities that may exist relating to its business activities, whether incurred prior to or after the distribution, including any pending or future litigation, but we cannot guarantee that 2seventy will be able to satisfy its indemnification obligations. It is also possible that a court would disregard the allocation agreed to between us and 2seventy and require us to assume responsibility for obligations allocated to 2seventy. Third parties could also seek to hold us responsible for any of these liabilities or obligations, and the indemnity rights we have under the separation agreement may not be sufficient to fully cover

all of these liabilities and obligations. Even if we are successful in obtaining indemnification, we may have to bear costs temporarily. In addition, our indemnity obligations to 2seventy, including those related to assets or liabilities allocated to us, may be significant. These risks could negatively affect our business, financial condition or results of operations.

The separation of 2seventy continues to involve a number of additional risks, including, among other things, the potential that management's and our employees' attention will be significantly diverted by the provision of transitional services or that we may incur other operational challenges or difficulties as a result of the separation. Certain of the agreements described above provide for the performance of services by each company for the benefit of the other for a period of time. If 2seventy is unable to satisfy its obligations under these agreements, we could incur losses and may not have sufficient resources available for such services. These arrangements could also lead to disputes over rights to certain shared property and over the allocation of costs and revenues for products and operations. Our inability to effectively manage the transition activities and related events could adversely affect our business, financial condition or results of operations.

We may fail to realize some or all of the anticipated benefits of the separation of 2seventy.

The anticipated operational, financial, strategic and other benefits of the separation of 2seventy may not be achieved. The combined value of the common stock of the two publicly-traded companies may not be equal to or greater than what the value of our common stock would have been had the separation not occurred. The combined value of the common stock of the two companies could be lower than anticipated for a variety of reasons, including the failure of either company to operate and compete effectively as an independent company. The common stock price of each company may experience periods of extreme volatility. In addition, following the separation we are smaller and less diversified, with a narrower business focus, and may be more vulnerable to changing market conditions. The separation also presents a number of significant risks to our internal processes, including the failure to maintain an adequate control environment due to changes to our infrastructure technology systems and financial reporting processes.

Completion of the separation of 2seventy resulted in substantial changes in our board of directors and management.

Completion of the separation of 2seventy resulted in substantial changes in our board of directors and management. In particular, our former chief executive officer, Nick Leschly, resigned from that position (although Mr. Leschly continues to serve on our board of directors). In addition, Philip Gregory, our former chief scientific officer, and Chip Baird, our former chief financial officer, resigned from their positions with us to join management positions with 2seventy. Furthermore, Dan Lynch, Ramy Ibrahim, Denice Torres, William Sellers, Sarah Glickman and Marcela Maus resigned as members of our board of directors upon the completion of the separation. These senior officer and board level changes could be disruptive to our operations, present significant management challenges and could harm our business.

The separation may result in disruptions to, and harm our relationships with, our strategic business partners.

Uncertainty related to the separation may lead the suppliers, research organizations, and other parties with which we currently do business or may do business in the future to terminate or attempt to negotiate changes in our existing business relationships, or cause them to delay entering into business relationships with us or consider entering into business relationships with parties other than us. These disruptions could have a material and adverse effect on our business, prospects, financial condition and results of operations.

If the distribution of shares of 2seventy bio, together with certain related transactions, does not qualify as a transaction that is generally tax-free for U.S. federal income tax purposes, we and our stockholders could be subject to significant tax liabilities.

The completion of the distribution was conditioned upon, among other things, our receipt of a private letter ruling from the IRS, and an opinion from Goodwin Procter LLP, both satisfactory to our board of directors and both continuing to be valid, together confirming that the distribution, together with certain related transactions, generally is tax-free for U.S. federal income tax purposes under Sections 355 and 368(a)(1)(D) of the Code. We have received a favorable private letter ruling from the IRS addressing one significant issue of the qualification of the distribution under Section 355 of the Code. However, the private letter ruling does not address the remaining issues that are relevant to determining whether the distribution, together with certain related transactions, qualifies as a transaction that is generally tax-free for U.S. federal income tax purposes. The IRS private letter ruling and opinion of Goodwin Procter LLP were based, among other things, on various facts and assumptions, as well as certain representations, statements and undertakings from us and 2seventy bio (including those relating to the past and future conduct of us and 2seventy bio) and were subject to certain caveats. If any of these facts, assumptions, representations, statements or undertakings is, or becomes, inaccurate or incomplete, or if we or 2seventy bio breach any of our respective covenants relating to the separation, the IRS private letter ruling and tax opinion may be invalid. Moreover, the opinion is not

binding on the IRS or any courts. Accordingly, notwithstanding receipt of the IRS private letter ruling and an opinion of Goodwin Procter LLP, the IRS could determine that the distribution and certain related transactions should be treated as taxable transactions for U.S. federal income tax purposes.

If the distribution, together with certain related transactions, were to fail to qualify as a transaction that is generally tax-free under Sections 355 and 368(a)(1)(D) of the Code, in general, for U.S. federal income tax purposes, we would recognize taxable gain as if we have sold 2seventy bio's distributed common stock in a taxable sale for its fair market value and our stockholders who receive shares of 2seventy bio common stock in the distribution would be subject to tax as if they had received a taxable distribution equal to the fair market value of such shares.

In connection with the distribution, we and 2seventy bio entered into a tax matters agreement pursuant to which each party is responsible for certain liabilities and obligations following the distribution. In general, under the terms of the tax matters agreement, if the distribution, together with certain related transactions, were to fail to qualify as a transaction that is generally tax-free for U.S. federal income tax purposes under Sections 355 and 368(a)(1)(D) of the Code, and if and to the extent that such failure results from a prohibited change of control in us under Section 355(e) of the Code, or an acquisition of our stock or assets or certain actions, omissions or failures to act, by us, then we will bear any resulting taxes, interest, penalties and other costs. If and to the extent that such failure results from a prohibited change of control in 2seventy bio under Section 355(e) of the Code or an acquisition of 2seventy bio stock or assets or certain actions by 2seventy bio, then 2seventy bio will be obligated to indemnify us for any resulting taxes, interest, penalties and other costs, including any reductions in our net operating loss carryforwards or other tax assets. If such failure does not result from a prohibited change of control in bluebird bio or 2seventy bio under Section 355(e) of the Code and both we and 2seventy bio are responsible for such failure, liability will be shared according to relative fault. If neither we nor 2seventy bio is responsible for such failure, we will bear any resulting taxes, interest, penalties and other costs.

Risks related to our intellectual property

If we are unable to obtain or protect intellectual property rights related to our product candidates, we may not be able to compete effectively in our markets.

We rely upon a combination of patents, trade secret protection and confidentiality agreements to protect the intellectual property related to our product candidates. The strength of patents in the biotechnology and pharmaceutical field involves complex legal and scientific questions and can be uncertain. The patent applications that we own or in-license may fail to result in issued patents with claims that cover our product candidates in the United States or in other foreign countries. There is no assurance that all of the potentially relevant prior art relating to our patents and patent applications has been found, which can invalidate a patent or prevent a patent from issuing from a pending patent application. Even if patents do successfully issue and even if such patents cover our product candidates, third parties may challenge their validity, enforceability or scope, which may result in such patents being narrowed or invalidated. Furthermore, even if they are unchallenged, our patents and patent applications may not adequately protect our intellectual property, provide exclusivity for our product candidates or prevent others from designing around our claims. Any of these outcomes could impair our ability to prevent competition from third parties, which may have an adverse impact on our business.

If the patent applications we hold or have in-licensed with respect to our programs or product candidates fail to issue, if their breadth or strength of protection is threatened, or if they fail to provide meaningful exclusivity for our product candidates, it could dissuade companies from collaborating with us to develop product candidates, and threaten our ability to commercialize, future products. Several patent applications covering our product candidates have been filed recently. We cannot offer any assurances about which, if any, patents will issue, the breadth of any such patent or whether any issued patents will be found invalid and unenforceable or will be threatened by third parties. Any successful opposition to these patents or any other patents owned by or licensed to us could deprive us of rights necessary for the successful commercialization of any product candidates that we may develop. Further, if we encounter delays in regulatory approvals, the period of time during which we could market a product candidate under patent protection could be reduced. Since patent applications in the United States and most other countries are confidential for a period of time after filing, and some remain so until issued, we cannot be certain that we were the first to file any patent application related to a product candidate. Furthermore, if third parties have filed such patent applications, an interference proceeding in the United States can be initiated by a third-party to determine who was the first to invent any of the subject matter covered by the patent claims of our applications. In addition, patents have a limited lifespan. In the United States, the natural expiration of a patent is generally 20 years after it is filed. Various extensions may be available however the life of a patent, and the protection it affords, is limited. Even if patents covering our product candidates are obtained, once the patent life has expired for a product, we may be open to competition from generic medications.

In addition to the protection afforded by patents, we rely on trade secret protection and confidentiality agreements to protect proprietary know-how that is not patentable or that we elect not to patent, processes for which patents are difficult to enforce and any other elements of our product candidate discovery and development processes that involve proprietary know-how, and information or technology that is not covered by patents. However, trade secrets can be difficult to protect. We seek to protect our proprietary technology and processes, in part, by entering into 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.

Although we expect all of our employees and consultants to assign their inventions to us, and all of our employees, consultants, advisors and any third parties who have access to our proprietary know-how, information or technology to enter into confidentiality agreements, we cannot provide any assurances that all such agreements have been duly executed or that our trade secrets and other confidential proprietary information will not be disclosed or that competitors will not otherwise gain access to our trade secrets or independently develop substantially equivalent information and techniques. Misappropriation or unauthorized disclosure of our trade secrets could impair our competitive position and may have a material adverse effect on our business. Additionally, if the steps taken to maintain our trade secrets are deemed inadequate, we may have insufficient recourse against third parties for misappropriating the trade secret. In addition, others may independently discover our trade secrets and proprietary information. For example, the FDA, as part of its Transparency Initiative, is currently considering whether to make additional information publicly available on a routine basis, including information that we may consider to be trade secrets or other proprietary information, and it is not clear at the present time how the FDA's disclosure policies may change in the future, if at all.

Further, the laws of some foreign countries do not protect proprietary rights to the same extent or in the same manner as the laws of the United States. As a result, we may encounter significant problems in protecting and defending our intellectual property both in the United States and abroad. If we are unable to prevent material disclosure of the non-patented intellectual property related to our technologies to third parties, and there is no guarantee that we will have any such enforceable trade secret protection, we may not be able to establish or maintain a competitive advantage in our market, which could materially adversely affect our business, results of operations and financial condition.

Third-party claims of intellectual property infringement may prevent or delay our development and commercialization efforts.

Our commercial success depends in part on our avoiding infringement of the patents and proprietary rights of third parties. There is a substantial amount of litigation, both within and outside the United States, involving patent and other intellectual property rights in the biotechnology and pharmaceutical industries, including patent infringement lawsuits, interferences, oppositions, *ex parte* reexaminations, post-grant review, and *inter partes* review proceedings before the U.S. Patent and Trademark Office ("U.S. PTO") and corresponding foreign patent offices. Numerous U.S. and foreign issued patents and pending patent applications, which are owned by third parties, exist in the fields in which we are pursuing development candidates. As the biotechnology and pharmaceutical industries expand and more patents are issued, the risk increases that our product candidates may be subject to claims of infringement of the patent rights of third parties.

Third parties have asserted and in the future may assert that we are employing their proprietary technology without authorization. There may be third-party patents or patent applications with claims to materials, formulations, methods of manufacture or methods for treatment related to the use or manufacture of our product candidates. Because patent applications can take many years to issue, there may be currently pending patent applications which may later result in issued patents that our product candidates may infringe. In addition, third parties may obtain patents in the future and claim that use of our technologies infringes upon these patents. If any third-party patents were held by a court of competent jurisdiction to cover the manufacturing process of any of our product candidates, any molecules formed during the manufacturing process or any final product itself, the holders of any such patents may be able to block our ability to commercialize such product candidate unless we obtained a license under the applicable patents, or until such patents expire. Similarly, if any third-party patents were held by a court of competent jurisdiction to cover aspects of our formulations, processes for manufacture or methods of use, including combination therapy, the holders of any such patents may be able to block our ability to develop and commercialize the applicable product candidate unless we obtained a license or until such patent expires. In either case, such a license may not be available on commercially reasonable terms or at all.

Parties making claims against us may obtain injunctive or other equitable relief, which could effectively block our ability to further develop and commercialize one or more of our product candidates. Defense of these claims, regardless of their merit,

would involve substantial litigation expense and would be a substantial diversion of employee resources from our business. In the event of a successful claim of infringement against us, we may have to pay substantial damages, including treble damages and attorneys' fees for willful infringement, pay royalties, redesign our infringing products or obtain one or more licenses from third parties, which may be impossible or require substantial time and monetary expenditure.

We may not be successful in obtaining or maintaining necessary rights to gene therapy product components and processes for our development pipeline through acquisitions and in-licenses.

Presently we have rights to the intellectual property, through licenses from third parties and under patents that we own, to develop our product candidates and commercialize our potential products. Because our programs may involve additional product candidates that may require the use of proprietary rights held by third parties, the growth of our business will likely depend in part on our ability to acquire, in-license or use these proprietary rights. In addition, our product candidates may require specific formulations to work effectively and efficiently and these rights may be held by others. We may be unable to acquire or in-license any compositions, methods of use, processes or other third-party intellectual property rights from third parties that we identify. The licensing and acquisition of third-party intellectual property rights is a competitive area, and a number of more established companies are also pursuing strategies to license or acquire third-party intellectual property rights that we may consider attractive. These established companies may have a competitive advantage over us due to their size, cash resources and greater clinical development and commercialization capabilities.

For example, we sometimes collaborate with U.S. and foreign academic institutions to accelerate our preclinical research or clinical development under written agreements with these institutions. Typically, these institutions provide us with an option to negotiate a license to any of the institution's rights in technology resulting from the collaboration. Regardless of such right of first negotiation for intellectual property, we may be unable to negotiate a license within the specified time frame or under terms that are acceptable to us. If we are unable to do so, the institution may offer the intellectual property rights to other parties, potentially blocking our ability to pursue our program.

In addition, companies that perceive us to be a competitor may be unwilling to assign or license rights to us. We also may be unable to license or acquire third-party intellectual property rights on terms that would allow us to make an appropriate return on our investment. If we are unable to successfully obtain rights to required third-party intellectual property rights, our business, financial condition and prospects for growth could suffer.

If we fail to comply with our obligations in the agreements under which we license intellectual property rights from third parties or otherwise experience disruptions to our business relationships with our licensors, we could lose license rights that are important to our business.

We are a party to a number of intellectual property license agreements that are important to our business and expect to enter into additional license agreements in the future. Our existing license agreements impose, and we expect that future license agreements will impose, various diligence, milestone payment, royalty and other obligations on us. Pursuant to an intellectual property license agreement with 2seventy, we granted sublicenses to 2seventy to certain existing license agreements. If we fail to comply with our obligations under these agreements, we or 2seventy materially breach these agreements, or we are subject to a bankruptcy, the licensor may have the right to terminate the license, in which event we would not be able to market products covered by the license.

We may need to obtain licenses from third parties to advance the development of our product candidates or allow commercialization of our potential products, and we have done so from time to time. We may fail to obtain any of these licenses at a reasonable cost or on reasonable terms, if at all. In that event, we may be required to expend significant time and resources to develop or license replacement technology. If we are unable to do so, we may be unable to develop or commercialize the affected product candidates, which could harm our business significantly. We cannot provide any assurances that third-party patents do not exist which might be enforced against our current product candidates, approved product, or future products, resulting in either an injunction prohibiting our sales, or, with respect to our sales, an obligation on our part to pay royalties and/or other forms of compensation to third parties.

In many cases, patent prosecution of our licensed technology is controlled solely by the licensor. If our licensors fail to obtain and maintain patent or other protection for the proprietary intellectual property we license from them, we could lose our rights to the intellectual property or our exclusivity with respect to those rights, and our competitors could market competing products using the intellectual property. In certain cases, we control the prosecution of patents resulting from licensed technology. In the event we breach any of our obligations related to such prosecution, we may incur significant liability to our licensing partners. Licensing of intellectual property is of critical importance to our business and involves complex legal,

business and scientific issues and is complicated by the rapid pace of scientific discovery in our industry. Disputes may arise regarding intellectual property subject to a licensing agreement, including:

- the scope of rights granted under the license agreement and other interpretation-related issues;
- the extent to which our technology and processes infringe on intellectual property of the licensor that is not subject to the licensing agreement;
- the sublicensing of patent and other rights under our collaborative development relationships;
- our diligence obligations under the license agreement and what activities satisfy those diligence obligations;
- the ownership of inventions and know-how resulting from the joint creation or use of intellectual property by our licensors and us and our partners; and
- the priority of invention of patented technology.

If disputes over intellectual property that we have licensed prevent or impair our ability to maintain our current licensing arrangements on acceptable terms, we may be unable to successfully develop and commercialize the affected approved product or product candidates.

We may be involved in lawsuits to protect or enforce our patents or the patents of our licensors, which could be expensive, time-consuming and unsuccessful.

Competitors may infringe our patents or the patents of our licensors. To counter infringement or unauthorized use, we may be required to file infringement claims, which can be expensive and time-consuming. In addition, in an infringement proceeding, a court may decide that a patent of ours or our licensors is not valid, is unenforceable and/or is not infringed, 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. In patent litigation in the United States, defendant counterclaims alleging invalidity and/or unenforceability are commonplace. Grounds for a validity challenge could be an alleged failure to meet any of several statutory requirements, including patent eligible subject matter, lack of novelty, obviousness or non-enablement. Grounds for an unenforceability assertion could be an allegation that someone connected with prosecution of the patent withheld relevant information from the U.S. PTO, or made a misleading statement, during prosecution. Third parties may also raise similar claims before administrative bodies in the United States or abroad, even outside the context of litigation. Such mechanisms include re-examination, post grant review, and equivalent proceedings in foreign jurisdictions (e.g., opposition proceedings). Such proceedings could result in revocation or amendment to our patents in such a way that they no longer cover our product candidates. The outcome following legal assertions of invalidity and unenforceability is unpredictable. With respect to the validity question, for example, we cannot be certain that there is no invalidating prior art, of which we and the patent examiner were unaware during prosecution. If a defendant were to prevail on a legal assertion of invalidity and/or unenforceability, we would lose at least part, and perhaps all, of the patent protection on our potential products. Such a loss of patent protection would have a material adverse impact on our business.

Interference proceedings provoked by third parties or brought by us may be necessary to determine the priority of inventions with respect to our patents or patent applications or those of our licensors. An unfavorable outcome could require us to cease using the related technology or to attempt to license rights to it from the prevailing party. Our business could be harmed if the prevailing party does not offer us a license on commercially reasonable terms. Our defense of litigation or interference proceedings may fail and, even if successful, may result in substantial costs and distract our management and other employees. We may not be able to prevent, alone or with our licensors, misappropriation of our intellectual property rights, particularly in countries where the laws may not protect those rights as fully as in the United States.

Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation, there is a risk that some of our confidential information could be compromised by disclosure during this type of litigation. There could also 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 material adverse effect on the price of our common stock.

We may be subject to claims that our employees, consultants or independent contractors have wrongfully used or disclosed confidential information of third parties or that our employees have wrongfully used or disclosed alleged trade secrets of their former employers.

We employ individuals who 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, consultants and independent contractors 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 our employees, consultants or independent contractors have inadvertently or otherwise used or disclosed intellectual property, including trade secrets or other proprietary information, of any of our employee's former employer or other third parties. Litigation may be necessary to defend against these claims. If we fail in defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights or personnel, which could adversely impact our business. Even if we are successful in defending against such claims, litigation could result in substantial costs and be a distraction to management and other employees.

We may be subject to claims challenging the inventorship or ownership of our patents and other intellectual property.

We may also be subject to claims that former employees, collaborators or other third parties have an ownership interest in our patents or other intellectual property. We have had in the past, and we may also have in the future, ownership disputes arising, for example, from conflicting obligations of consultants or others who are involved in developing our product candidates. Litigation may be necessary to defend against these and other claims challenging inventorship or ownership. If we fail in defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights, such as exclusive ownership of, or right to use, valuable intellectual property. Such an outcome could have a material adverse effect on our business. Even if we are successful in defending against such claims, litigation could result in substantial costs and be a distraction to management and other employees.

Obtaining and maintaining our patent protection depends on compliance with various procedural, document submission, fee payment and other requirements imposed by governmental patent agencies, and our patent protection could be reduced or eliminated for non-compliance with these requirements.

Periodic maintenance fees, renewal fees, annuity fees and various other governmental fees on patents and/or applications will be due to be paid to the U.S. PTO and various governmental patent agencies outside of the United States in several stages over the lifetime of the patents and/or applications. We have systems in place to remind us to pay these fees, and we employ an outside firm and rely on our outside counsel to pay these fees due to non-U.S. patent agencies. The U.S. PTO and various non-U.S. governmental patent agencies require compliance with a number of procedural, documentary, fee payment and other similar provisions during the patent application process. We employ reputable law firms and other professionals to help us comply, and in many cases, an inadvertent lapse can be cured by payment of a late fee or by other means in accordance with the applicable rules. However, there are situations in which non-compliance can result in abandonment or lapse of the patent or patent application, resulting in partial or complete loss of patent rights in the relevant jurisdiction. In such an event, our competitors might be able to enter the market and this circumstance would have a material adverse effect on our business.

Changes in U.S. patent law could diminish the value of patents in general, thereby impairing our ability to protect our potential products.

As is the case with other biotechnology companies, our success is heavily dependent on intellectual property, particularly patents. Obtaining and enforcing patents in the biotechnology industry involve both technological and legal complexity, and is therefore costly, time-consuming and inherently uncertain. In addition, the United States has recently enacted and is currently implementing wide-ranging patent reform legislation. Recent U.S. Supreme Court rulings have narrowed the scope of patent protection available in certain circumstances and weakened the rights of patent owners in certain situations. In addition to increasing uncertainty with regard to our ability to obtain patents in the future, this combination of events has created uncertainty with respect to the value of patents, once obtained. Depending on decisions by the U.S. Congress, the federal courts, and the U.S. PTO, the laws and regulations governing patents could change in unpredictable ways that would weaken our ability to obtain new patents or to enforce our existing patents and patents that we might obtain in the future.

We may not be able to protect our intellectual property rights throughout the world.

Filing, prosecuting and defending patents on product candidates in all countries throughout the world would be prohibitively expensive, and our intellectual property rights in some countries outside the United States can be less extensive than those in the United States. In addition, the laws of some foreign countries do not protect intellectual property rights to the same extent as federal and state laws in the United States. Consequently, we may not be able to prevent third parties from

practicing our inventions in all countries outside the United States, or from selling or importing products made using our inventions in and into the United States or other jurisdictions. Competitors may use our technologies in jurisdictions where we have not obtained patent protection to develop their own products and further, may export otherwise infringing products to territories where we have patent protection, but enforcement is not as strong as that in the United States. These products may compete with our potential products and our patents or other intellectual property rights may not be effective or sufficient to prevent them from competing.

Many companies have encountered significant problems in protecting and defending intellectual property rights in foreign jurisdictions. The legal systems of certain countries, particularly certain developing countries, do not favor the enforcement of patents, trade secrets and other intellectual property protection, particularly those relating to biotechnology products, which could make it difficult for us to stop the infringement of our patents or marketing of competing products in violation of our proprietary rights generally. Proceedings to enforce our patent rights in foreign jurisdictions could result in substantial costs and divert our efforts and attention from other aspects of our business, could put our patents at risk of being invalidated or interpreted narrowly and our patent applications at risk of not issuing and could provoke third parties to assert claims against us. We may not prevail in any lawsuits that we initiate and the damages or other remedies awarded, if any, may not be commercially meaningful. Accordingly, our efforts to enforce our intellectual property rights around the world may be inadequate to obtain a significant commercial advantage from the intellectual property that we develop or license.

Risks related to ownership of our common stock

The market price of our common stock may be highly volatile, and you may not be able to resell your shares at or above the price at which you purchase them.

Companies trading in the stock market in general, and The Nasdaq Global Select Market in particular, have experienced extreme price and volume fluctuations that have often been unrelated or disproportionate to the operating performance of these companies. Broad market and biotechnology and pharmaceutical industry factors may negatively affect the market price of our common stock, regardless of our actual operating performance.

The market price of our common stock has been volatile in the past, and may continue to be volatile for the foreseeable future. Our stock price could be subject to wide fluctuations in response to a variety of factors, including the following:

- adverse results or delays in preclinical or clinical studies;
- reports of adverse events in our product candidates or other gene therapy products, or in clinical studies of such products;
- inability to obtain additional funding;
- any delay in filing an IND or BLA for any of our product candidates, and any adverse development or perceived adverse development with respect to the regulatory authority's review of that IND or BLA;
- failure to successfully manage the commercial launch of beti-cel, eli-cel, or lovo-cel following marketing approval, if and when obtained, including failure to manage our supply chain operations in the coordination and delivery of drug product to patients at qualified treatment centers;
- failure to obtain sufficient pricing and reimbursement for beti-cel, eli-cel, or lovo-cel from private and governmental payers following marketing approval, if and when obtained;
- failure to obtain market acceptance and adoption of beti-cel, eli-cel, or lovo-cel following marketing approval, if and when obtained;
- developments concerning the separation of our programs into two independent, publicly-traded companies;
- failure to maintain our existing strategic collaborations or enter into new collaborations;
- failure by us or our licensors and strategic collaboration partners to prosecute, maintain or enforce our intellectual property rights;
- changes in laws or regulations applicable to future products;
- inability to obtain adequate product supply for beti-cel, eli-cel, or lovo-cel, or the inability to do so at acceptable prices;

- adverse regulatory decisions;
- announcements of clinical trial results or progress in the development of programs by our competitors, and the introduction of new products, services or technologies by our competitors;
- failure to meet or exceed financial projections we may provide to the public;
- failure to meet or exceed the financial projections of the investment community;
- the perception of the pharmaceutical industry by the public, legislatures, regulators and the investment community;
- the effects of the separation of 2seventy bio;
- announcements of significant acquisitions, strategic partnerships, joint ventures or capital commitments by us, our strategic collaboration partner or our competitors;
- disputes or other developments relating to proprietary rights, including patents, litigation matters and our ability to obtain patent protection for our technologies;
- additions or departures of key scientific or management personnel;
- significant lawsuits, including patent or stockholder litigation;
- changes in the market valuations of similar companies;
- sales of our common stock by us or our stockholders in the future; and
- trading volume of our common stock.

Actual or potential sales of our common stock by our employees, including our executive officers, pursuant to pre-arranged stock trading plans could cause our stock price to fall or prevent it from increasing for numerous reasons, and actual or potential sales by such persons could be viewed negatively by other investors.

In accordance with the guidelines specified under Rule 10b5-1 of the Securities Exchange Act of 1934, as amended, and our policies regarding stock transactions, a number of our employees, including executive officers and members of our board of directors, have adopted and may continue to adopt stock trading plans pursuant to which they have arranged to sell shares of our common stock from time to time in the future. Generally, sales under such plans by our executive officers and directors require public filings. Actual or potential sales of our common stock by such persons could cause the price of our common stock to fall or prevent it from increasing for numerous reasons.

Future sales and issuances of our common stock or rights to purchase common stock, including pursuant to our equity incentive plans, could result in additional dilution of the percentage ownership of our stockholders and could cause our stock price to fall.

Additional capital will be needed in the future to continue our planned operations. To the extent we raise additional capital by issuing equity securities, our stockholders may experience substantial dilution. We may sell common stock, convertible securities or other equity securities in one or more transactions at prices and in a manner we determine from time to time. If we sell common stock, convertible securities or other equity securities, investors may be materially diluted by subsequent sales. These sales may also result in material dilution to our existing stockholders, and new investors could gain rights superior to our existing stockholders.

Pursuant to our 2013 Stock Option and Incentive Plan (the "2013 Plan") our management is authorized to grant stock options and other equity-based awards to our employees, directors and consultants. The number of shares available for future grant under the 2013 Plan automatically increases each year by up to 4% of all shares of our capital stock outstanding as of December 31 of the prior calendar year, subject to the ability of our board of directors or compensation committee to take action to reduce the size of the increase in any given year. Currently, we plan to register the increased number of shares available for issuance under the 2013 Plan each year. If our board of directors or compensation committee elects to increase the number of shares available for future grant by the maximum amount each year, our stockholders may experience additional dilution, which could cause our stock price to fall. We make equity grants to certain new employees joining the company pursuant to an inducement plan, and our compensation committee may elect to increase the number of shares available for future grant without stockholder approval. We also have an Employee Stock Purchase Plan and any shares of common stock purchased pursuant to that plan will also cause dilution.

We are subject to securities class action litigation, which may result in substantial costs and a diversion of management's attention and resources, which could harm our business.

In the past, securities class action litigation has often been brought against a company following a decline in the market price of its securities, and we are litigating class action complaints in the United States District Court for the District of Massachusetts and for the District of Delaware, filed by purported stockholders against us and certain of our directors and officers. We may face additional securities class action litigation in the future. This risk is especially relevant for us because biotechnology and pharmaceutical companies have experienced significant stock price volatility in recent years, and we expect to experience continued stock price volatility. Defending against the current litigation and any future litigation could result in substantial costs and a diversion of management's attention and resources, which could harm our business.

Our ability to use our net operating loss carryforwards and certain other tax attributes may be limited.

Under Section 382 of the Internal Revenue Code of 1986, as amended, if a corporation undergoes an "ownership change," generally defined as a greater than 50% change (by value) in its equity ownership over a three-year period, the corporation's ability to use its pre-change net operating loss carryforwards ("NOLs") and other pre-change tax attributes (such as research tax credits) to offset its post-change income may be limited. We have completed several financings since our inception and prior to our initial public offering in 2013, which we believe have resulted in a change in control as defined by IRC Section 382. We completed a study through December 2020 confirming no ownership changes have occurred since our initial public offering in 2013. We may also experience ownership changes in the future as a result of subsequent shifts in our stock ownership. As a result, if we earn net taxable income, our ability to use our pre-change net operating loss carryforwards to offset U.S. federal taxable income may be subject to limitations, which could potentially result in increased future tax liability to us. In addition, at the state level, there may be periods during which the use of NOLs is suspended or otherwise limited, which could accelerate or permanently increase state taxes owed.

We do not intend to pay cash dividends on our common stock so any returns will be limited to the value of our stock.

We have never declared or paid any cash dividends on our common stock. We currently anticipate that we will retain future earnings for the development, operation and expansion of our business and do not anticipate declaring or paying any cash dividends for the foreseeable future. Any return to stockholders will therefore be limited to the appreciation of their stock.

Provisions in our amended and restated certificate of incorporation and by-laws, as well as provisions of Delaware law, could make it more difficult for a third-party to acquire us or increase the cost of acquiring us, even if doing so would benefit our stockholders or remove our current management.

Our amended and restated certificate of incorporation, amended and restated by-laws and Delaware law contain provisions that may have the effect of delaying or preventing a change in control of us or changes in our management. Our amended and restated certificate of incorporation and by-laws, include provisions that:

- authorize "blank check" preferred stock, which could be issued by our board of directors without stockholder approval and may contain voting, liquidation, dividend and other rights superior to our common stock;
- create a classified board of directors whose members serve staggered three-year terms;
- specify that special meetings of our stockholders can be called only by our board of directors, the chairperson of our board of directors, our chief executive officer or our president;
- prohibit stockholder action by written consent;
- establish an advance notice procedure for stockholder approvals to be brought before an annual meeting of our stockholders, including proposed nominations of persons for election to our board of directors;
- provide that our directors may be removed only for cause;
- provide that vacancies on our board of directors may be filled only by a majority of directors then in office, even though less than a quorum;
- specify that no stockholder is permitted to cumulate votes at any election of directors;
- expressly authorize our board of directors to modify, alter or repeal our amended and restated by-laws; and

- require supermajority votes of the holders of our common stock to amend specified provisions of our amended and restated certificate of incorporation and amended and restated by-laws.

These provisions, alone or together, could delay or prevent hostile takeovers and changes in control or changes in our management.

In addition, because we are incorporated in Delaware, we are governed by the provisions of Section 203 of the Delaware General Corporation Law, which limits the ability of stockholders owning in excess of 15% of our outstanding voting stock to merge or combine with us.

Any provision of our amended and restated certificate of incorporation or amended and restated by-laws or Delaware law that has the effect of delaying or deterring a change in control could limit the opportunity for our stockholders to receive a premium for their shares of our common stock, and could also affect the price that some investors are willing to pay for our common stock.

Our amended and restated certificate of incorporation and amended and restated by-laws designate specific courts as the exclusive forum for certain litigation that may be initiated by our stockholders, which could limit our stockholders' ability to obtain a favorable judicial forum for disputes with us.

Our amended and restated certificate of incorporation and amended and restated by-laws specify that, unless we consent in writing to the selection of an alternative forum, the Court of Chancery of the State of Delaware will be the sole and exclusive forum for most legal actions involving claims brought against us by stockholders, other than suits brought to enforce any liability or duty created by the Securities Exchange Act of 1934, as amended (the "Exchange Act") or any other claim for which the federal courts have exclusive jurisdiction and any action that the Court of Chancery of the State of Delaware has dismissed for lack of subject matter jurisdiction, which may be brought in another state or federal court sitting in the State of Delaware. Our amended and restated by-laws also specify that, unless we consent in writing to the selection of an alternate forum, the United States District Court for the District of Massachusetts shall be the sole and exclusive forum for the resolution of any complaint asserting a cause of action arising under the Securities Act of 1933, as amended (the "Securities Act"). Any person or entity purchasing or otherwise acquiring any interest in shares of our capital stock shall be deemed to have notice of and to have consented to the provisions of our amended and restated certificate of incorporation and amended and restated by-laws described above.

We believe these provisions benefit us by providing increased consistency in the application of Delaware law by chancellors particularly experienced in resolving corporate disputes or federal judges experienced in resolving Securities Act disputes, efficient administration of cases on a more expedited schedule relative to other forums and protection against the burdens of multi-forum litigation. However, the provision may have the effect of discouraging lawsuits against our directors, officers, employees, and agents as it may limit any stockholder's ability to bring a claim in a judicial forum that such stockholder finds favorable for disputes with us or our directors, officers, employees, or agents and result in increased costs for stockholders to bring a claim. The enforceability of similar choice of forum provisions in other companies' certificates of incorporation and by-laws has been challenged in legal proceedings, and it is possible that, in connection with any applicable action brought against us, a court could find the choice of forum provisions contained in our amended and restated certificate of incorporation and amended and restated by-laws to be inapplicable or unenforceable in such action. If a court were to find the choice of forum provision contained in our amended and restated certificate of incorporation or amended and restated by-laws to be inapplicable or unenforceable in an action, we may incur additional costs associated with resolving such action in other jurisdictions, which could adversely affect our business, financial condition, or results of operations.

Changes in tax law could adversely affect our business and financial condition.

The rules dealing with U.S. federal, state, and local income taxation are constantly under review by persons involved in the legislative process and by the IRS and the U.S. Treasury Department. Changes to tax laws (which changes may have retroactive application) could adversely affect us or holders of our common stock. In recent years, many such changes have been made and changes are likely to continue to occur in the future. Future changes in tax laws could have a material adverse effect on our business, cash flow, financial condition or results of operations. We urge investors to consult with their legal and tax advisers regarding the implications of potential changes in tax laws on an investment in our common stock.

Item 1B. Unresolved Staff Comments

Not applicable.

Item 2. Properties

Below is a summary of our material owned and leased properties as of December 31, 2021:

Massachusetts

Our current corporate headquarters encompasses approximately 72,988 square feet of office and laboratory space and is located at 60 Binney Street, Cambridge, Massachusetts. The lease commenced on November 3, 2021 and will continue until December 31, 2023.

In April 2019, we entered into a sublease agreement for approximately 267,278 square feet of office space located at 50 Binney Street, Cambridge, Massachusetts. In December 2021, we entered into a sub-sublease agreement with Meta Platforms, Inc. to sublease the entirety of the 50 Binney Street premises which we have rights to under the sublease. The sub-sublease will commence when the space is available for use, which is anticipated to be in the first half of 2022, and is expected to terminate on December 31, 2030.

In November 2021, we entered into a lease agreement for approximately 61,180 square feet of office space located at 455 Grand Union Boulevard, Somerville, Massachusetts. This space will be our future corporate headquarters. The lease will commence when the space is available for use, which is anticipated to be in the first half of 2022.

We believe that our existing facilities are adequate for our current needs.

Item 3. Legal Proceedings

In the ordinary course of business, we are from time to time involved in lawsuits, claims, investigations, proceedings, and threats of litigation relating to intellectual property, commercial arrangements, employment and other matters. While the outcome of these proceedings and claims cannot be predicted with certainty, as of December 31, 2021, we were not party to any legal or arbitration proceedings that may have, or have had in the recent past, significant effects on our financial position or profitability. We believe no governmental proceedings are pending or, to our knowledge, contemplated against us. We are not a party to any material proceedings in which any director, member of senior management or affiliate of ours is either a party adverse to us or our subsidiaries or has a material interest adverse to us or our subsidiaries.

On February 12, 2021, a class action complaint was filed in the United States District Court for the Eastern District of New York, *Leung v. bluebird bio, Inc., et. al.*, Case No. 1:21-cv-00777, by a purported stockholder against us and certain of our officers. The complaint alleges violations of Section 10(b) of the Securities Exchange Act and Rule 10b-5 promulgated thereunder against all defendants and violations of Section 20(a) of the Exchange Act against the officers and seeks unspecified damages. The allegations relate to our disclosure on November 4, 2020 that we were adjusting the expected timing of submission of a BLA to the FDA for LentiGlobin for sickle cell disease to late 2022.

On October 21, 2021, Errant Gene Therapeutics, LLC filed a complaint against us in the United States District Court for the District of Delaware for alleged infringement of U.S. Patents 7,541,179 and 8,058,061. The allegations relate to our use of the BB305 lentiviral vector in the beti-cel program and seeks injunctive relief and money damages. On February 21, 2022, the parties stipulated to amend the case caption, in light of the Plaintiff's name change, from Errant Gene Therapeutics, LLC to San Rocco Therapeutics, LLC. The Court granted this stipulation and, accordingly, the case is now captioned, *San Rocco Therapeutics, LLC v. bluebird bio, Inc. and Third Rock Ventures, LLC*, C.A. No. 21-1478-RGA.

Item 4. Mine Safety Disclosures

Not applicable.

PART II

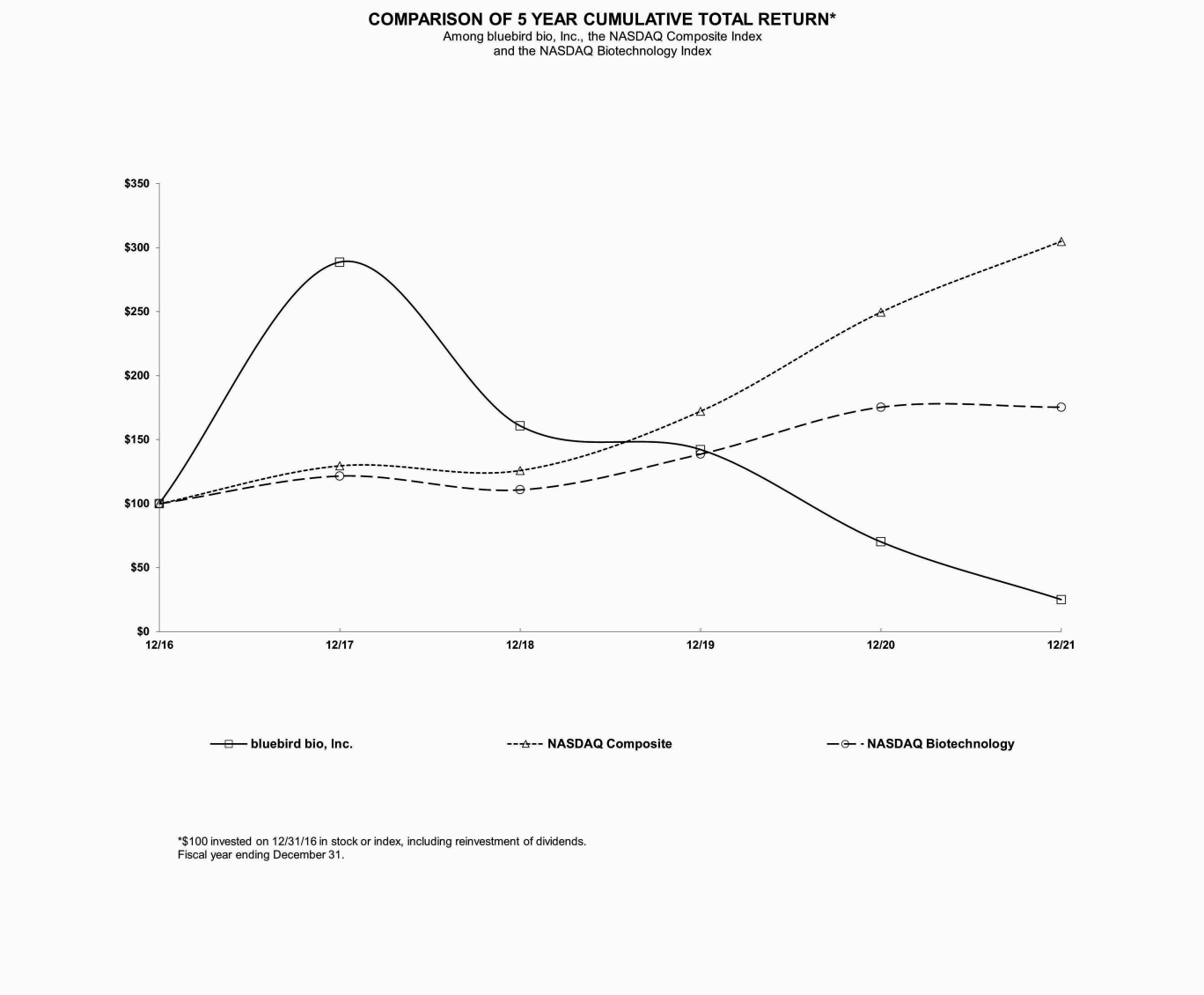
Item 5. Market for Registrant's Common Equity, Related Stockholder Matters and Issuer Purchases of Equity Securities

Our common stock has been traded on the Nasdaq Global Select Market under the symbol "BLUE." On February 28, 2022, the last reported sale price for our common stock on the Nasdaq Global Select Market was $6.04 per share.

Stock Performance Graph

The graph set forth below compares the cumulative total stockholder return on our common stock between December 31, 2016 and December 31, 2021, with the cumulative total return of (a) the Nasdaq Biotechnology Index and (b) the Nasdaq Composite Index, over the same period. This graph assumes the investment of $100 on December 31, 2016 of our common stock, the Nasdaq Biotechnology Index and the Nasdaq Composite Index and assumes the reinvestment of dividends, if any.

The comparisons shown in the graph below are based upon historical data. We caution that the stock price performance shown in the graph below is not necessarily indicative of, nor is it intended to forecast, the potential future performance of our common stock.



Holders

As of February 28, 2022, there were approximately 10 holders of record of our common stock. The actual number of stockholders is greater than this number of record holders, and includes stockholders who are beneficial owners, but whose shares are held in street name by brokers and other nominees. This number of holders of record also does not include stockholders whose shares may be held in trust by other entities.

Dividends

We have not paid any cash dividends on our common stock since inception and do not anticipate paying cash dividends in the foreseeable future.

Securities Authorized for Issuance Under Equity Compensation Plans

Information about our equity compensation plans is provided in Item 12 of Part III of this Annual Report on Form 10-K.

Item 6. Reserved

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

The following information should be read in conjunction with the consolidated financial statements and related notes thereto included in this Annual Report on Form 10-K.

In addition to historical information, this report contains forward-looking statements that involve risks and uncertainties which may cause our actual results to differ materially from plans and results discussed in forward-looking statements. We encourage you to review the risks and uncertainties discussed in the sections entitled Item 1A. "Risk Factors" and "Forward-Looking Statements" included at the beginning of this Annual Report on Form 10-K. The risks and uncertainties can cause actual results to differ significantly from those forecast in forward-looking statements or implied in historical results and trends.

We caution readers not to place undue reliance on any forward-looking statements made by us, which speak only as of the date they are made. We disclaim any obligation, except as specifically required by law and the rules of the SEC, to publicly update or revise any such statements to reflect any change in our expectations or in events, conditions or circumstances on which any such statements may be based, or that may affect the likelihood that actual results will differ from those set forth in the forward-looking statements.

Overview

We are a biotechnology company committed to researching, developing, and commercializing potentially transformative gene therapies for severe genetic diseases. We have built an integrated product platform with broad therapeutic potential in a variety of indications based on our lentiviral gene addition platform. Our gene therapy programs in severe genetic diseases include programs for β-thalassemia, SCD, and CALD. We also expect to make focused investments in research and development efforts on optimizing our existing programs as well as on pipeline programs in severe genetic diseases. The BLA for beti-cel as a treatment for patients with β-thalassemia who receive regular RBC transfusions was accepted for priority review by the FDA, and the PDUFA goal date is August 19, 2022. The BLA for eli-cel as a treatment for patients less than 18 years of age with early CALD was accepted for priority review by the FDA, and the PDUFA goal date is September 16, 2022. We are developing lovo-cel as a treatment for patients with SCD. Based on our discussions with the FDA, we believe that we may be able to seek approval for lovo-cel in the United States on the basis of clinical data from HGB-206 Group C, with supporting data from HGB-210. We have treated all of the patients who will form the primary basis of efficacy for approval, with the demonstration of analytical comparability and validation of our commercial manufacturing process as the key remaining actions prior to submission of our planned BLA for lovo-cel. In December 2021, the FDA placed a partial clinical hold on our clinical program for lovo-cel for enrolling patients under the age of 18. During the partial clinical hold, we anticipate continuing our clinical study activities as planned for patients 18 and older in HGB-210, as well as follow-up activities for treated patients of all ages in all studies.

We are focusing our development and commercialization efforts in the U.S. market. We have submitted a request for the withdrawal of the marketing authorization for beti-cel in the European Union, to be effective in the first half of 2022. As of December 31, 2021, we have withdrawn the marketing authorization for eli-cel in the European Union. We are continuing the long-term follow-up of patients previously enrolled within the clinical trial programs in Europe as planned but do not intend to initiate any new clinical trials in Europe for β-thalassemia, CALD or SCD. As a result, we anticipate a reduction of selling, general and administrative costs and an impact on our excess inventory analysis as future lots are produced, which is based on forecasted consumption levels driven by sales forecasts.

Since our inception in 1992, we have devoted substantially all of our resources to our development efforts relating to our product candidates, including activities to manufacture product candidates in compliance with good manufacturing practices ("GMP") to conduct clinical studies of our product candidates, to provide selling, general and administrative support for these operations and to protect our intellectual property. We have not generated material revenue from product sales. We have funded our operations primarily through the sale of common stock in our public offerings, private placements of preferred stock and warrants and through collaborations.

As of December 31, 2021, we had cash, cash equivalents and marketable securities of approximately $396.6 million. We have never been profitable and have incurred net losses in each year since inception. Our net loss from continuing operations was $562.6 million for the year ended December 31, 2021 and our accumulated deficit was $3.72 billion as of December 31, 2021. Substantially all of our net losses resulted from costs incurred in connection with our research and development programs and from selling, general and administrative costs associated with our operations. We expect to continue to incur significant expenses and operating losses for at least the next several years, as we:

- fund activities related to the potential commercial launches of our late-stage product candidates in the United States;
- seek regulatory approval for our product candidates;
- scale our manufacturing capabilities in support of potential commercialization following any regulatory approvals;
- conduct clinical studies for our clinical programs in β-thalassemia and SCD, and advance our preclinical programs into clinical development; and
- increase research and development-related activities for the discovery and development of product candidates and technologies in severe genetic diseases.

Because of the numerous risks and uncertainties associated with product development and commercialization, we are unable to predict the timing or amount of increased expenses or when or if we will be able to achieve or maintain profitability. Even if we are able to generate revenues from the sale of our products, we may not become profitable. If we fail to become profitable or are unable to sustain profitability on a continuing basis, then we may be unable to continue our operations at planned levels and be forced to reduce our operations.

Business update

We continue to experience disruptions and increased risk related to the ongoing COVID-19 pandemic in our operations and those of third parties upon whom we rely, which may materially and adversely affect our business. These include disruptions and risks related to the conduct of our clinical trials, manufacturing, and commercialization efforts, as policies at various clinical sites and federal, state, local and foreign laws, rules and regulations continue to evolve, including quarantines, travel restrictions, and direction of healthcare resources toward pandemic response efforts. The effects of the COVID-19 pandemic impacted the timing of patient treatment in Europe in the commercial context, and the timing of our ongoing clinical studies, with the result of slower patient enrollment and treatment in our clinical studies and delays in post-treatment follow up visits, the impact of which has varied by clinical study and by program. It has also affected our activities with and operations at our third-party manufacturers. It is unknown how long these disruptions could continue. As a result of the demands upon healthcare regulatory authorities, review, inspection, and other activities related to review of regulatory submissions in drug development may be impacted, and may result in delays for an unknown period of time.

We continue to evaluate the impact of the COVID-19 global pandemic on patients, healthcare providers and our employees, as well as our operations and the operations of our business partners and healthcare communities. In response to the COVID-19 pandemic, we have implemented policies to mitigate the risk of exposure to COVID-19 by our personnel, including restrictions on the number of staff in any given research and development laboratory, and a flexible work-from-home policy applicable to the majority of our personnel.

We are working with our clinical study sites to mitigate the impact of the COVID-19 pandemic on activities for our ongoing clinical studies. However, the ultimate impact of the COVID-19 pandemic on our business operations is highly uncertain and subject to change and will depend on future developments which are difficult to predict.

In March 2021, we placed a portion of our internal LVV manufacturing facility into service, while still completing qualification of the remaining portion. In September 2021, we completed the sale of this LVV manufacturing facility to National Resilience, Inc. Currently all of our manufacturing activities are contracted out to third parties and we utilize third-party contract research organizations ("CROs") to carry out our clinical development activities. As we seek to obtain regulatory approval for our product candidates and begin commercialization following marketing approval, if obtained, we expect to incur significant commercialization expenses as we prepare for and begin product sales, marketing, commercial manufacturing, and distribution at such time. Accordingly, until we generate significant revenues from product sales at such time, we will continue to seek to fund our operations through public or private equity or debt financings, strategic collaborations, or other sources. However, we may be unable to raise additional funds or enter into such other arrangements when needed on favorable terms or at all. Our failure to raise capital or enter into such other arrangements as and when needed would have a negative impact on our financial condition and our ability to develop our product candidates.

In April 2021, we announced our decision to withdraw ZYNTEGLO from the German market because reimbursement negotiations in Germany did not result in a price for ZYNTEGLO that reflects the value of the one-time gene therapy with potential life-long benefit for people living with transfusion dependent β-thalassemia. A total of approximately 50 employees were impacted by this reduction. During the three months ended June 30, 2021, we substantially completed the implementation of this reduction and, in accordance with ASC 420, Exit and Disposal Activities, and ASC 712, *Nonretirement Postemployment*

Benefits, recorded approximately $4.6 million of costs including severance, the portion of the employees' 2021 retention bonuses to be paid in cash, and the pro rata portion of the employees' 2021 performance bonus.

In July 2021, we made the decision to focus our efforts on the U.S. market for beti-cel, eli-cel, and lovo-cel and are executing an orderly wind down of our European operations. A total of approximately 90 employees were impacted by the reduction in workforce associated with this decision. We recorded $21.2 million of expense, in accordance with the related accounting standards mentioned above, for the affected employees.

All costs associated with the April 2021 and July 2021 reductions are reflected within restructuring expenses in our condensed consolidated statements of operations and comprehensive loss. See Note 17, *Reduction in Workforce,* in the notes to the consolidated financial statements.

We had cash, cash equivalents and marketable securities of approximately $396.6 million as of December 31, 2021. In accordance with Accounting Standards Codification ("ASC") 205-40, Going Concern, we evaluated whether there are conditions and events, considered in the aggregate, that raise substantial doubt about our ability to continue as a going concern within one year after the date that the consolidated financial statements are issued. This evaluation initially does not take into consideration the potential mitigating effect of our plans that have not been fully implemented as of the date the financial statements are issued. When substantial doubt exists under this methodology, we evaluate whether the mitigating effect of its plans sufficiently alleviates substantial doubt about our ability to continue as a going concern. The mitigating effect of our plans, however, is only considered if both (1) it is probable that the plans will be effectively implemented within one year after the date that the financial statements are issued, and (2) it is probable that the plans, when implemented, will mitigate the relevant conditions or events that raise substantial doubt about our ability to continue as a going concern within one year after the date that the financial statements are issued. In performing this analysis, we excluded certain elements of our operating plan that cannot be considered probable. Under ASC 205-40, the future receipt of potential funding from future equity or debt issuances, the release of restricted cash related to the Company's 50 Binney Street sublease, and the potential sale of priority review vouchers, if received, cannot be considered probable at this time because none of the plans are entirely within the Company's control or have been approved by the Board of Directors as of the date of the financial statements.

Our expectation to generate operating losses and negative operating cash flows in the future and the need for additional funding to support our planned operations raise substantial doubt regarding our ability to continue as a going concern for a period of one year after the date that the financial statements are issued. Our plan to alleviate the conditions that raise substantial doubt include reduced 2022 spending, including projected savings through the move of the Company's headquarters to Assembly Row in Somerville, Massachusetts, the orderly wind down of European operations, the potential sale of priority review vouchers that would be issued with anticipated U.S. regulatory approvals of BLAs for beti-cel and eli-cel, and the pursuit of additional cash resources through public or private equity or debt financings. We have concluded the likelihood that its plan to successfully obtain sufficient funding from one or more of these sources or adequately reduce expenditures, while reasonably possible, is less than probable. Accordingly, we have concluded that substantial doubt exists about our ability to continue as a going concern for a period of at least 12 months from the date of issuance of these consolidated financial statements.

The accompanying financial statements have been prepared on a going concern basis, which contemplates the realization of assets and satisfaction of liabilities in the ordinary course of business. The financial statements do not include any adjustments relating to the recoverability and classification of recorded asset amounts or the amounts and classification of liabilities that might result from the outcome of the uncertainties described above.

Our legacy business

On November 4, 2021, we completed the separation of our severe genetic disease and oncology programs into two separate, publicly traded companies: bluebird bio, Inc. and 2seventy bio, Inc. ("2seventy bio"), a Delaware corporation and wholly-owned subsidiary prior to the separation (the "Separation"). The Separation was effected by means of a distribution of all of the outstanding shares of common stock of 2seventy bio in which each bluebird stockholder received one share of common stock, par value $0.0001 per share, of 2seventy bio for every three shares of common stock, par value $0.01 per share, of bluebird held as of the close of business on October 19, 2021 (the "Distribution").

We intend to focus on our severe genetic disease programs and 2seventy bio is expected to focus on the separated oncology programs. In collaboration with Bristol-Myers Squibb ("BMS"), 2seventy bio is commercializing idecabtagene vicleucel ("ide-cel") and developing bb21217 as treatments for multiple myeloma, a hematologic malignancy that develops in the bone marrow and is fatal if untreated. 2seventy bio is co-developing and co-promoting ide-cel as ABECMA in the United States with BMS and has exclusively licensed to BMS the development and commercialization rights for ide-cel outside of the United States. It

has exclusively licensed the development and commercialization rights for the bb21217 product candidate to BMS, with an option for 2seventy bio to elect to co-develop and co-promote bb21217 within the United States. In March 2021, BMS received marketing approval from the FDA for ide-cel, marketed as ABECMA, as a treatment of adult patients with relapsed or refractory multiple myeloma after four or more prior lines of therapy, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody. Sales of ABECMA by BMS began in the second quarter of 2021.

In connection with the Separation, we entered into a separation agreement with 2seventy bio, dated as of November 3, 2021, that, among other things, sets forth our agreements with 2seventy bio regarding the principal actions to be taken in connection with the Separation, including the Distribution. In connection with the Separation, we also entered into certain other agreements with 2seventy bio, including transition services agreements. Pursuant to the transition services agreements, we are obligated to provide and are entitled to receive certain transition services related to corporate functions, such as finance, human resources, internal audit, research and development, financial reporting, and information technology. The separation and the aforementioned agreements are more fully described in Note 3, *Discontinued operations*, to our consolidated financial statements appearing elsewhere in this Annual Report on Form 10-K.

Financial operations overview

Product revenue

Our revenues have primarily been derived from product revenues associated with the sale of ZYNTEGLO in Germany.

Other revenue

We have recognized an immaterial amount of revenue associated with grants and collaboration agreements.

Research and development expenses

Research and development expenses consist primarily of costs incurred for the development of our product candidates, which include:

- employee-related expenses, including salaries, benefits, travel and stock-based compensation expense;
- expenses incurred under agreements with CROs and clinical sites that conduct our clinical studies;
- reimbursable costs to our partners for collaborative activities;
- facilities, depreciation, and other expenses, which include direct and allocated expenses for rent and maintenance of facilities, information technology, insurance, and other supplies in support of research and development activities;
- costs associated with our research platform and preclinical activities;
- milestones and upfront license payments;
- costs associated with our regulatory, quality assurance and quality control operations; and
- amortization of certain intangible assets.

Research and development costs are expensed as incurred. Costs for certain development activities are recognized based on an evaluation of the progress to completion of specific tasks using information and data provided to us by our vendors and our clinical sites. We cannot determine with certainty the duration and completion costs of the current or future clinical studies of our product candidates or if, when, or to what extent we will generate revenues from the commercialization and sale of any of our product candidates that obtain regulatory approval. We may not succeed in achieving regulatory approval for all of our product candidates. The duration, costs, and timing of clinical studies and development of our product candidates will depend on a variety of factors, any of which could mean a significant change in the costs and timing associated with the development of our product candidates, including:

- the scope, rate of progress, and expense of our ongoing as well as any additional clinical studies and other research and development activities we undertake;
- future clinical study results;

- uncertainties in clinical study enrollment rates;
- new manufacturing processes or protocols that we may choose to or be required to implement in the manufacture of our LVV or drug product;
- regulatory feedback on requirements for regulatory approval, as well as changing standards for regulatory approval; and
- the timing and receipt of any regulatory approvals.

We plan to increase our research and development expenses for the foreseeable future as we continue to advance the development of beti-cel, eli-cel, and lovo-cel, and conduct research and development activities in our pipeline programs. Our research and development expenses include expenses associated with the following activities:

- for the clinical studies of beti-cel, consisting of HGB-207, HGB-212, and the associated long-term follow-up protocol;
- for the clinical studies of lovo-cel, consisting of HGB-206, HGB-210, and the associated long-term follow-up protocol;
- for the clinical studies of eli-cel, consisting of ALD-104, and the associated long-term follow-up protocol;
- research and development activities for platform technology and our preclinical pipeline programs; and
- for the manufacture of clinical study materials in support of our clinical studies.

We expect that the timing of investment in our ongoing clinical studies will reflect COVID-19 related delays in these studies.

Our direct research and development expenses consist principally of external costs, such as fees paid to investigators, consultants, central laboratories and CROs in connection with our clinical studies, and costs related to acquiring and manufacturing clinical study materials. We allocate salary and benefit costs directly related to specific programs. We do not allocate personnel-related discretionary bonus or stock-based compensation costs, laboratory and related expenses, certain license and other collaboration costs, depreciation or other indirect costs that are deployed across multiple projects under development and, as such, the costs are separately classified as other research and development expenses in the table below:

	Year ended December 31,		
	2021	2020 [2]	2019 [2]
	(in thousands)		
beti-cel	$ 53,292	$ 66,141	$ 73,896
lovo-cel (formerly LentiGlobin for SCD)	64,861	58,862	50,796
eli-cel	54,581	48,028	40,352
Preclinical programs	7,252	6,644	1,195
Total direct research and development expense	179,986	179,675	166,239
Employee- and contractor-related expenses	48,297	39,255	40,619
Stock-based compensation expense	42,989	49,766	59,378
Laboratory and related expenses[1]	5,466	8,956	12,208
License and other collaboration expenses[1]	—	40	1,984
Facility expenses	41,898	37,377	39,291
Other expenses	1,310	4,240	7,400
Total other research and development expenses	139,960	139,634	160,880
Total research and development expense	$ 319,946	$ 319,309	$ 327,119

(1) Prior to 2020, costs within these categories were disclosed as "platform-related expenses."

(2) Prior period amounts have been retrospectively adjusted to reflect the effects of the Separation.

Selling, general and administrative expenses

Selling, general and administrative expenses consist primarily of salaries and related costs for personnel, including stock-based compensation and travel expenses for our employees in executive, operational, finance, legal, business development, commercial, information technology, and human resource functions. Other selling, general and administrative expenses include facility-related costs, professional fees for accounting, tax, legal and consulting services, directors' fees and expenses associated with obtaining and maintaining patents.

We anticipate that our selling, general and administrative expenses, including payroll and sales and marketing expenses, will continue to increase in the future relative to current levels as we perform commercial readiness activities in the United States for our product candidates.

Cost of product revenue

Cost of product revenue includes costs associated with the sale of ZYNTEGLO in Germany.

Restructuring expenses

We record costs and liabilities associated with exit and disposal activities in accordance with ASC 420, *Exit and Disposal Cost Obligations,* and other costs and liabilities associated with postemployment nonretirement benefits in accordance with ASC 712, *Postemployment Nonretirement Benefits*. Such costs are based on the estimate of fair value in the period the liabilities are incurred. We evaluate and adjust costs as appropriate for changes in circumstances as additional information becomes available.

Interest income, net

Interest income, net consists primarily of interest income earned on investments.

Other income (expense), net

Other income (expense), net consists primarily of gains and losses on equity securities held by us, gains and losses on disposal of fixed assets, and gains and losses on foreign currency transactions.

Discontinued operations

Net loss from discontinued operations consists of the results of our oncology business and our manufacturing facility in Durham, North Carolina and is reported as a separate component of income.

Critical accounting policies and significant judgments and estimates

Our management's discussion and analysis of our financial condition and results of operations are based on our financial statements, which have been prepared in accordance with generally accepted accounting principles in the U.S. The preparation of these financial statements requires us to make estimates and judgments that affect the reported amounts of assets, liabilities, and expenses and the disclosure of contingent assets and liabilities in our financial statements. On an ongoing basis, we evaluate our estimates and judgments, including expected business and operational changes, sensitivity and volatility associated with the assumptions used in developing estimates, and whether historical trends are expected to be representative of future trends. We base our estimates on historical experience, known trends and events and various other factors that are believed to be reasonable under the circumstances, the results of which form the basis for making judgments about the carrying values of assets and liabilities that are not readily apparent from other sources. Actual results may differ from these estimates under different assumptions or conditions. In making estimates and judgments, management employs critical accounting policies.

While our significant accounting policies are described in more detail in the notes to our financial statements appearing elsewhere in this annual report, we believe the following accounting policies to be most critical to the judgments and estimates used in the preparation of our financial statements.

Discontinued operations

We determined that the Separation of our oncology business on November 4, 2021 and the sale of our manufacturing facility in Durham, North Carolina in July 2021 represented multiple components of a single disposal plan that met the criteria for classification as a discontinued operation in accordance with ASC Subtopic 205-20, *Discontinued Operations*. Accordingly, the accompanying consolidated financial statements for all periods have been updated to present the assets and liabilities associated with the oncology business and the manufacturing facility separately as discontinued operations on the consolidated balance sheet and the results of all discontinued operations reported as a separate component of income in the consolidated statements of operations and comprehensive loss.

For additional information related to discontinued operations, refer to Note 3, *Discontinued operations*, to our consolidated financial statements appearing elsewhere in this Annual Report on Form 10-K.

Revenue recognition

Revenue recognition

Under Topic 606, *Revenue from Contracts with Customers,* an entity recognizes revenue when its customer obtains control of promised goods or services, in an amount that reflects the consideration that the entity expects to receive in exchange for those goods or services. To determine revenue recognition for arrangements that an entity determines are within the scope of Topic 606, the entity performs the following five steps: (i) identify the contract(s) with a customer; (ii) identify the performance obligations in the contract; (iii) determine the transaction price, including variable consideration, if any; (iv) allocate the transaction price to the performance obligations in the contract; and (v) recognize revenue when (or as) the entity satisfies a performance obligation. We only apply the five-step model to contracts when it is probable that the entity will collect the consideration to which it is entitled in exchange for the goods or services it transfers to the customer.

Once a contract is determined to be within the scope of Topic 606, we assess the goods or services promised within each contract and determine those that are performance obligations. Arrangements that include rights to additional goods or services that are exercisable at a customer's discretion are generally considered options. We assess if these options provide a material right to the customer and if so, they are considered performance obligations.

We assess whether each promised good or service is distinct for the purpose of identifying the performance obligations in the contract. This assessment involves subjective determinations and requires management to make judgments about the individual promised goods or services and whether such are separable from the other aspects of the contractual relationship. Promised goods and services are considered distinct provided that: (i) the customer can benefit from the good or service either on its own or together with other resources that are readily available to the customer (that is, the good or service is capable of being distinct) and (ii) the entity's promise to transfer the good or service to the customer is separately identifiable from other promises in the contract (that is, the promise to transfer the good or service is distinct within the context of the contract).

The transaction price is then determined and allocated to the identified performance obligations in proportion to their standalone selling prices ("SSP") on a relative SSP basis. SSP is determined at contract inception and is not updated to reflect changes between contract inception and when the performance obligations are satisfied.

If the consideration promised in a contract includes a variable amount, we estimate the amount of consideration to which we will be entitled in exchange for transferring the promised goods or services to a customer. We determine the amount of variable consideration by using the expected value method or the most likely amount method. We include the unconstrained amount of estimated variable consideration in the transaction price. The amount included in the transaction price is constrained to the amount for which it is probable that a significant reversal of cumulative revenue recognized will not occur. At the end of each subsequent reporting period, we re-evaluate the estimated variable consideration included in the transaction price and any related constraint, and if necessary, adjust our estimate of the overall transaction price. Any such adjustments are recorded on a cumulative catch-up basis in the period of adjustment.

If an arrangement includes development and regulatory milestone payments, we evaluate whether the milestones are considered probable of being reached and estimate the amount to be included in the transaction price using the most likely amount method. If it is probable that a significant revenue reversal would not occur, the associated milestone value is included in the transaction price. Milestone payments that are not within our control or the licensee's control, such as regulatory approvals, are generally not considered probable of being achieved until those approvals are received.

We then recognize as revenue the amount of the transaction price that is allocated to the respective performance obligation when (or as) each performance obligation is satisfied, either at a point in time or over time, and if over time recognition is based on the use of an output or input method.

Product revenue

We recognize product revenue in accordance with ASC 606, *Revenue from Contracts with Customers*. Product revenue represents sales of ZYNTEGLO. In 2021, we distributed ZYNTEGLO directly to hospitals in Germany. We determined that our contracted sales with hospitals formed a single performance obligation and we recognize revenue from product sales at the point in time that we satisfy our performance obligation, which is upon transferring control of ZYNTEGLO to the hospital. Control of the product generally transfers upon infusion of the product. Costs to manufacture and deliver the product and those associated with administering the therapy are included in cost of product revenue.

Leases

Under ASU 2016-02, *Leases (Topic 842),* ("ASU 2016-02" or "ASC 842"), at the inception of an arrangement, we determine whether the arrangement is or contains a lease based on the unique facts and circumstances present in the arrangement. Leases with a term greater than one year are recognized on the balance sheet as right-of-use assets and short-term and long-term lease liabilities, as applicable. We do not have material financing leases.

Operating lease liabilities and their corresponding right-of-use assets are initially recorded based on the present value of lease payments over the expected remaining lease term. Certain adjustments to the right-of-use asset may be required for items such as incentives received. The interest rate implicit in lease contracts is typically not readily determinable. As a result, we utilize our incremental borrowing rate to discount lease payments, which reflects the fixed rate at which we could borrow on a collateralized basis the amount of the lease payments in the same currency, for a similar term, in a similar economic environment. To estimate our incremental borrowing rate, a credit rating applicable to us is estimated using a synthetic credit rating analysis since we do not currently have a rating agency-based credit rating. Prospectively, we will adjust the right-of-use assets for straight-line rent expense or any incentives received and remeasure the lease liability at the net present value using the same incremental borrowing rate that was in effect as of the lease commencement or transition date.

We have elected not to recognize leases with an original term of one year or less on the balance sheet. We typically only include an initial lease term in our assessment of a lease arrangement. Options to renew a lease are not included in our assessment unless there is reasonable certainty that we will renew.

Assumptions that we made at the commencement date are re-evaluated upon occurrence of certain events, including a lease modification. A lease modification results in a separate contract when the modification grants the lessee an additional right of use not included in the original lease and when lease payments increase commensurate with the standalone price for the additional right of use. When a lease modification results in a separate contract, it is accounted for in the same manner as a new lease.

In accordance with ASC 842, components of a lease should be split into three categories: lease components, non-lease components, and non-components. The fixed and in-substance fixed contract consideration (including any consideration related to non-components) must be allocated based on the respective relative fair values to the lease components and non-lease components.

Entities may elect not to separate lease and non-lease components. Rather, entities would account for each lease component and related non-lease component together as a single lease component. We have elected to account for lease and non-lease components together as a single lease component for all underlying assets and allocate all of the contract consideration to the lease component only.

ASC 842 allows for the use of judgment in determining whether the assumed lease term is for a major part of the remaining economic life of the underlying asset and whether the present value of lease payments represents substantially all of the fair value of the underlying asset. We apply the bright line thresholds referenced in ASC 842-10-55-2 to assist in evaluating leases for appropriate classification. The aforementioned bright lines are applied consistently to our entire portfolio of leases.

Accrued research and development expenses

As part of the process of preparing our financial statements, we are required to estimate our accrued expenses. This process involves reviewing open contracts and purchase orders, communicating with our 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 the actual cost. The majority of our service providers invoice us monthly in arrears for services performed or when contractual milestones are met. 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 at that time.

We recognize expenses related to clinical studies based on our estimates of the services received and efforts expended pursuant to contracts with multiple CROs that conduct and manage clinical studies on our behalf. The financial terms of these agreements are subject to negotiation, vary from contract to contract and may result in uneven payment flows. There may be instances in which payments made to our vendors will exceed the level of services provided and result in a prepayment of the clinical expense. Payments under some of these contracts depend on factors such as the successful enrollment of subjects and the completion of clinical study milestones. In accruing service fees, we estimate the time period over which services will be performed and the level of effort to be expended in each period and adjust accordingly.

Other examples of estimated accrued research and development expenses include fees paid to:

- investigative sites in connection with clinical studies;
- vendors in connection with preclinical development activities; and
- vendors related to the development, manufacturing, and distribution of clinical trial materials.

Stock-based compensation

We issue stock-based awards to employees and non-employees, generally in the form of stock options and restricted stock units. We account for our stock-based awards in accordance with FASB ASC Topic 718, *Compensation—Stock Compensation* ("ASC 718"). ASC 718 requires all stock-based payments to employees, including grants of employee stock options and modifications to existing stock options, to be recognized in the consolidated statements of operations and comprehensive loss based on their fair values. Prior to the adoption of Accounting Standards Update ("ASU") No. 2018-07, *Compensation - Stock Compensation (Topic 718): Improvements to Nonemployee Share-Based Payment Accounting* ("ASU 2018-07"), the measurement date for non-employee awards was generally the date the services are completed, resulting in financial reporting period adjustments to stock-based compensation during the vesting terms for changes in the fair value of the awards. After the adoption of ASU 2018-07, the measurement date for non-employee awards is the date of grant without changes in the fair value of the award. Stock-based compensation costs for non-employees are recognized as expense over the vesting period on a straight-line basis.

Our stock-based awards are subject to either service or performance-based vesting conditions. Compensation expense related to awards to employees, non-employees, and directors, with service-based vesting conditions is recognized on a straight-line basis based on the grant date fair value over the associated service period of the award, which is generally the vesting term. Compensation expense related to awards to employees and non-employees with performance-based vesting conditions is recognized based on the grant date fair value over the requisite service period using the accelerated attribution method to the extent achievement of the performance condition is probable. We estimate the probability that certain performance criteria will be met and do not recognize compensation expense until it is probable that the performance-based vesting condition will be achieved.

We estimate the fair value of our stock-based awards to employees, non-employees, and directors, using the Black-Scholes option pricing model, which requires the input of subjective assumptions, including (i) the expected volatility of our stock, (ii) the expected term of the award, (iii) the risk-free interest rate, and (iv) expected dividends. Effective January 1, 2020, we eliminated the use of a representative peer group and use only our own historical volatility data in our estimate of expected volatility given that there is now a sufficient amount of historical information regarding the volatility of our own stock price. We estimate the expected life of our employee stock options using the "simplified" method, whereby, the expected life equals the average of the vesting term and the original contractual term of the option, unless there are more appropriate indicators of the expected life when measuring the fair value of a modified award. The risk-free interest rates for periods within the expected life of the option were based on the U.S. Treasury yield curve in effect during the period the options were granted.

Conversion and modification of equity awards outstanding at Separation date

In connection with the Separation on November 4, 2021, under the provisions of the existing plans, we adjusted our outstanding equity awards in accordance with the terms of the Employee Matters Agreement (an equitable adjustment) to preserve the intrinsic value of the awards immediately before and after the Distribution. Upon the Distribution, employees

holding stock options, restricted stock units and performance restricted stock units denominated in pre-Distribution bluebird stock received a number of otherwise-similar awards either in post-Distribution bluebird stock or in a combination of post-Distribution bluebird stock and 2seventy bio stock based on conversion ratios outlined for each group of employees in the Employee Matters Agreement that we entered into in connection with the Distribution. The equity awards that were granted prior to 2021 were converted under the shareholder method, wherein employees holding outstanding equity awards received equity awards in both bluebird and 2seventy bio. The conversion ratio for the shareholder method took into consideration a distribution ratio of one share of 2seventy bio common stock for every three shares of bluebird common stock. For equity awards granted in 2021, the number of awards that were outstanding at the Separation were proportionately adjusted to maintain the aggregate intrinsic value of the awards at the date of the Separation. The conversion ratio was determined based on the volume weighted-average trading price for bluebird common stock for the five trading days before and after the Separation.

These modified awards otherwise retained substantially the same terms and conditions, including term and vesting provisions. Additionally, we will not incur any future compensation cost related to equity awards held by 2seventy bio employees and directors. We will incur future compensation cost related to 2seventy bio equity awards held by our employees.

Recent accounting pronouncements

See Note 2, *Summary of significant accounting policies and basis of presentation,* in the notes to consolidated financial statements for a description of recent accounting pronouncements applicable to our business.

Results of Operations

Comparison of the years ended December 31, 2021 and 2020:

	Year ended December 31,		
	2021	2020	Change
		(in thousands)	
Revenue:			
Product revenue	$ 2,850	$ —	$ 2,850
Other revenue	812	—	812
Total revenues	3,662	—	3,662
Operating expenses:			
Research and development	319,946	319,309	637
Selling, general and administrative	209,969	239,950	(29,981)
Cost of product revenue	38,857	—	38,857
Restructuring expense	25,801	—	25,801
Total operating expenses	594,573	559,259	35,314
Loss from operations	(590,911)	(559,259)	(31,652)
Interest income, net	879	5,770	(4,891)
Other income (expense), net	27,652	(6,881)	34,533
Loss before income taxes	(562,380)	(560,370)	(2,010)
Income tax (expense) benefit	(258)	(686)	428
Net loss from continuing operations	$ (562,638)	$ (561,056)	$ (1,582)
Net loss from discontinued operations	$ (256,740)	$ (57,639)	$ (199,101)
Net loss	$ (819,378)	$ (618,695)	$ (200,683)

Revenue. Total revenue was $3.7 million for the year ended December 31, 2021 and is comprised primarily of product revenue from sales of ZYNTEGLO in Germany. For the year ended December 31, 2020 we had no sales of ZYNTEGLO as we had not yet obtained pricing approval in Germany.

Research and development expenses. Research and development expenses were $319.9 million for the year ended December 31, 2021, compared to $319.3 million for the year ended December 31, 2020. The increase of $0.6 million was primarily attributable to the following:

- $13.1 million of increased information technology and facility-related costs;
- $4.8 million of increased material production fees; and
- $2.1 million of increased value-added taxes.

These increased costs were partially offset by:

- $5.5 million of decreased clinical trial costs primarily driven by the clinical hold from February 2021 to June 2021 on our studies of lovo-cel;
- $5.4 million of decreased lab expenses and platform costs;
- $3.1 million of decreased net employee compensation, benefit, and other headcount related expenses, which is primarily driven by a decrease of $6.8 million in stock-based compensation expense due to an overall decrease in the value of awards, offset by an increase due to our employee retention program in 2021.
- $2.5 million of decreased consulting expenses; and
- $2.2 million of decreased medical research costs.

Selling, general and administrative expenses. Selling, general and administrative expenses were $210.0 million for the year ended December 31, 2021, compared to $240.0 million for the year ended December 31, 2020. The decrease of $30.0 million was primarily due to the following:

- $17.3 million of decreased employee compensation, benefit, and other headcount related expenses, which is primarily driven by a decrease of $17.1 million in stock-based compensation expense due to an overall decrease in the value of awards, partially offset by an increase primarily driven by our employee retention program in 2021;
- $7.4 million of decreased costs related to consultants;
- $7.2 million of decreased costs related to commercial readiness activities due to delays in commercialization as a result of the COVID-19 pandemic and our decision to focus our efforts on the U.S. market for beti-cel, eli-cel, and lovo-cel; and
- $2.6 million of decreased costs related to professional service costs.

These decreased costs were partially offset by:

- $4.6 million of increased costs related to information technology and facility-related costs.

Cost of product revenue. Cost of product revenue was $38.9 million for the year ended December 31, 2021. We did not have cost of product revenue for the year ended December 31, 2020. The increase is attributable to costs of sales associated with product sales of ZYNTEGLO in Germany as well as the reserves for excess inventory recognized during the second and third quarters of 2021 based on forecasted consumption levels due to the winddown of our European operations.

Restructuring expenses. Restructuring expenses were $25.8 million for the year ended December 31, 2021. We did not have restructuring expenses for the year ended December 31, 2020. The increase in restructuring expenses is primarily related to the costs associated with the reduction in workforce as a result of our decision to wind down our European operations.

Interest income, net. The decrease in interest income, net was primarily related to decreased interest income earned on investments due to an overall decrease in investments.

Other income (expense), net. The change in other income (expense), net was primarily related to the gain recognized on equity securities.

Comparison of the years ended December 31, 2020 and 2019:

	Year ended December 31,		
	2020	2019	Change
	(in thousands)		
Operating expenses:			
Research and development	319,309	327,119	(7,810)
Selling, general and administrative	239,950	235,844	4,106
Total operating expenses	559,259	562,963	(3,704)
Loss from operations	(559,259)	(562,963)	3,704
Interest income, net	5,770	17,380	(11,610)
Other expense, net	(6,881)	(9,984)	3,103
Loss before income taxes	(560,370)	(555,567)	(4,803)
Income tax (expense) benefit	(686)	545	(1,231)
Net loss from continuing operations	(561,056)	(555,022)	(6,034)
Net loss from discontinued operations	(57,639)	(234,586)	176,947
Net loss	$ (618,695)	$ (789,608)	$ 170,913

Research and development expenses. Research and development expenses were $319.3 million for the year ended December 31, 2020, compared to $327.1 million for the year ended December 31, 2019. The decrease of $7.8 million was primarily attributable to the following:

- $6.9 million of decreased value-added taxes;

- $3.6 million of decreased employee compensation, benefit, and other headcount related expenses, which is primarily driven by a decrease of $9.6 million in stock-based compensation expense offset by an increase in research and development headcount to support overall growth;
- $2.2 million of decreased medical research costs;
- $2.1 million of decreased information technology and facility-related costs;
- $1.6 million of decreased lab costs; and
- $1.3 million of decreased collaboration research funding costs.

These decreased costs were partially offset by:

- $8.7 million of increased material production and non-clinical services costs; and
- $1.8 million of increased consulting costs.

Selling, general and administrative expenses. Selling, general and administrative expenses were $240.0 million for the year ended December 31, 2020, compared to $235.8 million for the year ended December 31, 2019. The increase of approximately $4.1 million was primarily due to the following:

- $8.4 million of increased information technology and facility-related costs primarily due to increased investment in software applications and technology; and
- $5.3 million of increased employee compensation, benefit, and other headcount related expenses, which is primarily driven by an increase in selling, general, and administrative headcount to support overall growth, including an increase of $1.1 million in stock-based compensation expense.

These increased costs were partially offset by:

- $8.3 million of decreased costs related to commercial readiness activities due to delays in commercial launch activities during 2020 as a result of the COVID-19 pandemic; and
- $1.6 million of decreased consulting and professional service fees primarily related to commercial strategy and product marketing.

Interest income, net. The decrease in interest income, net was primarily related to decreased interest income earned on investments due to an overall decrease in interest rates.

Other expense, net. The decrease in other expense, net was primarily related to changes in fair value on equity securities.

Liquidity and Capital Resources

As of December 31, 2021, we had cash, cash equivalents and marketable securities of approximately $396.6 million. Cash in excess of immediate requirements is invested in accordance with our investment policy, primarily with a view to liquidity and capital preservation. As of December 31, 2021, our funds are primarily held in U.S. government agency securities and treasuries, equity securities, corporate bonds, commercial paper, and money market accounts.

We have incurred losses and cumulative negative cash flows from operations since our inception in April 1992, and as of December 31, 2021, we had an accumulated deficit of $3.72 billion. We expect that we will continue to incur significant research and development and selling, general and administrative expenses and, as a result, we will need additional capital to fund our operations within the next twelve months, which we may raise through public or private equity or debt financings, strategic collaborations, or other sources which are not entirely within our control nor have been approved by our Board of Directors as of the date of this filing. Potential additional funding from other sources includes the sale of priority review vouchers, if received.

The likelihood of our long-term success must be considered in light of the expenses, difficulties, and potential delays to be encountered in the development and commercialization of new pharmaceutical products, competitive factors in the marketplace and the complex regulatory environment in which we operate. We may never achieve significant revenue or profitable operations. These factors create substantial doubt about the Company’s ability to continue as a going concern. The

accompanying Consolidated Financial Statements ("CFS") were prepared on a going concern basis, which contemplates the realization of assets and the settlement of liabilities and commitments in the normal course of business. The CFS do not include any adjustments that might be necessary if the Company is unable to continue as a going concern.

We have funded our operations principally from the sale of common stock in public offerings and through our collaborations with BMS as outlined below:

- In May 2020, we entered into the First Amendment to the Amended and Restated Co-Development, Co-Promote and Profit Share Agreement (as amended, the "Amended Ide-cel CCPS") and the Second Amended and Restated bb21217 License Agreement ("Amended bb21217 License Agreement") with BMS (relating to our ide-cel and bb21217 programs which were assigned to 2seventy bio effective upon completion of the Separation), pursuant to which BMS modified its obligations to pay us for future ex-U.S. milestones and royalties on commercial sales by making a one-time up-front payment of $200.0 million.
- In May 2020, we sold 10.5 million shares of common stock (inclusive of shares sold pursuant to an option granted to the underwriters in connection with the offering) through an underwritten public offering at a price of $55.00 per share for aggregate net proceeds of $541.5 million.
- On July 2021, we sold our bluebird Research Triangle manufacturing facility in North Carolina as part of an agreement with National Resilience, Inc ("Resilience"). In consideration, upon closing of the transaction we received $110.3 million from Resilience.
- In September 2021, we sold 2.3 million shares of common stock through a private placement offering of securities at a price of $16.50 per share as well as pre-funded warrants to purchase up to 2.3 million shares of common stock at an effective price of $16.49 per share ($16.49 paid to us upon the closing of the offering and $0.01 to be paid upon exercise of such pre-funded warrants) for aggregate gross proceeds of $75.0 million.

Sources of Liquidity

The discussion of our cash flows that follows does not include the impact of any adjustments to remove discontinued operations, unless otherwise noted, and is stated on a total company consolidated basis. The separation of our oncology business may have a negative impact on our cash flows in future periods.

Cash Flows

The following table summarizes our cash flow activity:

	Year ended December 31,		
	2021	2020	2019
		(in thousands)	
Net cash used in operating activities	$ (635,639)	$ (470,351)	$ (564,384)
Net cash provided by (used in) investing activities	562,557	(84,345)	507,807
Net cash (used in) provided by financing activities	(93,954)	546,715	21,187
Decrease in cash, cash equivalents and restricted cash	$ (167,036)	$ (7,981)	$ (35,390)

Operating Activities. The net cash used in operating activities was $635.6 million for the year ended December 31, 2021 and primarily consisted of a net loss of $819.4 million adjusted for non-cash items including stock-based compensation of $127.9 million, the recognition of a reserve for excess inventories of $29.9 million and depreciation and amortization of $19.6 million, change in net working capital of $18.0 million, and other non-cash items of $17.2 million, offset by an unrealized gain on equity securities of $29.4 million.

The net cash used in operating activities was $470.4 million for the year ended December 31, 2020 and primarily consisted of a net loss of $618.7 million adjusted for non-cash items including stock-based compensation of $156.6 million and depreciation and amortization of $19.4 million, as well as the change in our net working capital.

The net cash used in operating activities was $564.4 million for the year ended December 31, 2019 and primarily consisted of a net loss of $789.6 million adjusted for non-cash items including stock-based compensation of $160.6 million and depreciation and amortization of $17.4 million, as well as the change in our net working capital.

Discontinued operations contributed net losses of $256.7 million, $57.6 million and $234.6 million for the years ended December 31, 2021, 2020 and 2019, respectively.

Investing Activities. Net cash provided by investing activities for the year ended December 31, 2021 was $562.6 million and was primarily due to proceeds from the maturities of available-for-sale marketable securities of $895.3 million, proceeds from the sale of the Durham, North Carolina manufacturing facility of $110.3 million, and proceeds from sales of marketable securities of $31.3 million, offset by the purchase of $451.4 million of available-for-sale marketable securities and the purchase of $14.5 million of property, plant and equipment.

Net cash used in investing activities for the year ended December 31, 2020 was $84.3 million and was primarily due to the purchase of $1.00 billion of marketable securities and the purchase of $29.0 million of property, plant and equipment offset by proceeds from the maturities of available-for-sale marketable securities of $918.3 million and proceeds from sales of marketable securities of $29.9 million.

Net cash provided by investing activities for the year ended December 31, 2019 was $507.8 million and was primarily due to proceeds from the maturities of available-for-sale marketable securities of $1.34 billion offset by the purchase of $756.6 million of marketable securities and the purchase of $71.0 million of property, plant and equipment.

Financing Activities: Net cash used in financing activities for the year ended December 31, 2021 was $94.0 million and was primarily due to net cash of $174.3 million transferred to 2seventy bio in connection with the Separation offset by net cash proceeds from our issuance of common stock and warrants of $75.0 million.

Net cash provided by financing activities for the year ended December 31, 2020 was $546.7 million and was primarily due to net cash proceeds from our May 2020 common stock offering.

Net cash provided by financing activities for the year ended December 31, 2019 was $21.2 million and was due to net cash proceeds from employee option exercises and ESPP contributions.

Contractual Obligations and Commitments

Lease commitments

60 Binney Street sublease

In October 2021, we entered into a consent to assignment and amendment to our lease agreement for our 60 Binney Street lease (the "Assignment"). The Assignment transfers our interest in the lease to 2seventy bio and releases us from our obligation to maintain the $13.8 million collateralized letter of credit required under the original 60 Binney Street lease. Although the lease was legally transferred to 2seventy bio, the lessor required that we remain secondarily liable as a guarantor for payment obligations accruing under the 60 Binney Street lease from the date of Assignment until (i) we have completely vacated the premises and (ii) 2seventy bio has reached a market capitalization of $900 million. Upon Separation, the lease assignment was accounted for as the termination of the original lease and we de-recognized the right-of-use asset and lease liability related to the 60 Binney Street lease and recognized the fair value of the guarantee pursuant to ASC 405, *Liabilities*. The fair value of the guarantee was not material.

Concurrent with the Assignment of the 60 Binney Street lease, we entered into a sublease agreement with 2seventy bio for office, laboratory and storage space located at 60 Binney Street (the "60 Binney Street Sublease") while we construct and outfit our new office and laboratory space. Under the terms of the 60 Binney Street Sublease, we will lease 72,988 square feet for $0.5 million per month in base rent for the period beginning from the Assignment through March 2022 and 58,004 square feet for $0.4 million per month in base rent for the period from April 2022 through March 2024. We will also pay monthly fees for use of the facilities and support personnel, calculated based on our pro-rata share of operating costs during the term of the 60 Binney Street Sublease. We accounted for the 60 Binney Street Sublease as a new lease under ASC 842, and in November 2021, we recognized a right-of-use asset and lease liability related to the 60 Binney Street Sublease.

50 Binney Street sublease

In April 2019, we entered into a sublease agreement for office space located at 50 Binney Street in Cambridge, Massachusetts (the "50 Binney Street Sublease") to supplement our corporate headquarters located at 60 Binney Street in Cambridge, Massachusetts. Under the terms of the 50 Binney Street Sublease, we will lease 267,278 square feet of office space for $99.95 per square foot, or $26.7 million per year in base rent subject to certain operating expenses, taxes and annual rent increases of approximately 3%. The lease will commence when the space is available for use, which is anticipated to be in the

first half of 2022, which reflects the sublessor's exercise of its option to postpone the commencement date of the sublease, and end on December 31, 2030, unless other conditions specified in the 50 Binney Street Sublease occur. Upon signing the 50 Binney Street Sublease, we executed a $40.1 million cash-collateralized letter of credit, which may be reduced in the future subject to the terms of the 50 Binney Street Sublease and certain reduction requirements specified therein. The $40.1 million of cash collateralizing the letter of credit is classified as restricted cash and other non-current assets on our consolidated balance sheets. Payments will commence at the earlier of (i) the date which is 90 days following the commencement date and (ii) the date we take occupancy of all or any portion of the premises. In connection with the execution of the 50 Binney Street Sublease, we also entered into a purchase agreement for furniture and equipment (the "Furniture Purchase Agreement") located on the premises upon lease commencement. Upon execution of the Furniture Purchase Agreement, we made an upfront payment of $7.5 million, all of which was recorded within restricted cash and other non-current assets on our consolidated balance sheets and assessed for recoverability on a recurring basis.

In December 2021, we entered into a sub-sublease agreement with Meta Platforms. Inc. ("Meta"). Under the terms of the sub-sublease, we are subleasing the entirety of the 50 Binney Street premises which we have rights to under the sublease. We are sub-subleasing the premises for $28.0 million in the first year with 3% annual increases in each subsequent year. Meta will receive access to 50 Binney Street at the lease commencement date, which is the same point that we would receive access under the sublease. We remain liable under the sublease, including for the maintenance of the $40.1 million collateralized letter of credit. As a result of the execution of the sub-sublease, we assessed the $7.5 million deposit related to the Furniture Purchase Agreement for recoverability and determined that the amount was not recoverable. As a result, we recorded $7.5 million in our consolidated statements of operations and comprehensive loss as selling, general and administrative expense during the year ended December 31, 2021.

Assembly Row lease

In November 2021, we entered into a lease agreement with Assembly Row 5B, LLC (the "Landlord") for office space located at 455 Grand Union Boulevard in Somerville, Massachusetts to serve as our future headquarters. Under the terms of the arrangement, we will lease approximately 61,180 square feet starting at an annual rate of $45 per square foot, subject to annual increases of 2.5%, plus operating expenses and taxes. In addition, we will be eligible for a tenant work allowance of $160 per rentable square foot of the premises. The lease will commence on the date on which the Landlord tenders possession of the premises to us with any tenant work required to be performed by the Landlord substantially completed, which is anticipated to occur in the first half of 2022.

Embedded leases

In June 2016, we entered into a manufacturing agreement for the future commercial production of our beti-cel and eli-cel drug products with a contract manufacturing organization. Under this 12-year agreement, the contract manufacturing organization will complete the design, construction, validation and process validation of the leased suites prior to anticipated commercial launch of the product candidates. During construction, we paid $12.0 million upon the achievement of certain contractual milestones. We paid $5.0 million for the achievement of the first and second contractual milestones during 2016 and paid $5.5 million for the third and fourth contractual milestones achieved during 2017. In March 2018, $1.5 million of the possible $2.0 million related to the fifth contractual milestone was achieved and was paid in the second quarter of 2018. Construction was completed in March 2018, and beginning in April 2018 we paid $5.1 million per year in fixed suite fees as well as certain fixed labor, raw materials, testing and shipping costs for manufacturing services. We may terminate this agreement at any time upon payment of a one-time termination fee and up to 24 months of fixed suite and labor fees. We concluded that this agreement contains an embedded lease as the suites are designated for our exclusive use during the term of the agreement. We concluded that we are not the deemed owner during construction nor is it a capital lease under ASC 840-10, Leases – Overall. As a result, in prior periods we accounted for the agreement as an operating lease under ASC 840 and recognized straight-line rent expense over the non-cancellable term of the embedded lease. As part of our adoption of ASC 842, effective January 1, 2019, we carried forward the existing lease classification under ASC 840. Additionally, we recorded a right-of-use asset and lease liability for this operating lease on the effective date and are recognizing rent expense on a straight-line basis throughout the remaining term of the embedded lease.

In November 2016, we entered into an agreement for clinical and commercial production of our beti-cel, lovo-cel, and eli-cel drug products with a contract manufacturing organization at an existing facility. We concluded that this agreement contains an embedded operating lease as the clean rooms are designated for our exclusive use during the term of the agreement. The term of the agreement is five years with subsequent three-year renewals at the mutual option of each party. As a result, we recorded a right-of-use asset and lease liability for this operating lease on the effective date of ASC 842, and are recognizing rent expense on a straight-line basis throughout the estimated remaining term of the embedded lease. In March 2020, we amended this agreement with the contract manufacturing organization, resulting in a lease modification. Under the terms of the

amended arrangement, we may be required to pay annual maintenance and production fees of up to €16.5 million, depending on its production needs, and may terminate this agreement with twelve months' notice and a one-time termination fee. The amendment also provides for an option to reserve an additional clean room for a one-time option fee plus annual maintenance fees. As a result, we increased the right-of-use asset and lease liability related to this embedded operating lease during the first quarter of 2020. In September 2021, we reassessed the term of this lease in light of the planned orderly wind down of its operations in Europe. As a result, we reduced the right-of-use asset and related lease liability to reflect a shortened expected term of the agreement. In November 2021, we exercised our right to terminate the lease agreement, and such termination will be effective in November 2022. Per the terms of the amended agreement, we were obligated to pay a one-time termination fee of €1.0 million upon termination, which was paid in December 2021. In connection with this termination, we will pay for services properly rendered through the date of termination in accordance with the contract manufacturing agreement, based on work completed and expenses incurred prior to the date of termination.

In July 2020, we entered into an agreement reserving manufacturing capacity with a contract manufacturing organization. We concluded that this agreement contains an embedded lease as a controlled environment room at the facility is designated for our exclusive use during the term of the agreement, with the option to sublease the space if we provide notice that we will not utilize it for a specified duration of time. Under the terms of the agreement, we will be required to pay up to $5.4 million per year in maintenance fees in addition to the cost of any services provided and may terminate this agreement with eighteen months' notice. The term of the agreement is five years, with the option to extend, and the agreement commenced in March 2021. We classified the embedded lease as an operating lease and recognized a right-of-use asset and lease liability upon lease commencement in March 2021 and are recognizing rent expense on a straight-line basis throughout the remaining term of the embedded lease.

In February 2021, we entered into another agreement reserving manufacturing capacity with a contract manufacturing organization. We concluded that this agreement contains an embedded lease as a controlled environment room at the facility is designated for our exclusive use during the term of the agreement. We also have the option to sublease the space if we provide notice that we will not utilize it for a specified duration of time. Under the terms of the agreement, we are required to pay up to $4.2 million per year in maintenance fees and an immaterial amount of other annual fees as well as per-batch fees for the cost of any services provided. Either party may terminate this agreement with eighteen months' notice at any time or with eight months' notice after stage 5 has commenced. The term of the agreement is five years, with the option to extend. The agreement commenced in November 2021 and upon commencement we classified the embedded lease as an operating lease and recognized a right-of-use asset and lease liability. We recognize rent expense on a straight-line basis throughout the remaining term of the embedded lease.

Contingent Milestone and Royalty Payments

We also have obligations to make future payments to third parties that become due and payable on the achievement of certain development, regulatory and commercial milestones (such as the start of a clinical trial, filing of a BLA, approval by the FDA or product launch). We do not recognize these commitments in our financial statements until they become payable or have been paid.

Based on our development plans as of December 31, 2021, we may be obligated to make future development, regulatory and commercial milestone payments and royalty payments on future sales of specified products associated with our collaboration and license agreements. Payments under these agreements generally become due and payable upon achievement of such milestones or sales. Because the achievement of these milestones or sales had not occurred as of December 31, 2021, such contingencies have not been recorded in our financial statements. Amounts related to contingent milestone payments and sales-based royalties are not yet considered contractual obligations as they are contingent upon success.

- Under a license agreement with Inserm-Transfert pursuant to which we license certain patents and know-how for use in adrenoleukodystrophy therapy, we will be required to make payments based upon development, regulatory and commercial milestones for any products covered by the in-licensed intellectual property. The maximum aggregate payments we may be obligated to pay for each of these milestone categories per product is €0.3, €0.2 and €1.6 million, respectively. We will also be required to pay a royalty on net sales of products covered by the in-licensed intellectual property in the low single digits. The royalty is subject to reduction for any third-party payments required to be made, with a minimum floor in the low single digits.

- Under a license agreement with Institut Pasteur pursuant to which we license certain patents for use in *ex vivo* gene therapy, we will be required to make payments per product covered by the in-licensed intellectual property upon the achievement of development and regulatory milestones, depending on the indication and the method of treatment. The maximum aggregate payments we may be obligated to pay for each of these milestone categories per product is €1.5

and €2.0 million, respectively. We will also be required to pay a royalty on net sales of products covered by the in-licensed intellectual property in the low single digits, which varies slightly depending on the indication of the product. We have the right to sublicense our rights under this agreement, and we will be required to pay a percentage of such license income varying from the low single digits to mid-range double digits depending on the nature of the sublicense and stage of development. We are required to make an annual maintenance payment, which is creditable against royalty payments on a year-by-year basis. On April 1, 2015, we amended this license agreement with Institut Pasteur, which resulted in a payment of €3.0 million that was paid during the second quarter of 2015.

- Under a license agreement with the Board of Trustees of the Leland Stanford Junior University ("Stanford") pursuant to which we license the HEK293T cell line for use in gene therapy products, we are required to pay a royalty on net sales of products covered by the in-licensed intellectual property in the low single digits that varies with net sales. The royalty is reduced for each third-party license that requires payments by us with respect to a licensed product, provided that the royalty to Stanford is not less than a specified percentage that is less than one percent. We have been paying Stanford an annual maintenance fee, which will be creditable against our royalty payments.

- Under a license agreement with the Massachusetts Institute of Technology ("MIT") pursuant to which we license various patents, we will be required to make a payment of $0.1 million based upon a regulatory filing milestone. We will also be required to pay a royalty on net sales of products covered by the in-licensed intellectual property by us or our sublicensees. The royalty is in the low single digits and is reduced for royalties payable to third parties, provided that the royalty to MIT is not less than a specified percentage that is less than one percent. We have the right to sublicense our rights under this agreement, and we will be required to pay a percentage of such license income varying from the mid-single digits to low double digits. We are required to pay MIT an annual maintenance fee based on net sales of licensed products, which is creditable against our royalty payments.

- Under a license agreement with Research Development Foundation pursuant to which we license patents that involve LVV, we will be required to make payments of $1.0 million based upon a regulatory milestone for each product covered by the in-licensed intellectual property. We will also be required to pay a royalty on net sales of products covered by the in-licensed intellectual property in the low single digits, which is reduced by half if during the ten years following first marketing approval the last valid claim within the licensed patent that covers the licensed product expires or ends.

- Under a license agreement with SIRION Biotech GmbH ("Sirion") pursuant to which we license certain patents directed to manufacturing related to our LentiGlobin product candidate, we will be required to make certain payments related to certain development milestone obligations and must report on our progress in achieving these milestones on a periodic basis. We may be obligated to pay up to $13.4 million in the aggregate for each product covered by the in-licensed intellectual property. Upon commercialization of our products covered by the in-licensed intellectual property, we will be obligated to pay Sirion a percentage of net sales as a royalty in the low single digits. The royalties payable under this license agreement are subject to reduction for any third-party payments required to be made, with a minimum floor in the low single digits.

Other Funding Commitments

We enter into contracts in the normal course of business with CROs for preclinical research studies and clinical trials, research supplies and other services and products for operating purposes. We have also entered into multi-year agreements with a manufacturing partner in the United States (Henogen, previously Novasep, and now part of Thermo Fisher Scientific, Inc.), which is partnering with us on production of LVV for lovo-cel. In addition, we have entered into a multi-year agreement with Lonza Houston, Inc. to produce drug product for beti-cel and eli-cel. Currently, SAFC Carlsbad, Inc. ("SAFC", a subsidiary of MilliporeSigma), is the sole manufacturer of the LVV for eli-cel and beti-cel. In our manufacturing agreement with Minaris, we reserve production capacity for the manufacture of our drug product. Our total non-cancelable contractual obligations arising from these manufacturing agreements is $53.8 million, with $43.9 million of these obligations due within the next twelve months. We believe our team of technical personnel has extensive manufacturing, analytical and quality experience as well as strong project management discipline to effectively oversee these contract manufacturing and testing activities, and to compile manufacturing and quality information for our regulatory submissions and potential commercial launch. We are engaging with apheresis and infusion centers, which we refer to as qualified treatment centers, that will be the centers for collection of HSCs from the patient and for infusion of drug product to the patient. For the treatment of patients with our drug product in the commercial setting, we are entering into agreements with participating qualified treatment centers in the jurisdictions where we plan to commercialize our products. These contracts generally provide for termination on notice. Wherever contracts include stipulated commitment payments, we have included such payments in the table of contractual obligations and commitments.

Item 7A. Quantitative and Qualitative Disclosures About Market Risks

We are exposed to market risk related to changes in interest rates. As of December 31, 2021 and 2020, we had cash, cash equivalents and marketable securities of $396.6 million and $741.7 million, respectively, primarily invested in U.S. government agency securities and treasuries, equity securities, corporate bonds, commercial paper and money market accounts. 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. If market interest rates were to increase immediately and uniformly by 100 basis points, or one percentage point, from levels at December 31, 2021, the net fair value of our interest-sensitive marketable securities would have resulted in a hypothetical decline of $1.8 million.

Item 8. Financial Statements and Supplementary Data

The financial statements required to be filed pursuant to this Item 8 are appended to this report. An index of those financial statements is found in Item 15.

Item 9. Changes in and Disagreements with Accountants on Accounting and Financial Disclosure

None.

Item 9A. Controls and Procedures

Limitations on Effectiveness of Controls and Procedures

In designing and evaluating our disclosure controls and procedures, our management recognizes that any controls and procedures, no matter how well designed and operated, can provide only reasonable assurance of achieving the desired control objectives. In addition, the design of disclosure controls and procedures must reflect the fact that there are resource constraints and that management is required to apply judgment in evaluating the benefits of possible controls and procedures relative to their costs.

Evaluation of Disclosure Controls and Procedures

Our management, with the participation of our principal executive officer and principal financial officer, has evaluated the effectiveness of our disclosure controls and procedures (as defined in Rules 13(a)- 15(e) and 15(d)- 15(e) under the Securities Exchange Act of 1934, as amended (the "Exchange Act")), as of the end of the period covered by this Annual Report on Form 10-K. Based on such evaluation, our principal executive officer and principal financial officer have concluded that as of such date, our disclosure controls and procedures were effective at the reasonable assurance level.

Management's Annual Report on Internal Control Over Financial Reporting

Our management is responsible for establishing and maintaining adequate internal control over financial reporting, as such term is defined in Rules 13(a)-15(f) and 15(d)-15(f) under the Exchange Act.

Under the supervision and with the participation of management, including our principal executive and financial officers, we assessed our internal control over financial reporting as of December 31, 2021, based on criteria for effective internal control over financial reporting established in Internal Control — Integrated Framework (2013), issued by the Committee of Sponsoring Organizations of the Treadway Commission (COSO). Our management's assessment of the effectiveness of our internal control over financial reporting included testing and evaluating the design and operating effectiveness of our internal controls. In our management's opinion, we have maintained effective internal control over financial reporting as of December 31, 2021, based on criteria established in the COSO 2013 framework.

The effectiveness of our internal control over financial reporting as of December 31, 2021 has been audited by Ernst & Young LLP, an independent registered public accounting firm, as stated in their report which is included herein.

Changes in Internal Control over Financial Reporting

There have been no changes in our internal control over financial reporting, as such term is defined in Rules 13(a)-15(f) and 15(d)-15(f) promulgated under the Securities Exchange Act of 1934, during the fourth quarter of 2021 that have materially affected, or are 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 bluebird bio, Inc.

Opinion on Internal Control over Financial Reporting

We have audited bluebird bio, Inc.'s internal control over financial reporting as of December 31, 2021, based on criteria established in Internal Control—Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission (2013 framework) (the COSO criteria). In our opinion, bluebird bio, Inc. (the Company) maintained, in all material respects, effective internal control over financial reporting as of December 31, 2021, based on the COSO criteria.

We also have audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States) (PCAOB), the consolidated balance sheets of the Company as of December 31, 2021 and 2020, the related consolidated statements of operations and comprehensive loss, stockholders' equity and cash flows for each of the three years in the period ended December 31, 2021, and the related notes and our report dated March 4, 2022 expressed an unqualified opinion thereon that included an explanatory paragraph regarding the Company's ability to continue as a going concern.

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 Annual 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
Boston, Massachusetts
March 4, 2022

Item 9B. Other Information

Our policy governing transactions in our securities by our directors, officers, and employees permits our officers, directors and certain other persons to enter into trading plans complying with Rule 10b5-1 under the Securities Exchange Act of 1934, as amended. We have been advised that none of our officers have entered into trading plans covering periods after the date of this annual report on Form 10-K in accordance with Rule 10b5-1 and our policy governing transactions in our securities. Generally, under these trading plans, the individual relinquishes control over the transactions once the trading plan is put into place. Accordingly, sales under these plans may occur at any time, including possibly before, simultaneously with, or immediately after significant events involving our company. We do not undertake to report Rule 10b5-1 trading plans that may be adopted by any officers or directors in the future, or to report any modifications or termination of any publicly announced trading plan, except to the extent required by law.

Item 9C. Disclosure Regarding Foreign Jurisdictions that Prevent Inspections

Not applicable.

PART III

Item 10. Directors, Executive Officers and Corporate Governance

Incorporated by reference from the information in our Proxy Statement for our 2022 Annual Meeting of Stockholders, which we will file with the SEC within 120 days of the end of the fiscal year to which this Annual Report on Form 10-K relates.

Item 11. Executive Compensation

Incorporated by reference from the information in our Proxy Statement for our 2022 Annual Meeting of Stockholders, which we will file with the SEC within 120 days of the end of the fiscal year to which this Annual Report on Form 10-K relates.

Item 12. Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters

Incorporated by reference from the information in our Proxy Statement for our 2022 Annual Meeting of Stockholders, which we will file with the SEC within 120 days of the end of the fiscal year to which this Annual Report on Form 10-K relates.

Item 13. Certain Relationships and Related Transactions and Director Independence

Incorporated by reference from the information in our Proxy Statement for our 2022 Annual Meeting of Stockholders, which we will file with the SEC within 120 days of the end of the fiscal year to which this Annual Report on Form 10-K relates.

Item 14. Principal Accountant Fees and Services

Incorporated by reference from the information in our Proxy Statement for our 2022 Annual Meeting of Stockholders, which we will file with the SEC within 120 days of the end of the fiscal year to which this Annual Report on Form 10-K relates.

PART IV

Item 15. Exhibits and Financial Statement Schedules

(a)(1) Financial Statements.

The response to this portion of Item 15 is set forth under Item 8 above.

(a)(2) Financial Statement Schedules.

All schedules have been omitted because they are not required or because the required information is given in the Consolidated Financial Statements or Notes thereto set forth under Item 8 above.

(a)(3) Exhibits.

See the Exhibit Index immediately before the signature page of this Annual Report on Form 10-K. The exhibits listed in the Exhibit Index are filed or incorporated by reference as part of this Annual Report on Form 10-K.

Item 16. Form 10-K Summary

Not applicable.

bluebird bio, Inc.

Index to Consolidated Financial Statements

Report of Independent Registered Public Accounting Firm

To the Stockholders and the Board of Directors of bluebird bio, Inc.

Opinion on the Financial Statements

We have audited the accompanying consolidated balance sheets of bluebird bio, Inc. (the Company) as of December 31, 2021 and 2020, the related consolidated statements of operations and comprehensive loss, stockholders' equity and cash flows for each of the three years in the period ended December 31, 2021, and the related notes (collectively referred to as the "consolidated financial statements"). In our opinion, the consolidated financial statements present fairly, in all material respects, the financial position of the Company at December 31, 2021 and 2020, and the results of its operations and its cash flows for each of the three years in the period ended December 31, 2021, in conformity with U.S. generally accepted accounting principles.

We also have audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States) (PCAOB), the Company's internal control over financial reporting as of December 31, 2021, based on criteria established in Internal Control-Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission (2013 framework) and our report dated March 4, 2022 expressed an unqualified opinion thereon.

The Company's Ability to Continue as a Going Concern

The accompanying consolidated financial statements have been prepared assuming that the Company will continue as a going concern. As discussed in Note 1 to the financial statements, the Company has suffered recurring losses from operations and has stated that substantial doubt exists about the Company's ability to continue as a going concern. Management's evaluation of the events and conditions and management's plans regarding these matters are also described in Note 1. The consolidated financial statements do not include any adjustments that might result from the outcome of this uncertainty.

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.

Critical Audit Matters

The critical audit matter communicated below is a matter arising from the current period audit of the financial statements that was communicated or required to be communicated to the audit committee and that: (1) relates to accounts or disclosures that are material to the financial statements and (2) involved our especially challenging, subjective or complex judgments. The communication of the critical audit matter does not alter in any way our opinion on the consolidated financial statements, taken as a whole, and we are not, by communicating the critical audit matter below, providing a separate opinion on the critical audit matter or on the account or disclosure to which it relates.

Accrued Clinical and Contract Research Organization Costs and Manufacturing Costs

Description of the Matter

As discussed in Note 2 to the consolidated financial statements, the Company records costs for clinical trial activities and manufacturing activities based upon estimates of costs incurred through the balance sheet date that have yet to be invoiced by the contract research organizations, clinical study sites, laboratories, consultants, contract manufacturing organizations or other vendors. The Company's accruals for clinical and contract research organization costs and manufacturing costs totaled $33.5 million at December 31, 2021.

Auditing the Company's accruals for clinical and contract research organization costs and manufacturing costs is especially complex due to the fact that information necessary to estimate the accruals is accumulated from multiple sources. In addition, in certain circumstances, the determination of the nature and level of services that have been received during the reporting period requires judgment because the timing and pattern of vendor invoicing does not correspond to the level of services provided and there may be delays in invoicing from clinical study sites and other vendors.

How We Addressed the Matter in Our Audit

We obtained an understanding, evaluated the design and tested the operating effectiveness of internal controls that addressed the information used in and the identified risks related to the Company's process for recording accrued clinical and contract research organization costs and manufacturing costs.

To test the completeness and valuation of the accruals for clinical and contract research organization costs and manufacturing costs, we performed audit procedures that included, among others, reading certain contracts with contract research organizations, contract manufacturing organizations, and clinical study sites to evaluate financial and certain other contractual terms, and testing the accuracy and completeness of the underlying data used in the accrual computations. We also compared the progress of clinical trials and the progress of manufacturing completed through the balance sheet date with information provided by the Company's operations personnel that oversee the clinical trials and manufacturing activities. Additionally, we obtained information from certain clinical study sites and contract manufacturing organizations which indicated the progress of clinical trials and the progress of manufacturing completed through the balance sheet date and compared that to the Company's accrual computations.

/s/ Ernst & Young LLP

We have served as the Company's auditor since 2012.

Boston, Massachusetts

March 4, 2022

bluebird bio, Inc.

Consolidated Balance Sheets
(in thousands, except per share amounts)

	As of December 31,	
	2021	**2020**
Assets		
Current assets:		
Cash and cash equivalents	$ 161,160	$ 260,629
Marketable securities	138,343	419,599
Prepaid expenses	25,628	25,718
Inventory	—	10,698
Receivables and other current assets	11,389	3,872
Current assets of discontinued operations	—	495,021
Total current assets	336,520	1,215,537
Marketable securities	97,114	61,445
Property, plant and equipment, net	9,706	17,373
Intangible assets, net	—	4,397
Goodwill	5,646	5,646
Operating lease right-of-use assets	91,532	67,563
Restricted cash and other non-current assets	53,277	65,727
Non-current assets of discontinued operations	—	343,564
Total assets	$ 593,795	$ 1,781,252
Liabilities and Stockholders' Equity		
Current liabilities:		
Accounts payable	$ 25,883	$ 13,811
Accrued expenses and other current liabilities	103,958	98,190
Operating lease liability, current portion	23,152	9,711
Current liabilities of discontinued operations	—	81,876
Total current liabilities	152,993	203,588
Operating lease liability, net of current portion	66,432	55,707
Other non-current liabilities	93	5,759
Non-current liabilities of discontinued operations	—	161,142
Total liabilities	$ 219,518	$ 426,196
Commitments and contingencies *Note 11*		
Stockholders' equity:		
Preferred stock, $0.01 par value, 5,000 shares authorized; 0 shares issued and outstanding at December 31, 2021 and December 31, 2020	$ —	$ —
Common stock, $0.01 par value, 125,000 shares authorized; 71,115 and 66,432 shares issued and outstanding at December 31, 2021 and December 31, 2020, respectively	711	665
Additional paid-in capital	4,096,402	4,260,443
Accumulated other comprehensive loss	(2,911)	(5,505)
Accumulated deficit	(3,719,925)	(2,900,547)
Total stockholders' equity	374,277	1,355,056
Total liabilities and stockholders' equity	$ 593,795	$ 1,781,252

See accompanying notes to consolidated financial statements.

bluebird bio, Inc.

Consolidated Statements of Operations and Comprehensive Loss
(in thousands, except per share amounts)

	Year ended December 31,		
	2021	**2020**	**2019**
Revenue:			
Product revenue	$ 2,850	$ —	$ —
Other revenue	812	—	—
Total revenues	3,662	—	—
Operating expenses:			
Research and development	319,946	319,309	327,119
Selling, general and administrative	209,969	239,950	235,844
Cost of product revenue	38,857	—	—
Restructuring expense	25,801	—	—
Total operating expenses	594,573	559,259	562,963
Loss from operations	(590,911)	(559,259)	(562,963)
Interest income, net	879	5,770	17,380
Other income (expense), net	27,652	(6,881)	(9,984)
Loss before income taxes	(562,380)	(560,370)	(555,567)
Income tax (expense) benefit	(258)	(686)	545
Net loss from continuing operations	(562,638)	(561,056)	(555,022)
Net loss from discontinued operations	(256,740)	(57,639)	(234,586)
Net loss	$ (819,378)	$ (618,695)	$ (789,608)
Net loss per share from continuing operations—basic and diluted	$ (8.16)	$ (9.02)	$ (10.06)
Net loss per share from discontinued operations—basic and diluted	$ (3.73)	$ (0.93)	$ (4.25)
Net loss per share—basic and diluted	$ (11.89)	$ (9.95)	$ (14.31)
Weighted-average number of common shares used in computing net loss per share—basic and diluted	68,910	62,178	55,191
Other comprehensive income (loss):			
Other comprehensive income (loss), net of tax benefit (expense) of $0.0 million, $0.0 million and $(1.2) million for the years ended December 31, 2021, 2020 and 2019, respectively	2,364	(3,612)	1,734
Total other comprehensive income (loss)	2,364	(3,612)	1,734
Comprehensive loss	$ (817,014)	$ (622,307)	$ (787,874)

See accompanying notes to consolidated financial statements.

bluebird bio, Inc.

Consolidated Statements of Stockholders' Equity
(in thousands)

	Common stock		Additional paid-in capital	Accumulated other comprehensive loss	Accumulated deficit	Total stockholders' equity
	Shares	Amount				
Balances at December 31, 2018	54,738	$ 547	$ 3,386,958	$ (3,627)	$(1,498,808)	$ 1,885,070
Adjustment to beginning accumulated deficit from adoption of ASU 2016-02	—	—	—	—	6,564	6,564
Vesting of restricted stock units	251	3	(3)	—	—	—
Exercise of stock options	354	4	17,834	—	—	17,838
Purchase of common stock under ESPP	25	—	2,766	—	—	2,766
Stock-based compensation	—	—	160,629	—	—	160,629
Other comprehensive income	—	—	—	1,734	—	1,734
Net loss	—	—	—	—	(789,608)	(789,608)
Balances at December 31, 2019	55,368	554	3,568,184	(1,893)	(2,281,852)	1,284,993
Issuance of common stock upon public offering, net of issuance costs of $33,645	10,455	105	541,431	—	—	541,536
Vesting of restricted stock units	434	4	(4)	—	—	—
Exercise of stock options	95	1	1,846	—	—	1,847
Purchase of common stock under ESPP	80	1	3,774	—	—	3,775
Stock-based compensation	—	—	145,212	—	—	145,212
Other comprehensive loss	—	—	—	(3,612)	—	(3,612)
Net loss	—	—	—	—	(618,695)	(618,695)
Balances at December 31, 2020	66,432	665	4,260,443	(5,505)	(2,900,547)	1,355,056
Vesting of restricted stock units	534	5	(5)	—	—	—
Exercise of stock options	218	2	1,486	—	—	1,488
Purchase of common stock under ESPP	120	1	2,580	—	—	2,581
Issuance of common stock for private equity placement	2,273	23	37,477	—	—	37,500
Issuance of pre-funded warrants	—	—	37,477	—	—	37,477
Issuance of unrestricted stock awards to settle accrued employee compensation	1,538	15	25,059	—	—	25,074
Stock-based compensation	—	—	110,260	—	—	110,260
Distribution of 2seventy bio	—	—	(378,375)	230	—	(378,145)
Other comprehensive income	—	—	—	2,364	—	2,364
Net loss	—	—	—	—	(819,378)	(819,378)
Balances at December 31, 2021	71,115	$ 711	$ 4,096,402	$ (2,911)	$(3,719,925)	$ 374,277

See accompanying notes to consolidated financial statements.

bluebird bio, Inc.

Consolidated Statements of Cash Flows
(in thousands)

	Year ended December 31,		
	2021	**2020**	**2019**
Cash flows from operating activities:			
Net loss	$ (819,378)	$ (618,695)	$ (789,608)
Adjustments to reconcile net loss to net cash used in operating activities:			
Change in fair value of contingent consideration	387	(6,468)	2,747
Depreciation and amortization	19,649	19,356	17,434
Stock-based compensation expense	127,915	156,631	160,629
Unrealized loss (gain) on equity securities	(29,356)	7,217	9,297
Excess inventory reserve	29,924	—	—
Other non-cash items	17,235	458	(11,000)
Changes in operating assets and liabilities:			
Prepaid expenses and other assets	(5,289)	(10,089)	(13,913)
Inventory	(18,447)	—	—
Operating lease right-of-use assets	30,148	21,281	22,496
Accounts payable	9,286	(20,100)	23,600
Accrued expenses and other liabilities	40,025	4,835	29,617
Operating lease liabilities	(32,142)	(17,380)	(9,944)
Collaboration research advancement	(5,596)	(7,397)	(5,739)
Net cash used in operating activities	(635,639)	(470,351)	(564,384)
Cash flows from investing activities:			
Purchase of property, plant and equipment	(14,503)	(28,986)	(71,028)
Purchases of marketable securities	(451,391)	(1,003,525)	(756,570)
Proceeds from maturities of marketable securities	895,333	918,288	1,340,629
Proceeds from sales of marketable securities	31,318	29,878	—
Proceeds from sale of Durham, North Carolina manufacturing facility	110,300	—	—
Purchase of intangible assets	(8,500)	—	(5,224)
Net cash provided by (used in) investing activities	562,557	(84,345)	507,807
Cash flows from financing activities:			
Net cash transferred to 2seventy bio at separation	(174,284)	—	—
Proceeds from public offering of common stock, net of issuance costs	—	541,536	—
Proceeds from issuance of common stock and warrants	74,975	—	—
Proceeds from exercise of stock options and ESPP contributions	5,355	5,179	21,187
Net cash provided by (used in) financing activities	(93,954)	546,715	21,187
Decrease in cash, cash equivalents and restricted cash	(167,036)	(7,981)	(35,390)
Cash, cash equivalents and restricted cash at beginning of year	373,728	381,709	417,099
Cash, cash equivalents and restricted cash at end of year	$ 206,692	$ 373,728	$ 381,709
Reconciliation of cash, cash equivalents and restricted cash:			
Cash and cash equivalents	$ 161,160	$ 317,705	$ 327,214
Restricted cash included in receivables and other current assets	$ 2,282	$ 1,500	$ —
Restricted cash included in restricted cash and other non-current assets	$ 43,250	$ 54,523	$ 54,495
Total cash, cash equivalents and restricted cash	$ 206,692	$ 373,728	$ 381,709
Supplemental cash flow disclosures:			
Purchases of property, plant and equipment included in accounts payable and accrued expenses	$ 411	$ 2,854	$ 5,286
Right-of-use assets obtained in exchange for operating lease liabilities	$ 202,221	$ 19,414	$ 23,939
Reduction of right of use asset and associated lease liability due to lease reassessment	$ (9,004)	$ —	$ —
Issuance of unrestricted stock awards to settle accrued employee compensation	$ 25,074	$ —	$ —
Cash paid during the period for interest	$ —	$ —	$ —
Cash paid during the period for income taxes	$ 617	$ 361	$ 637

See accompanying notes to consolidated financial statements.

1. Description of the business

bluebird bio, Inc. (the “Company” or “bluebird”) was incorporated in Delaware on April 16, 1992, and is headquartered in Cambridge, Massachusetts. The Company is a biotechnology company committed to researching, developing and commercializing potentially transformative gene therapies for severe genetic diseases. Since its inception, the Company has devoted substantially all of its resources to its research and development efforts relating to its product candidates, including activities to manufacture product candidates, conduct clinical studies of its product candidates, perform preclinical research to identify new product candidates and provide selling, general and administrative support for these operations, including commercial-readiness activities.

In August 2021, the Company announced its intent to focus its severe genetic disease business on the U.S. market and further invest in research and development for its core programs in β-thalassemia, sickle cell disease ("SCD"), and cerebral adrenoleukodystrophy ("CALD") in that market. As part of the strategy to focus on the U.S. market, it began executing an orderly wind down of its European operations, which will result in a reduction of selling, general and administrative costs and had an impact on the Company's excess inventory analysis, which is based on forecasted consumption levels driven by sales forecasts.

In November 2021, the Company completed the separation of its severe genetic disease and oncology programs into two separate, independent publicly traded companies, bluebird bio, Inc. and 2seventy bio, Inc. ("2seventy bio"), a Delaware corporation and wholly-owned subsidiary of the Company prior to the separation. bluebird intends to retain its severe genetic disease programs, with a focus on the U.S. market. The Company’s programs in severe genetic diseases include programs for β-thalassemia, SCD, and CALD. The Company also expects to make focused investments in research and development efforts on optimizing our existing programs as well as on pipeline programs in severe genetic diseases.

The Company’s programs in severe genetic diseases include betibeglogene autotemcel ("beti-cel", formerly "LentiGlobin for β-thalassemia gene therapy") as a treatment for β-thalassemia; lovotibeglogene autotemcel ("lovo-cel") as a treatment for SCD; and elivaldogene autotemcel ("eli-cel", formerly "Lenti-D gene therapy") as a treatment for CALD.

As of December 31, 2021, the Company had cash, cash equivalents and marketable securities of $396.6 million. The Company has incurred losses since inception and to date has financed its operations primarily through the sale of equity securities and, to a lesser extent, through collaboration agreements and grants from charitable foundations. As of December 31, 2021, the Company had an accumulated deficit of $3.72 billion. During the twelve months ended December 31, 2021, the Company incurred a loss from continuing operations of $562.6 million and used $635.6 million of cash in operations. The Company expects to continue to generate operating losses and negative operating cash flows for the next few years and will need additional funding to support its planned operating activities through profitability. The transition to profitability is dependent upon the successful development, approval, and commercialization of beti-cel, eli-cel, and lovo-cel, and the achievement of a level of revenues adequate to support its cost structure.

In accordance with Accounting Standards Codification (“ASC”) 205-40, *Going Concern*, the Company evaluated whether there are conditions and events, considered in the aggregate, that raise substantial doubt about its ability to continue as a going concern within one year after the date that these consolidated financial statements are issued. This evaluation initially does not take into consideration the potential mitigating effect of management’s plans that have not been fully implemented as of the date the financial statements are issued. When substantial doubt exists under this methodology, management evaluates whether the mitigating effect of its plans sufficiently alleviates substantial doubt about the Company’s ability to continue as a going concern. The mitigating effect of management’s plans, however, is only considered if both (1) it is probable that the plans will be effectively implemented within one year after the date that the financial statements are issued, and (2) it is probable that the plans, when implemented, will mitigate the relevant conditions or events that raise substantial doubt about the entity’s ability to continue as a going concern within one year after the date that these consolidated financial statements are issued. In performing its analysis, management excluded certain elements of its operating plan that cannot be considered probable. Under ASC 205-40, the future receipt of potential funding from future equity or debt issuances, the release of restricted cash related to the Company’s 50 Binney Street sublease, and the potential sale of priority review vouchers cannot be considered probable at this time because these plans are not entirely within the Company’s control nor have been approved by the Board of Directors as of the date of these consolidated financial statements.

The Company's expectation to generate operating losses and negative operating cash flows in the future and the need for additional funding to support its planned operations raise substantial doubt regarding the Company’s ability to continue as a

going concern for a period of one year after the date that these consolidated financial statements are issued. Management's plans to alleviate the conditions that raise substantial doubt include reduced 2022 spending, including projected savings through the move of the Company's headquarters to Assembly Row in Somerville, Massachusetts, the orderly wind down of European operations, the potential sale of priority review vouchers that would be issued with anticipated U.S. regulatory approvals of BLAs for beti-cel and eli-cel, and the pursuit of additional cash resources through public or private equity or debt financings. Management has concluded the likelihood that its plan to successfully obtain sufficient funding from one or more of these sources, or adequately reduce expenditures, while reasonably possible, is less than probable. Accordingly, the Company has concluded that substantial doubt exists about the Company's ability to continue as a going concern for a period of at least 12 months from the date of issuance of these consolidated financial statements.

The accompanying financial statements have been prepared on a going concern basis, which contemplates the realization of assets and satisfaction of liabilities in the ordinary course of business. The financial statements do not include any adjustments relating to the recoverability and classification of recorded asset amounts or the amounts and classification of liabilities that might result from the outcome of the uncertainties described above.

2. Summary of significant accounting policies and basis of presentation

Basis of presentation

The accompanying consolidated financial statements have been prepared by the Company in accordance with accounting principles generally accepted in the United States ("GAAP"). Any reference in these notes to applicable guidance is meant to refer to the authoritative United States GAAP as included in the ASC and the Accounting Standards Updates ("ASUs") of the Financial Accounting Standards Board ("FASB").

Certain items in the prior year's consolidated financial statements have been reclassified to conform to the current presentation. The Company has presented its oncology business together with its manufacturing facility in Durham, North Carolina as discontinued operations in its consolidated financial statements for all periods presented (see Note 3, *Discontinued operations*). The historical financial statements and footnotes have been recast accordingly.

Amounts reported are computed based on thousands, except percentages, per share amounts, or as otherwise noted. As a result, certain totals may not sum due to rounding.

Principles of consolidation

The accompanying consolidated financial statements include the accounts of the Company and its wholly-owned subsidiaries. 2seventy bio, Inc. ("2seventy bio") was a wholly-owned subsidiary until it became an independent publicly-traded company on November 4, 2021. All intercompany balances and transactions have been eliminated in consolidation.

Discontinued operations

The Company determined that the separation of its oncology business in November 2021 and the sale of its manufacturing facility in Durham, North Carolina in July 2021 represented multiple components of a single disposal plan that met the criteria for classification as a discontinued operation in accordance with ASC Subtopic 205-20, *Discontinued Operations* ("ASC 205-20"). Accordingly, the accompanying consolidated financial statements for all periods presented have been updated to present the assets and liabilities associated with the oncology business and the manufacturing facility separately as discontinued operations on the consolidated balance sheets and the results of all discontinued operations reported as a separate component of loss in the consolidated statements of operations and comprehensive loss (see Note 3, *Discontinued operations*).

Use of estimates

The preparation of financial statements in conformity with GAAP requires management to make estimates and assumptions that affect the reported amounts in the financial statements and accompanying notes. Actual results could materially differ from those estimates. Management considers many factors in selecting appropriate financial accounting policies and controls, and in developing the estimates and assumptions that are used in the preparation of these financial statements. Management must apply significant judgment in this process. In addition, other factors may affect estimates, including: expected business and operational changes, sensitivity and volatility associated with the assumptions used in developing estimates, and whether historical trends are expected to be representative of future trends. The estimation process often may yield a range of potentially reasonable estimates of the ultimate future outcomes and management must select an amount that falls within that range of

reasonable estimates. This process may result in actual results differing materially from those estimated amounts used in the preparation of the financial statements.

Estimates and judgments are used in the following areas, among others: future undiscounted cash flows and subsequent fair value estimates used to assess potential and measure any impairment of long-lived assets, including goodwill and intangible assets, and the measurement of right-of-use assets and lease liabilities, stock-based compensation expense, accrued expenses, income taxes, the assets and liabilities and losses related to discontinued operations and the assessment of the Company's ability to fund its operations for at least the next twelve months from the date of issuance of these financial statements.

Foreign currency translation

The financial statements of the Company's subsidiaries with functional currencies other than the U.S. dollar are translated into U.S. dollars using period-end exchange rates for assets and liabilities, historical exchange rates for stockholders' equity and weighted average exchange rates for operating results. Translation gains and losses are included in accumulated other comprehensive income (loss) in stockholders' equity. Foreign currency transaction gains and losses are included in other income (expense), net in the results of operations.

Segment information

The Company operates in a single segment, focusing on researching, developing and commercializing potentially transformative gene therapies for severe genetic diseases. Consistent with its operational structure, its chief operating decision maker manages and allocates resources at a global, consolidated level. Therefore, results of the Company's operations are reported on a consolidated basis for purposes of segment reporting. All material long-lived assets of the Company reside in the United States.

Cash and cash equivalents

The Company considers all highly liquid investments purchased with original final maturities of 90 days or less from the date of purchase to be cash equivalents. Cash equivalents comprise marketable securities with maturities of less than 90 days when purchased. Cash equivalents are reported at fair value.

Marketable securities

The Company's marketable securities are maintained by investment managers and consist of U.S. government agency securities and treasuries, equity securities, corporate bonds and commercial paper. Debt securities are carried at fair value with the unrealized gains and losses included in other comprehensive income (loss) as a component of stockholders' equity until realized. Any premium arising at purchase is amortized to the earliest call date and any discount arising at purchase is accreted to maturity. Amortization and accretion of premiums and discounts are recorded in interest income, net. Equity securities with readily determinable fair values are also carried at fair value with unrealized gains and losses included in other income (expense), net. Realized gains and losses on both debt and equity securities are determined using the specific identification method and are included in other income (expense), net.

The Company classifies equity securities with readily determinable fair values, which would be available for use in its current operations, as current assets even though the Company may not dispose of such marketable securities within the next 12 months. Equity securities are included in the balance of marketable securities on the Company's consolidated balance sheets. The Company classifies marketable securities with a remaining maturity when purchased of greater than three months as available-for-sale. Marketable securities with a remaining maturity date greater than one year are classified as non-current assets.

Effective January 1, 2020, the Company adopted ASU 2016-13, *Financial Instruments - Credit Losses (Topic 326): Measurement of Credit Losses on Financial Statements* ("ASU 2016-13" or "ASC 326"), using the effective date method. As the Company had never recorded any other-than-temporary-impairment adjustments to its available-for-sale debt securities prior to the effective date, no transition provisions are applicable to the Company.

The Company assesses its available-for-sale debt securities under the available-for-sale debt security impairment model in ASC 326 as of each reporting date in order to determine if a portion of any decline in fair value below carrying value recognized on its available-for-sale debt securities is the result of a credit loss. The Company records credit losses in the consolidated statements of operations and comprehensive loss as credit loss expense within other income (expense), net, which

is limited to the difference between the fair value and the amortized cost of the security. To date, the Company has not recorded any credit losses on its available-for-sale debt securities.

Accrued interest receivable related to the Company's available-for-sale debt securities is presented within receivables and other current assets on the Company's consolidated balance sheets. The Company has elected the practical expedient available to exclude accrued interest receivable from both the fair value and the amortized cost basis of available-for-sale debt securities for the purposes of identifying and measuring any impairment. The Company writes off accrued interest receivable once it has determined that the asset is not realizable. Any write offs of accrued interest receivable are recorded by reversing interest income, recognizing credit loss expense, or a combination of both. To date, the Company has not written off any accrued interest receivables associated with its marketable securities.

Concentrations of credit risk and off-balance sheet risk

Financial instruments that subject the Company to credit risk primarily consist of cash and cash equivalents and available-for-sale securities. The Company maintains its cash and cash equivalent balances with high-quality financial institutions and, consequently, the Company believes that such funds are subject to minimal credit risk. The Company's marketable securities, which primarily consist of U.S. government agency securities and treasuries, equity securities, corporate bonds and commercial paper, potentially subject the Company to concentrations of credit risk. The Company has adopted an investment policy that limits the amounts the Company may invest in any one type of investment and requires all investments held by the Company to be at least AA+/Aa1 rated, thereby reducing credit risk exposure.

Fair value of financial instruments

The Company has certain financial assets and liabilities recorded at fair value which have been classified as Level 1, 2 or 3 within the fair value hierarchy as described in the accounting standards for fair value measurements:

Level 1—Fair values are determined utilizing quoted prices (unadjusted) in active markets for identical assets or liabilities that the Company has the ability to access at the measurement date.

Level 2—Fair values are determined utilizing quoted prices for identical or similar assets or liabilities in active markets or other market observable inputs such as interest rates, yield curves and foreign currency spot rates.

Level 3—Prices or valuations that require inputs that are both significant to the fair value measurement and unobservable.

To the extent that valuation is based on models or inputs that are less observable or unobservable in the market, the determination of fair value requires more judgment. Accordingly, the degree of judgment exercised by the Company in determining fair value is greatest for instruments categorized in Level 3. A financial instrument's level within the fair value hierarchy is based on the lowest level of any input that is significant to the fair value measurement.

Items measured at fair value on a recurring basis include marketable securities (see Note 4, *Marketable securities,* and Note 5, *Fair value measurements*). The carrying amounts of accounts payable and accrued expenses approximate their fair values due to their short-term nature.

Business combinations

Business combinations are accounted for using the acquisition method of accounting. Using this method, the tangible and intangible assets acquired and the liabilities assumed are recorded as of the acquisition date at their respective fair values. The Company evaluates a business as an integrated set of activities and assets that is capable of being managed for the purpose of providing a return in the form of dividends, lower costs or other economic benefits and consists of inputs and processes that provide or have the ability to provide outputs. In an acquisition of a business, the excess of the fair value of the consideration transferred over the fair value of the net assets acquired is recorded as goodwill. In an acquisition of net assets that does not constitute a business, no goodwill is recognized.

Goodwill

Goodwill represents the excess of the purchase price over the fair value of the net assets acquired when accounted for using the acquisition method of accounting for business combinations. Goodwill is not amortized but is evaluated for impairment within the Company's single reporting unit on an annual basis, during the fourth quarter, or more frequently if an event occurs or circumstances change that would more-likely-than-not reduce the fair value of the Company's reporting unit below its

carrying amount. The Company performs a one-step quantitative test and records the amount of goodwill impairment, if any, as the excess of a reporting unit's carrying amount over its fair value, not to exceed the total amount of goodwill allocated to the reporting unit. The Company has not recognized any impairment charges related to goodwill to date.

Upon disposal of a portion of a reporting unit that constitutes a business, goodwill is assigned based on the relative fair values of the portion of the reporting unit being disposed and the portion of the reporting unit remaining. This approach requires a determination of the fair value of both the business to be disposed of and the business (or businesses) within the reporting unit that will be retained. As a result of the separation of the Company's oncology business and the sale of the Company's manufacturing facility in Durham, North Carolina, the Company assigned goodwill based on the relative fair value of the business to be disposed of, and such goodwill has been reclassified to discontinued operations.

Intangible assets, net

Intangible assets, net consist of in-licensed rights with finite lives, net of accumulated amortization. The Company amortizes its intangible assets using the straight-line method over their estimated economic lives and periodically reviews for impairment. During the third quarter of 2021, the Company recognized impairment charges related to intangible assets. In accordance with FASB ASC Topic 350, *General Intangibles Other than Goodwill* ("ASC 350"), the Company reviewed its intangible assets for recoverability. During the third quarter of 2021, the Company determined that the intangible assets were impaired, resulting in the impairment of the remaining carrying value of the intangible assets.

Property, plant and equipment

Property, plant and equipment is stated at cost. Maintenance and repairs that do not improve or extend the lives of the respective assets are expensed to operations as incurred. Depreciation and amortization is calculated using the straight-line method over the estimated useful lives of the assets, which are as follows:

Asset	Estimated useful life
Building	40 years
Computer equipment and software	3 years
Furniture and fixtures	2-5 years
Laboratory equipment	2-5 years
Leasehold improvements	Shorter of the useful life or remaining lease term

Impairment of long-lived assets

The Company reviews long-lived assets when events or changes in circumstances indicate the carrying value of the assets may not be recoverable. Recoverability is measured by comparison of the book values of the assets to future net undiscounted cash flows that the assets are expected to generate. If such assets are considered to be impaired, the impairment to be recognized is measured by the amount by which the book value of the assets exceed their fair value, which is measured based on the projected discounted future net cash flows arising from the assets.

Leases

Effective January 1, 2019, the Company adopted ASC 842 using the required modified retrospective approach and utilizing the effective date as its date of initial application.

At the inception of an arrangement, the Company determines whether the arrangement is or contains a lease based on the unique facts and circumstances present in the arrangement. Leases with a term greater than one year are recognized on the balance sheet as right-of-use assets and current and non-current lease liabilities, as applicable.

Operating lease liabilities and their corresponding right-of-use assets are initially recorded based on the present value of lease payments over the expected remaining lease term. Certain adjustments to the right-of-use asset may be required for items such as incentives received. The interest rate implicit in lease contracts is typically not readily determinable. As a result, the Company utilizes its incremental borrowing rate to discount lease payments, which reflects the fixed rate at which the Company could borrow on a collateralized basis the amount of the lease payments in the same currency, for a similar term, in a similar economic environment. To estimate its incremental borrowing rate, a credit rating applicable to the Company is estimated using a synthetic credit rating analysis since the Company does not currently have a rating agency-based credit rating. Prospectively,

the Company will adjust the right-of-use assets for straight-line rent expense or any incentives received and remeasure the lease liability at the net present value using the same incremental borrowing rate that was in effect as of the lease commencement or transition date.

The Company has elected not to recognize leases with an original term of one year or less on the balance sheet. The Company typically only includes an initial lease term in its assessment of a lease arrangement. Options to renew a lease are not included in the Company's assessment unless there is reasonable certainty that the Company will renew.

Assumptions made by the Company at the commencement date are re-evaluated upon occurrence of certain events, including a lease modification. A lease modification results in a separate contract when the modification grants the lessee an additional right of use not included in the original lease and when lease payments increase commensurate with the standalone price for the additional right of use. When a lease modification results in a separate contract, it is accounted for in the same manner as a new lease.

In accordance with ASC 842, components of a lease should be split into three categories: lease components, non-lease components, and non-components. The fixed and in-substance fixed contract consideration (including any consideration related to non-components) must be allocated based on the respective relative fair values to the lease components and non-lease components.

Entities may elect not to separate lease and non-lease components. Rather, entities would account for each lease component and related non-lease component together as a single lease component. The Company has elected to account for lease and non-lease components together as a single lease component for all underlying assets and allocate all of the contract consideration to the lease component only.

ASC 842 allows for the use of judgment in determining whether the assumed lease term is for a major part of the remaining economic life of the underlying asset and whether the present value of lease payments represents substantially all of the fair value of the underlying asset. The Company applies the bright line thresholds referenced in ASC 842-10-55-2 to assist in evaluating leases for appropriate classification. The aforementioned bright lines are applied consistently to the Company's entire portfolio of leases.

Common stock warrants

The Company's common stock warrants are evaluated pursuant to ASC 480, *Distinguishing Liabilities from Equity* ("ASC 480"), and ASC 815, *Derivatives and Hedging* ("ASC 815"). Management classifies its freestanding warrants as (i) liabilities, if the warrant terms allow settlement of the warrant exercise in cash, or (ii) equity, if the warrant terms only allow settlement in shares of common stock.

Inventory

Inventories are stated at the lower of cost or net realizable value under the first-expired, first-out ("FEFO") methodology. Given human gene therapy products are a new and novel category of therapeutics and future economic benefit is not probable until regulatory approval for the product has been obtained, the Company has only considered inventory for capitalization upon regulatory approval. Manufacturing costs incurred prior to regulatory approval for pre-launch inventory that did not qualify for capitalization and clinical manufacturing costs are charged to research and development expense in the Company's consolidated statements of operations and comprehensive loss as costs are incurred. Additionally, inventory that initially qualifies for capitalization but that may ultimately be used for the production of clinical drug product is expensed as research and development expense when it has been designated for the manufacture of clinical drug product.

Inventory consists of cell banks, plasmids, LVV, other materials and compounds sourced from third party suppliers and utilized in the manufacturing process, and drug product, which has been produced for the treatment of specific patients, that are owned by the Company.

Management periodically reviews inventories for excess or obsolescence, considering factors such as sales forecasts compared to quantities on hand and firm purchase commitments as well as remaining shelf life of on hand inventories. The Company writes-down its inventory that is obsolete or otherwise unmarketable to its estimated net realizable value in the period in which the impairment is first identified. Any such adjustments are included as a component of cost of goods sold within cost of product revenue on the Company's consolidated statements of operations and comprehensive loss.

Revenue recognition

Under ASC Topic 606, *Revenue from Contracts with Customers* ("Topic 606"), an entity recognizes revenue when its customer obtains control of promised goods or services, in an amount that reflects the consideration that the entity expects to receive in exchange for those goods or services. To determine revenue recognition for arrangements that an entity determines are within the scope of Topic 606, the entity performs the following five steps: (i) identify the contract(s) with a customer; (ii) identify the performance obligations in the contract; (iii) determine the transaction price, including variable consideration, if any; (iv) allocate the transaction price to the performance obligations in the contract; and (v) recognize revenue when (or as) the entity satisfies a performance obligation. The Company only applies the five-step model to contracts when it is probable that the entity will collect the consideration to which it is entitled in exchange for the goods or services it transfers to the customer.

Once a contract is determined to be within the scope of Topic 606, the Company assesses the goods or services promised within each contract and determines those that are performance obligations. Arrangements that include rights to additional goods or services that are exercisable at a customer's discretion are generally considered options. The Company assesses if these options provide a material right to the customer and if so, they are considered performance obligations.

The Company assesses whether each promised good or service is distinct for the purpose of identifying the performance obligations in the contract. This assessment involves subjective determinations and requires management to make judgments about the individual promised goods or services and whether such are separable from the other aspects of the contractual relationship. Promised goods and services are considered distinct provided that: (i) the customer can benefit from the good or service either on its own or together with other resources that are readily available to the customer (that is, the good or service is capable of being distinct) and (ii) the entity's promise to transfer the good or service to the customer is separately identifiable from other promises in the contract (that is, the promise to transfer the good or service is distinct within the context of the contract).

The transaction price is then determined and allocated to the identified performance obligations in proportion to their standalone selling prices ("SSP") on a relative SSP basis. SSP is determined at contract inception and is not updated to reflect changes between contract inception and when the performance obligations are satisfied.

If the consideration promised in a contract includes a variable amount, the Company estimates the amount of consideration to which it will be entitled in exchange for transferring the promised goods or services to a customer. The Company determines the amount of variable consideration by using the expected value method or the most likely amount method. The Company includes the unconstrained amount of estimated variable consideration in the transaction price. The amount included in the transaction price is constrained to the amount for which it is probable that a significant reversal of cumulative revenue recognized will not occur. At the end of each subsequent reporting period, the Company re-evaluates the estimated variable consideration included in the transaction price and any related constraint, and if necessary, adjusts its estimate of the overall transaction price. Any such adjustments are recorded on a cumulative catch-up basis in the period of adjustment.

If an arrangement includes development and regulatory milestone payments, the Company evaluates whether the milestones are considered probable of being reached and estimates the amount to be included in the transaction price using the most likely amount method. If it is probable that a significant revenue reversal would not occur, the associated milestone value is included in the transaction price. Milestone payments that are not within the Company's control or the licensee's control, such as regulatory approvals, are generally not considered probable of being achieved until those approvals are received.

In determining the transaction price, the Company adjusts consideration for the effects of the time value of money if the timing of payments provides the Company with a significant benefit of financing. The Company does not assess whether a contract has a significant financing component if the expectation at contract inception is such that the period between payment by the licensees and the transfer of the promised goods or services to the licensees will be one year or less. The Company assessed each of its revenue generating arrangements in order to determine whether a significant financing component exists and concluded that a significant financing component does not exist in any of its arrangements.

The Company then recognizes as revenue the amount of the transaction price that is allocated to the respective performance obligation when (or as) each performance obligation is satisfied, either at a point in time or over time, and if over time recognition is based on the use of an output or input method.

The Company recognizes revenue within the following financial statement captions:

Product revenue

The Company recognizes product revenue in accordance with Topic 606. Product revenue represents sales of ZYNTEGLO. In 2021, the Company distributed ZYNTEGLO directly to hospitals in Germany. The Company determined that contracted sales with hospitals formed a single performance obligation and it recognizes revenue from product sales at the point in time it satisfies the performance obligation, which is upon transferring control of ZYNTEGLO to the hospital. Control of the product generally transfers upon infusion of the product.

Other revenue

In 2021, the Company entered into a grant agreement with the Bill and Melinda Gates Foundation. The Company recognizes grant revenue in accordance with ASC 958-605, *Revenue Recognition Not-for-Profit Entities*, when qualifying costs are incurred and barriers to restriction have been overcome. When grant funds are received after costs have been incurred, the Company records revenue and a corresponding grant receivable. Cash received from grants in advance of incurring qualifying costs is recorded as deferred revenue and recognized as revenue when qualifying costs are incurred. In addition, the Company entered into strategic collaborations and recognized an immaterial amount of revenue associated with those collaboration agreements.

Research and development expenses

Research and development costs are charged to expense as costs are incurred in performing research and development activities, including salaries and benefits, facilities costs, overhead costs, clinical study and related clinical manufacturing costs, license and milestone fees, contract services, manufacturing costs for pre-launch inventory that did not qualify for capitalization, and other related costs. Up-front fees and milestones paid to third parties in connection with technologies which have not reached technological feasibility and do not have an alternative future use are expensed as research and development expense as incurred. In circumstances where amounts have been paid in excess of costs incurred, the Company records a prepaid expense. The Company accrues costs for clinical trial activities based upon estimates of the services received and related expenses incurred that have yet to be invoiced by the contract research organizations, clinical study sites, laboratories, consultants, or other clinical trial vendors that perform the activities. Where amounts owed to a collaboration partner exceed the Company's collaborative arrangement revenues in each quarterly period, such amounts are classified as research and development expense.

Cost of product revenue

Costs to manufacture and deliver the product and those associated with administering the therapy are included in cost of product revenue which are associated with the sale of ZYNTEGLO in Germany. Reserves for excess inventories are also included in cost of product revenue.

Stock-based compensation

The Company's share-based compensation programs grant awards that have included stock options, restricted stock units, restricted stock awards, unrestricted stock awards and shares issued under its employee stock purchase plan. Grants are awarded to employees and non-employees, including the Company's board of directors.

The Company accounts for its stock-based compensation awards in accordance with FASB ASC Topic 718, *Compensation —Stock Compensation* ("ASC 718"). ASC 718 requires all stock-based payments, including grants of stock options and restricted stock units and modifications to existing stock options, to be recognized in the consolidated statements of operations and comprehensive loss based on their fair values.

The Company's stock-based awards are subject to either service or performance-based vesting conditions. Compensation expense related to awards with service-based vesting conditions is recognized on a straight-line basis based on the grant date fair value over the associated service period of the award, which is generally the vesting term. Compensation expense related to awards with performance-based vesting conditions is recognized based on the grant date fair value over the requisite service period using the accelerated attribution method to the extent achievement of the performance condition is probable.

The Company estimates the fair value of its option awards using the Black-Scholes option pricing model, which requires the input of subjective assumptions, including (i) the expected stock price volatility, (ii) the calculation of expected term of the award, (iii) the risk-free interest rate, and (iv) expected dividends. Effective January 1, 2020, the Company eliminated the use of a representative peer group and uses only its own historical volatility data in its estimate of expected volatility given that there

is now a sufficient amount of historical information regarding the volatility of its own stock price. For both employee and non-employee awards, the measurement date is the date of grant. The Company has estimated the expected term of its employee stock options using the "simplified" method, whereby, the expected term equals the arithmetic average of the vesting term and the original contractual term of the option due to its lack of sufficient historical data. The risk-free interest rates for periods within the expected term of the option are based on the U.S. Treasury securities with a maturity date commensurate with the expected term of the associated award. The Company has never paid, and does not expect to pay, dividends in the foreseeable future.

The Company accounts for forfeitures as they occur. Stock-based compensation expense recognized in the financial statements is based on awards for which performance or service conditions are expected to be satisfied.

Conversion and modification of equity awards outstanding at date of separation of 2seventy bio

In connection with the separation of 2seventy bio on November 4, 2021, under the provisions of the existing plans, the Company adjusted its outstanding equity awards in accordance with the terms of the Employee Matters Agreement (an equitable adjustment) to preserve the intrinsic value of the awards immediately before and after the separation. These modified awards otherwise retained substantially the same terms and conditions, including term and vesting provisions. The Company will recognize future expense for awards denominated in bluebird stock and 2seventy bio stock granted to the Company's employees as a result of the separation of 2seventy bio. Expense related to awards denominated in bluebird stock granted to 2seventy bio employees will be incurred by 2seventy bio.

Stock-based compensation expense related to modified awards is measured based on the fair value for the awards as of the modification date. Any incremental stock-based compensation expense arising from the excess of the fair value of the awards on the modification date compared to the fair value of the awards immediately before the modification date is recognized at the modification date or ratably over the requisite remaining service period, as appropriate.

Interest income, net

Interest income, net consists primarily of interest income earned on investments, net of amortization of premium and accretion of discount.

Other income (expense), net

Other income (expense), net consists primarily of gains and losses on equity securities held by the Company, gains and losses on disposal of assets, and gains and losses on foreign currency.

Net loss per share

Basic net loss per share is calculated by dividing net loss from continuing operations attributable to common stockholders, net loss from discontinued operations attributable to common stockholders and net loss attributable to common stockholders by the weighted average number of common shares outstanding during the period, including the shares of common stock issuable upon the exercise of warrants that are exercisable for little or no consideration. Diluted net loss per share is calculated by dividing the net loss from continuing operations attributable to common stockholders, net loss from discontinued operations attributable to common stockholders and net loss attributable to common stockholders by the weighted-average number of common equivalent shares outstanding for the period, including the shares of common stock issuable upon the exercise of warrants that are exercisable for little or no consideration as well as any dilutive effect from outstanding stock options, unvested restricted stock, restricted stock units, and employee stock purchase plan stock using the treasury stock method. Given that the Company recorded a net loss for each of the periods presented, there is no difference between basic and diluted net loss per share since the effect of common stock equivalents would be anti-dilutive and are, therefore, excluded from the diluted net loss per share calculation.

The Company follows the two-class method when computing net loss per share in periods when issued shares that meet the definition of participating securities are outstanding. The two-class method determines net loss per share for each class of common and participating securities according to dividends declared or accumulated and participation rights in undistributed earnings. The two-class method requires income available to common stockholders for the period to be allocated between common and participating securities based upon their respective rights to receive dividends as if all income for the period had been distributed. Accordingly, in periods in which the Company reports a net loss attributable to common stockholders when participating securities are outstanding, losses are not allocated to the participating securities.

Income taxes

Income taxes are recorded in accordance with FASB ASC Topic 740, *Income Taxes* (“ASC 740”), which provides for deferred taxes using an asset and liability approach. The Company recognizes deferred tax assets and liabilities for the expected future tax consequences of events that have been included in the financial statements or tax returns. Deferred tax assets and liabilities are determined based on the difference between the financial statement and tax bases of assets and liabilities using enacted tax rates in effect for the year in which the differences are expected to reverse. Valuation allowances are provided, if based upon the weight of available evidence, it is more likely than not that some or all of the deferred tax assets will not be realized.

The Company accounts for uncertain tax positions in accordance with the provisions of ASC 740. When uncertain tax positions exist, the Company recognizes the tax benefit of tax positions to the extent that the benefit will more likely than not be realized. The determination as to whether the tax benefit will more likely than not be realized is based upon the technical merits of the tax position as well as consideration of the available facts and circumstances. The Company accrues for potential interest and penalties related to unrecognized tax benefits in income tax expense.

Comprehensive loss

Comprehensive loss is composed of net loss and other comprehensive income (loss). Other comprehensive income (loss) consists of unrealized gains and losses on debt securities, foreign currency translation adjustments and other items.

Restructuring expenses

The Company records costs and liabilities associated with exit and disposal activities in accordance with FASB ASC Topic 420, *Exit or Disposal Cost Obligations* ("ASC 420"). Such costs are based on estimates of fair value in the period liabilities are incurred. The Company evaluates and adjusts these costs as appropriate for changes in circumstances as additional information becomes available. Refer to Note 18, *Reduction in workforce,* for more information.

Recent accounting pronouncements

Recently adopted

ASU No. 2019-12, Income Taxes (Topic 740): Simplifying the Accounting for Income Taxes

In December 2019, the FASB issued ASU 2019-12, *Income Taxes (Topic 740): Simplifying the Accounting for Income Taxes* (“ASU 2019-12”), which is intended to simplify the accounting for income taxes. ASU 2019-12 removes certain exceptions to the general principles in Topic 740 and also clarifies and amends existing guidance to improve consistent application. The new standard was effective beginning January 1, 2021. The adoption of ASU 2019-12 did not have a material impact on the Company's financial position or results of operations upon adoption.

ASU No. 2020-06, Debt—Debt with Conversion and Other Options (Subtopic 470-20) and Derivatives and Hedging—Contracts in Entity’s Own Equity (Subtopic 815-40): Accounting for Convertible Instruments and Contracts in an Entity’s Own Equity

In August 2020, the FASB issued ASU 2020-06, *Debt—Debt with Conversion and Other Options (Subtopic 470-20) and Derivatives and Hedging—Contracts in Entity’s Own Equity (Subtopic 815-40): Accounting for Convertible Instruments and Contracts in an Entity’s Own Equity* (“ASU 2020-06”). ASU 2020-06 simplifies the complexity associated with applying U.S. GAAP for certain financial instruments with characteristics of liabilities and equity. More specifically, the amendments focus on the guidance for convertible instruments and derivative scope exception for contracts in an entity's own equity. The Company early adopted the new standard, effective January 1, 2021. The adoption of ASU 2020-06 did not have an impact on the Company's financial position or results of operations upon adoption.

ASU No. 2020-08, Codification Improvements to Subtopic 310-20, Receivables - Nonrefundable Fees and Other Costs

In October 2020, the FASB issued ASU 2020-08, *Codification Improvements to Subtopic 310-20, Receivables - Nonrefundable Fees and Other Costs* (“ASU 2020-08”) to provide further clarification and update the previously issued guidance in ASU 2017-08, *Receivables - Nonrefundable Fees and Other Costs (Subtopic 310-20: Premium Amortization on Purchased Callable Debt Securities)* (“ASU 2017-08”). ASU 2017-08 shortened the amortization period for certain callable debt securities purchased at a premium by requiring that the premium be amortized to the earliest call date. ASU 2020-08

requires that at each reporting period, to the extent that the amortized cost of an individual callable debt security exceeds the amount repayable by the issuer at the next call date, the excess premium shall be amortized to the next call date. The new standard was effective beginning January 1, 2021. The adoption of ASU 2020-08 did not have a material impact on the Company's financial position or results of operations upon adoption.

ASU No. 2020-10, Codification Improvements

In October 2020, the FASB issued ASU 2020-10, *Codification Improvements* ("ASU 2020-10"). The amendments in this ASU represent changes to clarify the ASC, correct unintended application of the guidance, or make minor improvements to the ASC that are not expected to have a significant effect on current accounting practice or create a significant administrative cost to most entities. This new standard was effective beginning January 1, 2021. The adoption of ASU 2020-10 did not have a material impact on the Company's financial position or results of operations upon adoption.

3. Discontinued operations

Sale of bluebird Research Triangle manufacturing facility

In November 2017, the Company acquired a manufacturing facility in Durham, North Carolina ("bRT") for the future manufacture of LVV for the Company’s therapies related to its oncology programs. In July 2021, the Company and Resilience US, Inc., an affiliate of National Resilience, Inc. ("Resilience"), signed an Asset Purchase Agreement (the “Agreement”). As part of the Agreement, and upon the closing of the transaction which occurred in September 2021, Resilience acquired the Company's LVV manufacturing facility located in Durham, North Carolina and retained staff currently employed at the site. As a result of the transaction, the Company disposed of $111.2 million of net assets, primarily consisting of the building and laboratory equipment, that were associated with the Company's oncology programs. The Company recognized a loss on disposal of assets of $2.0 million. As the sale of the bRT manufacturing facility and the separation of 2seventy bio (as described below) were deemed to represent multiple components of a single disposal plan, the assets, liabilities and results of operations related to bRT have been included as a component of discontinued operations.

2seventy bio Separation

On November 4, 2021, the Company completed the previously announced separation of its oncology programs and portfolio, and the certain related assets and liabilities, into a separate, independent publicly traded company (the “Separation”). The Separation was effected by means of a distribution of all of the outstanding shares of common stock of 2seventy bio in which each bluebird stockholder received one share of common stock, par value $0.0001 per share, of 2seventy bio for every three shares of common stock, par value $0.01 per share, of bluebird held as of the close of business on October 19, 2021 (the “Distribution”).

In connection with the Separation, bluebird entered into a separation agreement (the “Separation Agreement”) with 2seventy bio, dated as of November 3, 2021, that, among other things, set forth bluebird’s agreements with 2seventy bio regarding the principal actions to be taken in connection with the Separation, including the Distribution. The effective time of the Distribution was 12:01 a.m. on November 4, 2021. The Separation Agreement identified assets transferred to, liabilities assumed by and contracts assigned to 2seventy bio as part of the Separation, and it provided for when and how these transfers, assumptions and assignments occurred. The purpose of the Separation Agreement was to provide 2seventy bio and bluebird with assets to operate their respective businesses and retain or assume liabilities related to those assets. Each of 2seventy bio and bluebird agreed to releases, with respect to pre-Separation claims, and cross indemnities, with respect to post-Separation claims, that were principally designed to place financial responsibility for the obligations and liabilities allocated to 2seventy bio under the Separation Agreement with 2seventy bio and financial responsibility for the obligations and liabilities allocated to bluebird under the Separation Agreement with bluebird. bluebird and 2seventy bio are also each subject to mutual 12-month employee non-solicit and non-hire restrictions, subject to certain customary exceptions.

The transfer of assets and liabilities to 2seventy bio was effected through a contribution in accordance with the Separation Agreement, as summarized below (in thousands):

	As of November 4, 2021
Assets	
Current assets:	
Cash and cash equivalents	$ 174,284
Marketable securities	160,447
Prepaid expenses	8,732
Receivables and other current assets	21,637
Total current assets	365,100
Marketable securities	106,826
Property, plant and equipment, net	33,972
Intangible assets, net	10,664
Goodwill	6,410
Operating lease right-of-use assets	255,556
Restricted cash and other non-current assets	5,650
Total assets	$ 784,178
Liabilities	
Current liabilities:	
Accounts payable	$ 2,982
Accrued expenses and other current liabilities	85,659
Operating lease liability, current portion	6,938
Collaboration research advancement, current portion	8,957
Total current liabilities	104,536
Deferred revenue, net of current portion	25,762
Collaboration research advancement, net of current portion	16,264
Operating lease liability, net of current portion	257,575
Other non-current liabilities	1,896
Total liabilities	$ 406,033
Net assets transferred to 2seventy bio	$ 378,145

bluebird and 2seventy bio also entered into a tax matters agreement, dated as of November 3, 2021, governing bluebird's and 2seventy bio's respective rights, responsibilities and obligations with respect to taxes (including taxes arising in the ordinary course of business and taxes, if any, incurred as a result of any failure of the distribution and certain related transactions to qualify as tax-free for U.S. federal income tax purposes), tax attributes, the preparation and filing of tax returns, the control of audits and other tax proceedings, and assistance and cooperation in respect of tax matters.

In connection with the Separation, bluebird also entered into an employee matters agreement with 2seventy bio, dated as of November 3, 2021. The employee matters agreement allocates assets, liabilities and responsibilities relating to the employment, compensation and employee benefits of bluebird and 2seventy bio employees, and other related matters, in connection with the Separation, including the treatment of outstanding bluebird incentive equity awards and certain retirement and welfare benefit obligations. The employee matters agreement generally provides that, unless otherwise specified, 2seventy bio is responsible for liabilities associated with employees who transfer to 2seventy bio and employees whose employment terminated prior to the distribution but who primarily supported the 2seventy bio business, and bluebird is responsible for liabilities associated with other employees, including employees retained by bluebird. Pursuant to the employee matters agreement, the outstanding bluebird equity awards held by 2seventy bio and bluebird employees were adjusted immediately prior to the distribution, with the intent to maintain, immediately following the distribution, the economic value of the awards immediately before the distribution date.

bluebird and 2seventy bio also entered into an intellectual property license agreement on November 3, 2021, pursuant to which each party granted a license to certain intellectual property and technology to the other. bluebird granted 2seventy bio a perpetual, worldwide, non-exclusive, royalty-free, fully paid-up license (or, as the case may be, sublicense) to certain intellectual property to allow 2seventy bio to use such intellectual property in connection with 2seventy bio's ongoing and

future research and development activities and product candidates. 2seventy bio granted bluebird a perpetual, worldwide, non-exclusive, royalty-free, fully paid-up license (or, as the case may be, sublicense) to certain intellectual property for use in bluebird's existing products and product candidates. Such licenses between the parties generally allow current or future uses of the intellectual property in connection with each party's respective fields.

Additionally, bluebird entered into two transition services agreements with 2seventy bio, whose President is a member of the Company's Board of Directors. . Pursuant to the transition service agreements, bluebird is obligated to provide and is entitled to receive certain transition services related to corporate functions, such as finance, human resources, internal audit, research and development, financial reporting, and information technology. Services provided by bluebird to 2seventy bio will continue for an initial term of up to two years, unless earlier terminated or extended according to the terms of the transition services agreement. Services received and performed are paid at a mutually agreed upon rate. Amounts received for services provided to 2seventy bio are recorded as other income and amounts paid for services provided by 2seventy bio are recorded as selling, general and administrative expense and research and development expense, as applicable. During the year ended December 31, 2021, the Company incurred $0.7 million of net expense for services provided by 2seventy bio within Research and development and Selling, general and administrative expense in the Consolidated Statements of Operations and Comprehensive Loss. As of December 31, 2021, the Company had an immaterial amount of accounts receivable and accounts payable due from and to 2seventy bio.

Discontinued operations

In connection with the Separation, the Company determined its oncology business, together with the bRT manufacturing facility, qualified for discontinued operations accounting treatment in accordance with ASC 205-20. The following table summarizes revenue and expenses of the discontinued operations for the years ended December 31, 2021, 2020 and 2019 (in thousands):

	Year ended December 31,		
	2021	2020	2019
Revenue:			
Service revenue	$ 18,130	$ 114,064	$ 30,729
Collaborative arrangement revenue	18,602	115,594	5,740
Royalty and other revenue	5,762	21,076	8,205
Total revenues	42,494	250,734	44,674
Operating expenses:			
Research and development	204,287	268,647	255,294
Selling, general and administrative	82,078	46,945	35,518
Share of collaboration loss	10,071	—	—
Cost of royalty and other revenue	2,292	5,396	2,978
Change in fair value of contingent consideration	387	(6,468)	2,747
Total operating expenses	299,115	314,520	296,537
Loss from operations	(256,621)	(63,786)	(251,863)
Interest income, net	791	5,770	17,380
Other income (expense), net	(910)	377	(103)
Loss before income taxes	(256,740)	(57,639)	(234,586)
Net loss	$ (256,740)	$ (57,639)	$ (234,586)

There were no assets and liabilities related to discontinued operations as of December 31, 2021, as all balances were transferred to 2seventy bio upon Separation. The following table summarizes the assets and liabilities of the discontinued operations as of December 31, 2020 (in thousands):

	As of December 31, 2020
Assets	
Current assets:	
Cash and cash equivalents	$ 57,076
Marketable securities	413,947
Prepaid expenses	11,754
Receivables and other current assets	12,244
Total current assets of discontinued operations	495,021
Marketable securities	61,446
Property, plant and equipment, net	145,458
Intangible assets, net	5,644
Goodwill	7,482
Operating lease right-of-use assets	116,456
Restricted cash and other non-current assets	7,078
Total non-current assets of discontinued operations	343,564
Total assets of discontinued operations	$ 838,585
Liabilities	
Current liabilities:	
Accounts payable	$ 7,791
Accrued expenses and other current liabilities	48,716
Operating lease liability, current portion	15,313
Collaboration research advancement, current portion	9,236
Deferred revenue, current portion	820
Total current liabilities of discontinued operations	81,876
Deferred revenue, net of current portion	25,762
Collaboration research advancement, net of current portion	21,581
Operating lease liability, net of current portion	112,290
Other non-current liabilities	1,509
Total non-current liabilities of discontinued operations	161,142
Total liabilities of discontinued operations	$ 243,018

The following table summarizes the significant non-cash items and capital expenditures of the discontinued operations that are included in the consolidated statements of cash flows for the years ended December 31, 2021, 2020 and 2019 (in thousands):

	Year ended December 31,		
	2021	2020	2019
Operating activities:			
Change in fair value of contingent consideration	$ 387	$ (6,468)	$ 2,747
Depreciation and amortization	14,195	13,730	12,995
Stock-based compensation expense	29,175	34,036	29,545
Loss on fixed assets disposal	569	146	108
Loss on sale of Durham, North Carolina manufacturing facility	1,986	—	—
Investing activities:			
Purchase of property, plant and equipment	$ (11,256)	$ (23,159)	$ (57,196)
Proceeds from sale of Durham, North Carolina manufacturing facility	110,300	—	—
Purchase of intangible assets	(8,500)	—	—
Supplemental cash flow disclosures:			
Purchases of property, plant and equipment included in accounts payable and accrued expenses	$ 778	$ 2,039	$ 3,064
Right-of-use assets obtained in exchange for operating lease liabilities	151,520	4,989	9,745

4. Marketable securities

The following table summarizes the marketable securities held at December 31, 2021 and 2020 (in thousands):

	Amortized cost / cost	Unrealized gains	Unrealized losses	Fair value
December 31, 2021				
U.S. government agency securities and treasuries	$ 128,902	$ —	$ (509)	$ 128,393
Corporate bonds	49,366	—	(59)	49,307
Commercial paper	54,065	—	—	54,065
Equity securities	4,305	—	(614)	3,691
Total	$ 236,638	$ —	$ (1,182)	$ 235,456
December 31, 2020 [(1)]				
U.S. government agency securities and treasuries	$ 337,521	$ 151	$ (37)	$ 337,635
Corporate bonds	98,585	216	(20)	98,781
Commercial paper	38,975	—	—	38,975
Equity securities	20,017	—	(14,364)	5,653
Total	$ 495,098	$ 367	$ (14,421)	$ 481,044

[(1)] Prior period amounts have been retrospectively adjusted to reflect the effects of the Separation.

No available-for-sale debt securities held as of December 31, 2021 or 2020 had remaining maturities greater than five years.

5. Fair value measurements

The following table sets forth the Company's assets and liabilities that are measured at fair value on a recurring basis as of December 31, 2021 and 2020 (in thousands):

	Total	Quoted prices in active markets (Level 1)	Significant other observable inputs (Level 2)	Significant unobservable inputs (Level 3)
December 31, 2021				
Assets:				
Cash and cash equivalents	$ 161,160	$ 161,146	$ 14	$ —
Marketable securities:				
U.S. government agency securities and treasuries	128,393	—	128,393	—
Corporate bonds	49,308	—	49,308	—
Commercial paper	54,065	—	54,065	—
Equity securities	3,691	3,691	—	—
Total assets	$ 396,617	$ 164,837	$ 231,780	$ —
December 31, 2020 [(1)]				
Assets:				
Cash and cash equivalents	$ 260,629	$ 260,629	$ —	$ —
Marketable securities:				
U.S. government agency securities and treasuries	337,635	—	337,635	—
Corporate bonds	98,781	—	98,781	—
Commercial paper	38,975	—	38,975	—
Equity securities	5,653	5,653	—	—
Total assets	$ 741,673	$ 266,282	$ 475,391	$ —

[(1)] Prior period amounts have been retrospectively adjusted to reflect the effects of the Separation.

Cash and cash equivalents

As of December 31, 2021, cash and cash equivalents comprise funds in cash and money market accounts. As of December 31, 2020, cash and cash equivalents comprise funds in cash and money market accounts.

Marketable securities

Marketable securities classified as Level 2 within the valuation hierarchy generally consist of U.S. government agency securities and treasuries, corporate bonds, and commercial paper. The Company estimates the fair values of these marketable securities by taking into consideration valuations obtained from third-party pricing sources. These pricing sources utilize industry standard valuation models, including both income and market-based approaches, for which all significant inputs are observable, either directly or indirectly, to estimate fair value. These inputs include market pricing based on real-time trade data for the same or similar securities, issuer credit spreads, benchmark yields, and other observable inputs. The Company validates the prices provided by its third-party pricing sources by understanding the models used, obtaining market values from other pricing sources and analyzing pricing data in certain instances.

The amortized cost of available-for-sale debt securities is adjusted for amortization of premiums and accretion of discounts to the earliest call date for premiums or to maturity for discounts. At December 31, 2021 and 2020, the balance in the Company's accumulated other comprehensive loss was composed primarily of activity related to the Company's available-for-sale debt securities. There were no material realized gains or losses recognized on the sale or maturity of available-for-sale securities during the years ended December 31, 2021 or 2020.

Accrued interest receivable on the Company's available-for-sale debt securities totaled $0.3 million and $1.5 million as of December 31, 2021 and 2020, respectively. No accrued interest receivable was written off during the twelve months ended December 31, 2021 or 2020.

The following table summarizes available-for-sale debt securities in a continuous unrealized loss position for less than and greater than twelve months, and for which an allowance for credit losses has not been recorded at December 31, 2021 and 2020 (in thousands):

	Less than 12 months		12 months or greater		Total	
Description	Fair value	Unrealized losses	Fair value	Unrealized losses	Fair value	Unrealized losses
December 31, 2021						
U.S. government agency securities and treasuries	$ 108,695	$ (505)	$ 2,496	$ (4)	$ 111,191	$ (509)
Corporate bonds	45,042	(56)	3,896	(2)	48,938	(58)
Total	$ 153,737	$ (561)	$ 6,392	$ (6)	$ 160,129	$ (567)
December 31, 2020 [(1)]						
U.S. government agency securities and treasuries	$ 105,692	$ (37)	$ —	$ —	$ 105,692	$ (37)
Corporate bonds	38,299	(20)	603	—	38,902	(20)
Total	$ 143,991	$ (57)	$ 603	$ —	$ 144,594	$ (57)

[(1)] Prior period amounts have been retrospectively adjusted to reflect the effects of the Separation.

The Company determined that there was no material change in the credit risk of the above investments during the twelve months ended December 31, 2021. As such, an allowance for credit losses was not recognized. As of December 31, 2021, the Company does not intend to sell such securities and it is not more likely than not that the Company will be required to sell the securities before recovery of their amortized cost bases.

The Company holds equity securities with an aggregate fair value of $3.7 million and $5.7 million at December 31, 2021 and 2020, respectively, within current marketable securities on its consolidated balance sheets. In January 2021, the Company sold a portion of its equity securities for proceeds of $31.3 million. The Company recorded gains of $29.4 million and losses of $7.2 million and $9.3 million related to its equity securities during the years ended December 31, 2021, 2020 and 2019, respectively. Gains and losses related to equity securities are included in other income (expense), net in the consolidated statements of operations and comprehensive loss.

6. Inventory

Inventory consists of the following (in thousands):

	As of December 31, 2021	As of December 31, 2020
Raw materials	$ —	$ 8,967
Finished goods	—	1,731
Inventory	$ —	$ 10,698

During the year ended December 31, 2021, the Company recorded a reserve for excess inventories of $29.9 million, which is included within cost of product revenue in the consolidated statements of operations and comprehensive loss. During the year ended December 31, 2020, the Company did not record a reserve for excess inventories.

7. Property, plant and equipment, net

Property, plant and equipment, net, consists of the following (in thousands):

	As of December 31,	
	2021	2020 [1]
Laboratory equipment	$ 29,061	$ 27,146
Computer equipment and software	421	447
Office equipment	117	1,077
Leasehold improvements	12	5,949
Construction-in-progress	501	895
Total property, plant and equipment	30,112	35,514
Less accumulated depreciation and amortization	(20,406)	(18,141)
Property, plant and equipment, net	$ 9,706	$ 17,373

[1] Prior period amounts have been retrospectively adjusted to reflect the effects of the Separation.

Depreciation and amortization expense related to property, plant and equipment was $4.9 million, $5.1 million, and $4.1 million for the years ended December 31, 2021, 2020, and 2019, respectively.

8. Restricted cash

As of December 31, 2021 and 2020, the Company maintained letters of credit of $43.2 million and $54.5 million, respectively, which are collateralized with bank accounts at financial institutions in accordance with the agreements. Total restricted cash as of December 31, 2021 and 2020 consisted of the following (in thousands):

	As of December 31,	
	2021	2020
50 Binney Street lease	$ 40,072	$ 40,072
Assembly Row lease	2,753	—
60 Binney Street lease	—	13,763
Other	2,675	2,188
Total restricted cash	$ 45,500	$ 56,023

Refer to Note 10, *Leases,* for further information on the Company's letters of credit.

9. Accrued expenses and other current liabilities

Accrued expenses and other current liabilities consist of the following (in thousands):

	As of December 31,	
	2021	2020 [1]
Employee compensation	$ 41,095	$ 41,192
Accrued goods and services	24,273	14,855
Accrued clinical and contract research organization costs	17,769	20,912
Accrued manufacturing costs	15,722	15,763
Accrued professional fees	1,665	1,541
Deferred revenue, current portion	2,282	1,500
Other	1,152	2,427
Total accrued expenses and other current liabilities	$ 103,958	$ 98,190

[1] Prior period amounts have been retrospectively adjusted to reflect the effects of the Separation.

Accrued employee compensation includes severance costs associated with the Company's orderly wind down of its European operations. As of December 31, 2021, the Company had accrued expenses of $4.7 million related to these restructuring costs. Please refer to Note 17, *Reduction in workforce,* for further discussion.

10. Leases

The Company leases certain office and laboratory space. Additionally, the Company has embedded leases through its agreements with contract manufacturing organizations.

60 Binney Street lease & sublease

In October 2021, the Company entered into a consent to assignment and amendment to its lease agreement for its 60 Binney Street lease (the "Assignment"). The Assignment transfers the Company's interest in the lease to 2seventy bio and releases the Company from its obligation to maintain the $13.8 million collateralized letter of credit required under the original 60 Binney Street lease. Although the lease was legally transferred to 2seventy bio, the lessor required that the Company remain secondarily liable as a guarantor for payment obligations accruing under the 60 Binney Street lease from the date of Assignment until (i) the Company has completely vacated the premises and (ii) 2seventy bio has reached a market capitalization of $900 million. Upon Separation, the lease assignment was accounted for as the termination of the original lease and the Company de-recognized the right-of-use asset and lease liability related to the 60 Binney Street lease and recognized the fair value of the guarantee pursuant to ASC 405, *Liabilities*. The fair value of the guarantee was not material.

Concurrent with the Assignment of the 60 Binney Street Lease, the Company entered into a sublease agreement with 2seventy bio for office, laboratory and storage space located at 60 Binney Street (the "60 Binney Street Sublease") while it constructs and outfits its new office and laboratory space. Under the terms of the 60 Binney Street Sublease, the Company will lease 72,988 square feet for $0.5 million per month in base rent for the period beginning from the Assignment through March 2022 and 58,004 square feet for $0.4 million per month in base rent for the period from April 2022 through March 2024. The Company accounted for the 60 Binney Street Sublease as a new lease under ASC 842, and in November 2021, recognized a right-of-use asset and lease liability related to the 60 Binney Street Sublease.

50 Binney Street sublease & sub-sublease

In April 2019, the Company entered into a sublease agreement for office space located at 50 Binney Street in Cambridge, Massachusetts (the “50 Binney Street Sublease”) to supplement the Company’s corporate headquarters located at 60 Binney Street in Cambridge, Massachusetts. Under the terms of the 50 Binney Street Sublease, the Company will lease 267,278 square feet of office space for $99.95 per square foot, or $26.7 million per year in base rent subject to certain operating expenses, taxes and annual rent increases of approximately 3%. The lease will commence when the space is available for use by the Company, which is anticipated to be in the first half of 2022, which reflects the sublessor's exercise of its option to postpone the commencement date of the sublease. The lease term will end on December 31, 2030, unless other specific circumstances specified in the 50 Binney Street Sublease occur. The Company will assess the lease classification of the 50 Binney Street Sublease and commence recognition of the associated rent expense at the lease commencement date.

Upon signing the 50 Binney Street Sublease, the Company executed a $40.1 million cash-collateralized letter of credit, which may be reduced in the future subject to the terms of the 50 Binney Street Sublease and certain reduction requirements specified therein. The $40.1 million of cash collateralizing the letter of credit is classified as restricted cash and other non-current assets on the Company’s consolidated balance sheets. Payments will commence at the earlier of (i) the date which is 90 days following the commencement date and (ii) the date the Company takes occupancy of all or any portion of the premises.

In connection with the execution of the 50 Binney Street Sublease, the Company also entered into a purchase agreement for furniture and equipment (the “Furniture Purchase Agreement”) located on the premises upon lease commencement. Upon execution of the Furniture Purchase Agreement, the Company made an upfront payment of $7.5 million, all of which was recorded within restricted cash and other non-current assets on the Company’s consolidated balance sheets and assessed for recoverability on a recurring basis. The Company will be required to make another $7.5 million payment under the Furniture Purchase Agreement upon lease commencement.

In December 2021, the Company entered into a sub-sublease agreement (the "Sub-Sublease") with Meta Platforms, Inc. (“Meta”). Under the terms of the Sub-Sublease, the Company is subleasing the entirety of the 50 Binney Street premises which it has rights to under the 50 Binney Street Sublease. The Company is sub-subleasing the premises for $28.0 million in the first year with 3% annual increases in each subsequent year. Meta will receive access to 50 Binney Street at the lease commencement date, which is the same point that the Company would receive access under the 50 Binney Street Sublease. The Company remains liable under the 50 Binney Street Sublease, including for maintenance of the $40.1 million collateralized

letter of credit. As a result of the execution of the Sub-Sublease, the Company assessed the $7.5 million deposit related to the Furniture Purchase Agreement for recoverability and determined that the amount was not recoverable. As a result, the Company recorded $7.5 million in the Company's consolidated statements of operations and comprehensive loss as selling, general and administrative expense during the year ended December 31, 2021.

Assembly Row lease

In November 2021, the Company entered into a lease agreement with Assembly Row 5B, LLC ("Landlord") for office space located at 455 Grand Union Boulevard in Somerville, Massachusetts to serve as the Company's future corporate headquarters. Under the terms of the arrangement, the Company will lease approximately 61,180 square feet starting at an annual rate of $45 per square foot, subject to annual increases of 2.5%, plus operating expenses and taxes. In addition, the Company will be eligible for a tenant work allowance of $160 per rentable square foot of the premises. The lease will commence on the date on which the Landlord tenders possession of the premises to the Company with any tenant work required to be performed by the Landlord substantially completed, which is anticipated to occur in the first half of 2022.

Embedded leases

In June 2016, the Company entered into a manufacturing agreement for the future commercial production of the Company’s beti-cel and eli-cel drug products with a contract manufacturing organization. Under this 12-year agreement, the contract manufacturing organization will complete the design, construction, validation and process validation of the leased suites prior to anticipated commercial launch of the product candidates. During construction, the Company paid $12.0 million upon the achievement of certain contractual milestones. Construction was completed in March 2018 and beginning in April 2018, the Company pays $5.1 million per year, subject to annual inflationary adjustments, in fixed suite fees, as well as certain fixed labor, raw materials, testing and shipping costs for manufacturing services. The Company may terminate this agreement at any time upon payment of a one-time termination fee and up to 24 months of fixed suite and labor fees. The Company concluded in prior periods that this agreement contained an embedded lease as the suites are designated for the Company’s exclusive use during the term of the agreement. The Company recorded a right-of-use asset and lease liability for this operating lease on the effective date of ASC 842 and is recognizing rent expense on a straight-line basis throughout the remaining term of the embedded lease.

In November 2016, the Company entered into an agreement for clinical and commercial production of the Company’s beti-cel, lovo-cel, and eli-cel drug products with a contract manufacturing organization at an existing facility. The Company concluded that this agreement contains an embedded operating lease as the clean rooms are designated for the Company’s exclusive use during the term of the agreement. The term of the agreement is five years with subsequent three-year renewals at the mutual option of each party. As a result, the Company recorded a right-of-use asset and lease liability for this operating lease on the effective date of ASC 842, and is recognizing rent expense on a straight-line basis throughout the estimated remaining term of the embedded lease. In March 2020, the Company amended its agreement with the contract manufacturing organization, resulting in a lease modification. Under the terms of the amended agreement, the Company may be required to pay annual maintenance and production fees of up to €16.5 million, depending on its production needs, and may terminate this agreement with twelve months’ notice and a one-time termination fee. In September 2021, the Company reassessed the term of this lease in light of the planned orderly wind down of its operations in Europe. As a result, the Company reduced the right-of-use asset and related lease liability to reflect a shortened expected term of the agreement. In November 2021, the Company exercised its right to terminate the lease agreement, and such termination will be effective in November 2022. Per the terms of the amended agreement, the Company was obligated to pay a one-time termination fee of €1.0 million upon termination, which was paid in December 2021. In connection with this termination, the Company will pay for services properly rendered through the date of termination in accordance with the contract manufacturing agreement, based on work completed and expenses incurred prior to the date of termination.

In July 2020, the Company entered into an agreement reserving manufacturing capacity with a contract manufacturing organization. The Company concluded that this agreement contains an embedded lease as a controlled environment room at the facility is designated for the Company's exclusive use during the term of the agreement, with the option to sublease the space if the Company provides notice that it will not utilize it for a specified duration of time. Under the terms of the agreement, the Company will be required to pay up to $5.4 million per year in maintenance fees in addition to the cost of any services provided and may terminate this agreement with eighteen months' notice. The agreement commenced in March 2021, and it has a term of five years with the option to extend. The Company classified the embedded lease as an operating lease and recognized a right-of-use asset and lease liability upon lease commencement in March 2021 and is recognizing rent expense on a straight-line basis throughout the remaining term of the embedded lease.

In February 2021, the Company entered into another agreement reserving manufacturing capacity with a contract manufacturing organization. The Company concluded that this agreement contains an embedded lease as a controlled environment room at the facility is designated for the Company's exclusive use during the term of the agreement, with the option to sublease the space if the Company provides notice that it will not utilize it for a specified duration of time. Under the terms of the agreement, the Company will be required to pay up to $4.2 million per year in maintenance fees and an immaterial amount of other annual fees as well as per-batch fees for the cost of any services provided. Either party may terminate this agreement with eighteen months' notice at any time or with eight months' notice after stage 5 has commenced. The term of the agreement is five years, with the option to extend, and it commenced in November 2021. The Company classified the embedded lease as an operating lease and recognized a right-of-use asset and lease liability upon lease commencement in November 2021 and is recognizing rent expense on a straight-line basis throughout the remaining term of the embedded lease.

Summary of all lease costs recognized under ASC 842

The following table contains a summary of the lease costs recognized under ASC 842 and other information pertaining to the Company's operating leases for the years ended December 31, 2021 and 2020 (in thousands):

	For the year ended December 31,		
	2021	2020 [2]	2019 [2]
Lease cost [1]			
Operating lease cost	$ 25,067	$ 18,660	$ 20,005
Total lease cost	$ 25,067	$ 18,660	$ 20,005
Other information			
Operating cash flows used for operating leases	$ 22,805	$ 17,780	$ 17,205
Weighted average remaining lease term	4.7 years	6.3 years	7.3 years
Weighted average discount rate	5.02 %	5.98 %	6.66 %

[1] Short-term lease costs and variable lease costs incurred by the Company for the twelve months ended December 31, 2021, 2020 and 2019 were immaterial.

[2] Prior period amounts have been retrospectively adjusted to reflect the effects of the Separation.

Rent expense is calculated on a straight-line basis over the term of the lease. Rent expense recognized under all leases, including additional charges for utilities, parking, maintenance, and real estate taxes, was $36.2 million, $24.2 million, and $23.3 million for the years ended December 31, 2021, 2020 and 2019, respectively.

As of December 31, 2021, future minimum commitments under ASC 842 under the Company's operating leases were as follows (in thousands):

Maturity of lease liabilities	As of December 31, 2021
2022	$ 27,037
2023	21,460
2024	18,009
2025	14,639
2026	8,598
2027 and thereafter	12,356
Total lease payments	102,099
Less: imputed interest	(12,515)
Total operating lease liabilities	$ 89,584

The above table excludes legally binding minimum lease payments for leases executed but not yet commenced as of December 31, 2021.

11. Commitments and contingencies

Lease commitments

The Company leases certain office and laboratory space and has embedded leases at contract manufacturing organizations. Refer to Note 10, *Leases,* for further information on the terms of these lease agreements.

Other funding commitments

The Company is party to various agreements, principally relating to licensed technology, that require future payments relating to milestones that may be met in subsequent periods or royalties on future sales of specified products.

Additionally, the Company is party to various contracts with contract research organizations and contract manufacturers that generally provide for termination on notice, with the exact amounts in the event of termination to be based on the timing of the termination and the terms of the agreement.

Based on our development plans as of December 31, 2021, the Company may be obligated to make future development, regulatory and commercial milestone payments and royalty payments on future sales of specified products associated with the Company's collaboration and license agreements. Payments under these agreements generally become due and payable upon achievement of such milestones or sales. When the achievement of these milestones or sales have not occurred, such contingencies are not recorded in the Company’s financial statements.

The Company has various manufacturing development and license agreements to support clinical and commercial product needs. The following table presents non-cancelable contractual obligations arising from these arrangements:

Years ended December 31,	Purchase commitment
2022	$ 43,903
2023	9,918
2024 and thereafter	—
Total purchase commitments	$ 53,821

Litigation

From time to time, the Company is party to various claims and complaints arising in the ordinary course of business, including securities class action litigation. The Company enters into standard indemnification agreements in the ordinary course of business. Pursuant to the agreements, the Company indemnifies, holds harmless, and agrees to reimburse the indemnified party for losses suffered or incurred by the indemnified party, generally the Company’s business partners. The term of these indemnification agreements is generally perpetual any time after execution of the agreement. The maximum potential amount of future payments the Company could be required to make under these indemnification agreements is generally unlimited. Management does not believe that any ultimate liability resulting from any of these claims will have a material adverse effect on its results of operations, financial position, or liquidity. However, management cannot give any assurance regarding the ultimate outcome of any claims, and their resolution could be material to operating results for any particular period.

The Company also indemnifies each of its officers and directors for certain events or occurrences, subject to certain limits, while the officer or director is or was serving at the Company's request in such capacity, as permitted under Delaware law and in accordance with its certificate of incorporation and by-laws. The term of the indemnification period lasts as long as such officer or director may be subject to any proceeding arising out of acts or omissions of such officer or director in such capacity. The maximum amount of potential future indemnification is unlimited; however, the Company currently holds director and officer liability insurance. This insurance allows the transfer of risk associated with the Company's exposure and may enable it to recover a portion of any future amounts paid. The Company believes that the fair value of these indemnification obligations is minimal. Accordingly, it has not recognized any liabilities relating to these obligations.

12. Equity

The Company is authorized to issue 125.0 million shares of common stock. Holders of common stock are entitled to one vote per share. Holders of common stock are entitled to receive dividends, if and when declared by the Company’s board of directors, and to share ratably in the Company’s assets legally available for distribution to the Company’s shareholders in the

event of liquidation. Holders of common stock have no preemptive, subscription, redemption or conversion rights. As of December 31, 2021 and 2020, the Company had 71.1 million and 66.4 million shares of common stock issued and outstanding, respectively.

In September 2021, the Company entered into an equity purchase agreement with certain investors, pursuant to which the Company agreed to sell and issue, in a private placement offering of securities, an aggregate of (i) 2.3 million shares of the Company's common stock at a purchase price per share of $16.50 and (ii) pre-funded warrants to purchase up to 2.3 million shares of common stock (the "Pre-Funded Warrants") at an effective price of $16.49 per share ($16.49 paid to the Company upon the closing of the offering and $0.01 to be paid upon exercise of such Pre-Funded Warrants). This resulted in aggregate gross proceeds to the Company of approximately $75.0 million. The Pre-Funded Warrants can be exercised at any time or times on or after September 7, 2021, until exercised in full. The Pre-Funded Warrants have been evaluated to determine the appropriate accounting and classification pursuant to ASC 480 and ASC 815. Based on the terms of the Pre-Funded Warrants, management concluded that they should be classified within stockholders' equity on its consolidated balance sheets, with no subsequent remeasurement as long as the underlying warrant agreements are not modified or amended.

The Company is authorized to issue 5.0 million shares of preferred stock in one or more series and to fix the powers, designations, preferences and relative participating option or other rights thereof, including dividend rights, conversion rights, voting rights, redemption terms, liquidation preferences and the number of shares constituting any series, without any further vote or action by the Company's shareholders. As of December 31, 2021 and 2020, the Company had no shares of preferred stock issued or outstanding.

Reserved for future issuance

The Company has reserved for future issuance the following number of shares of common stock (in thousands):

	As of December 31,	
	2021	2020
Options to purchase common stock [(1)]	5,534	6,262
Restricted stock units [(1)]	3,427	1,495
2013 Stock Option and Incentive Plan	2,250	2,545
Pre-funded warrants	2,273	—
2013 Employee Stock Purchase Plan	1,347	67
	14,831	10,369

[(1)] Stock options and restricted stock units that are reserved for future issuance include awards outstanding to employees of 2seventy bio.

13. Intangible assets

Intangible assets, net of accumulated amortization, are summarized as follows (in thousands):

	As of December 31, 2021			
	Cost	Accumulated amortization	Impairment	Net
In-licensed rights	$ 5,224	(1,219)	(4,005)	—
Total	$ 5,224	$ (1,219)	$ (4,005)	$ —

	As of December 31, 2020[(1)]			
	Cost	Accumulated amortization	Impairment	Net
In-licensed rights	$ 5,224	(827)	—	4,397
Total	$ 5,224	$ (827)	$ —	$ 4,397

[(1)] Prior period amounts have been retrospectively adjusted to reflect the effects of the Separation.

Amortization expense for intangible assets was $0.4 million, $0.5 million, and $0.3 million for the years ended December 31, 2021, 2020 and 2019, respectively.

In August 2021, the Company announced its decision to focus its efforts on the U.S. market and to execute an orderly wind down of its European operations. In connection with this, in September 2021, the Company recognized an impairment loss of $4.0 million for the remaining unamortized balance of the intangible asset associated with in-licensed rights for the ZYNTEGLO product, which is reflected within cost of product revenue in the consolidated statements of operations and comprehensive loss for the year ended December 31, 2021.

14. Stock-based compensation

In June 2013, the Company's board of directors adopted its 2013 Stock Option and Incentive Plan ("2013 Plan"), which was subsequently approved by its stockholders and became effective upon the closing of the Company's IPO. The 2013 Plan replaces the 2010 Stock Option and Grant Plan ("2010 Plan").

The 2013 Plan allows for the granting of incentive stock options, non-qualified stock options, restricted stock units and restricted stock awards to the Company's employees, members of the board of directors, and consultants of the Company. The Company initially reserved 1.0 million shares of its common stock for the issuance of awards under the 2013 Plan. The 2013 Plan provides that the number of shares reserved and available for issuance under the 2013 Plan will automatically increase each January 1, beginning on January 1, 2014, by four percent of the outstanding number of shares of common stock on the immediately preceding December 31 or such lesser number of shares as determined by the Company's compensation committee. In January 2021 and January 2022, the number of common stock available for issuance under the 2013 Plan was increased by approximately 2.7 million and 2.8 million shares, respectively, as a result of this automatic increase provision.

Any options or awards outstanding under the Company's previous stock option plans, including both the 2010 Plan and the Second Amended and Restated 2002 Employee, Director and Consultant Stock Plan ("2002 Plan"), at the time of adoption of the 2013 Plan remain outstanding and effective. The shares of common stock underlying any awards that are forfeited, canceled, repurchased, expired or are otherwise terminated (other than by exercise) under the 2002 Plan and 2010 Plan are added to the shares of common stock available for issuance under the 2013 Plan. As of December 31, 2021, the total number of common stock that may be issued under all plans is 3.2 million.

The Company does not currently hold any treasury shares. Upon stock option exercise, the Company issues new shares and delivers them to the participant.

Conversion and modification of equity awards outstanding at the Separation

In connection with the Separation on November 4, 2021, under the provisions of the existing plans, the Company adjusted its outstanding equity awards in accordance with the terms of the Employee Matters Agreement (an equitable adjustment) to preserve the intrinsic value of the awards immediately before and after the Distribution. Upon the Distribution, employees holding stock options, restricted stock units ("RSUs") and performance restricted stock units ("PRSUs") denominated in pre-Distribution bluebird stock received a number of otherwise-similar awards either in post-Distribution bluebird stock or in a combination of post-Distribution bluebird stock and 2seventy bio stock based on conversion ratios outlined for each group of employees in the Employee Matters Agreement that the Company entered into in connection with the Distribution. The equity awards that were granted prior to 2021 were converted under the shareholder method, wherein employees holding outstanding equity awards received equity awards in both bluebird and 2seventy bio. The conversion ratio for the shareholder method took into consideration a distribution ratio of one share of 2seventy bio common stock for every three shares of bluebird common stock. For equity awards granted in 2021, the number of awards that were outstanding at the Separation were proportionately adjusted to maintain the aggregate intrinsic value of the awards at the date of the Separation. The conversion ratio was determined based on the volume weighted-average trading price for bluebird common stock for the five trading days before and after the Separation.

These modified awards otherwise retained substantially the same terms and conditions, including term and vesting provisions. Due to the modification of the equity awards as a result of the Distribution, the Company compared the fair value of the outstanding equity awards immediately before and after the Distribution. The modification resulted in an incremental fair value of $20.3 million, of which $4.5 million was immediately recognized as of the Distribution date.

Additionally, bluebird will not incur any future compensation cost related to equity awards held by 2seventy bio employees and directors. The Company will incur future compensation cost related to 2seventy bio equity awards held by bluebird employees.

Stock-based compensation expense

The Company recognized stock-based compensation expense totaling $98.7 million, $122.6 million, and $131.1 million during the years ended December 31, 2021, 2020 and 2019, respectively. Stock-based compensation expense recognized by award type is as follows (in thousands):

	Year ended December 31,		
	2021	2020	2019
Stock options	$ 54,660	$ 75,837	$ 79,912
Restricted stock units	30,767	38,123	50,158
Employee stock purchase plan and other	13,313	8,636	1,013
	$ 98,740	$ 122,596	$ 131,083

Stock-based compensation expense by classification included within the consolidated statements of operations and comprehensive loss was as follows (in thousands):

	Year ended December 31,		
	2021	2020	2019
Research and development	$ 42,989	$ 49,766	$ 59,378
Selling, general and administrative	55,751	72,830	71,705
	$ 98,740	$ 122,596	$ 131,083

Stock-based compensation of $1.0 million was capitalized into inventory during the year ended December 31, 2021. Stock-based compensation of $0.5 million was capitalized into inventory during the year ended December 31, 2020.

Unrestricted stock awards

During the first quarter of 2021, the Company granted 0.4 million unrestricted stock awards to employees as part of its 2020 annual incentive program. In addition, the Company implemented a retention program designed to incentivize and retain employees through the separation of its severe genetic disease and oncology programs. Under the retention program, employees are entitled to a one-time bonus payment, consisting of both a cash payment and unrestricted stock awards, with the condition that the employee remains employed at the end of 2021. For the twelve months ended December 31, 2021, the Company recognized $21.2 million in expense related to this program, which includes $10.6 million in stock compensation expense related to the anticipated grants of stock. During the third quarter of 2021, the Company granted 0.1 million unrestricted stock awards, related to the retention program, to those employees impacted by the orderly wind down of the Company's operations in Europe. During the fourth quarter of 2021, the Company granted 1.0 million unrestricted stock awards to employees as part of its retention program.

As of December 31, 2021, the Company had $34.2 million and $54.3 million of unrecognized compensation expense related to unvested stock options and restricted stock units (exclusive of those with service and performance conditions that have not yet been achieved), respectively, that is expected to be recognized over a weighted-average period of 2.19 years and 2.26 years, respectively.

Stock options

The fair value of each option issued to employees was estimated at the date of grant using the Black-Scholes option pricing model with the following weighted-average assumptions:

	Year ended December 31,		
	2021	2020	2019
Expected volatility	66.7 %	69.5 %	70.7 %
Expected term (in years)	6.0	6.0	6.0
Risk-free interest rate	0.8 %	1.4 %	2.3 %
Expected dividend yield	0.0 %	0.0 %	0.0 %

The following table summarizes the stock option activity under the Company's equity awards plans:

	Shares (in thousands)	Weighted-average exercise price per share	Weighted-average contractual life (in years)	Aggregate intrinsic value (a) (in thousands)
Outstanding at December 31, 2020	6,262	$ 105.02		
Granted	1,238	$ 27.19		
Exercised	(218)	$ 6.82		
Canceled or forfeited	(2,357)	$ 81.20		
Conversion and modification of awards	(1,339)	$ 42.90		
Outstanding at December 31, 2021	3,586	$ 39.23	6.8	$ 631
Exercisable at December 31, 2021	1,835	$ 57.09	5.5	$ 380
Vested and expected to vest at December 31, 2021	3,586	$ 39.23	6.8	$ 631

(a) The aggregate intrinsic value is calculated as the difference between the exercise price of the underlying options and the fair value of the common stock for the options that were in the money at December 31, 2021.

(b) Pursuant to the terms of Employee Matters Agreement, the company granted 4,375 option conversion awards to bluebird employees which are reflected within the "Conversion and modification of awards" above. The weighted-average exercise price per share reflected above is related to these awards, rather than the number of awards reflected in the table.

The weighted-average fair values of options granted during the years ended December 31, 2021, 2020 and 2019 was $16.32, $43.24, and $83.44, respectively. The intrinsic value of options exercised during the years ended December 31, 2021, 2020 and 2019 was $5.1 million, $4.0 million and $29.0 million, respectively.

Restricted stock units

The following table summarizes the restricted stock unit activity under the Company's equity award plans:

	Shares (in thousands)	Weighted-average grant date fair value
Unvested balance at December 31, 2020	1,495	$ 102.34
Granted	3,359	26.43
Vested	(526)	112.21
Forfeited	(987)	53.58
Conversion and modification of awards	(148)	16.84
Unvested balance at December 31, 2021	3,193	$ 16.21

(a) Pursuant to the terms of Employee Matters Agreement, the company granted 3,327 restricted stock unit conversion awards to bluebird employees which are reflected within the "Conversion and modification of awards" above. The weighted-average exercise price per share reflected above is related to these awards, rather than the number of awards reflected in the table.

The intrinsic value of restricted stock units vested during the years ended December 31, 2021, 2020 and 2019 was $44.0 million, $30.9 million and $28.4 million, respectively.

Employee Stock Purchase Plan

In June 2013, the Company's board of directors adopted its 2013 Employee Stock Purchase Plan ("2013 ESPP"), which was subsequently approved by its stockholders and became effective upon the closing of the Company's IPO. The 2013 ESPP authorizes the initial issuance of up to a total of 0.2 million shares of the Company's common stock to participating employees. In June 2021, the Company amended the 2013 ESPP to authorize an additional 1.4 million shares of the Company's common stock available to participating employees. During each of the years ended December 31, 2021 and 2020, approximately 0.1 million shares of common stock were issued under the 2013 ESPP.

15. 401(k) Savings plan

In 1997, the Company established a defined-contribution savings plan under Section 401(k) of the Internal Revenue Code (the "401(k) Plan"). The 401(k) Plan covers all employees who meet defined minimum age and service requirements, and allows participants to defer a portion of their annual compensation on a pretax basis. In March 2022, the Company expects to make matching contributions of approximately $2.8 million related to employee contributions made during 2021. At the same time, the Company anticipates making matching contributions to 2seventy bio employees of $2.0 million for their contributions under the 401(k) Plan during 2021 through the Separation. In March 2021, the Company made $6.0 million of matching contributions related to employee contributions made during 2020. The match contribution is included in accrued expenses and other current liabilities as of December 31, 2021 and 2020. Expense related to the 401(k) Plan from continuing operations totaled $2.8 million, $3.0 million, $2.9 million for the years ended December 31, 2021, 2020, and 2019, respectively.

16. Income taxes

The components of loss before income taxes were as follows (in thousands):

	Year ended December 31,		
	2021	2020	2019
U.S.	$ (487,404)	$ (431,452)	$ (414,586)
Foreign	(74,976)	(128,918)	(140,981)
Total	$ (562,380)	$ (560,370)	$ (555,567)

The provision for (benefit from) income taxes were as follows (in thousands):

	Year ended December 31,		
	2021	2020	2019
Current:			
Federal	$ —	$ —	$ —
State	—	2	7
Foreign	258	684	612
Deferred:			
Federal	—	—	(966)
State	—	—	(198)
Foreign	—	—	—
Total income tax expense (benefit)	$ 258	$ 686	$ (545)

A reconciliation of income tax expense (benefit) computed at the statutory federal income tax rate to the Company's effective income tax rate as reflected in the financial statements is as follows:

	Year ended December 31,		
	2021	2020	2019
Federal income tax expense at statutory rate	21.0 %	21.0 %	21.0 %
State income tax, net of federal benefit	3.9 %	3.1 %	3.7 %
Permanent differences	(0.6)%	(0.6)%	(0.8)%
Stock-based compensation	(3.1)%	(2.4)%	(0.7)%
Research and development credit	4.3 %	6.0 %	5.4 %
Foreign differential	(1.9)%	(4.6)%	(3.7)%
Other	— %	(0.3)%	0.8 %
Change in valuation allowance	(23.6)%	(22.3)%	(25.6)%
Effective income tax rate (expense) benefit	— %	(0.1)%	0.1 %

For the years ended December 31, 2021, 2020 and 2019, the Company recognized an income tax expense (benefit) of $0.3 million or 0.0%, $0.7 million or (0.1)%, and $(0.5) million or 0.1%, respectively. The Company did not recognize any significant tax expense for the years ended December 31, 2021, 2020, or 2019 as the Company was subject to a full valuation allowance. Tax expense associated with the sale of bRT and the Separation, accounted for as discontinued operations and discussed in Note 3, is $0 for the years ended December 31, 2021, 2020, or 2019 due to the full valuation allowance. Deferred taxes are recognized for temporary differences between the basis of assets and liabilities for financial statement and income tax purposes. The significant components of the Company's deferred tax assets and liabilities are composed of the following (in thousands):

	Year ended December 31,	
	2021	2020 [1]
Deferred tax assets:		
U.S. net operating loss carryforwards (federal and state)	$ 703,125	$ 546,098
Tax credit carryforwards (federal and state)	281,687	246,742
Capitalized license fees and research and development expenses	2,237	1,558
Deferred revenue	604	398
Stock-based compensation	25,181	37,164
Lease liabilities	22,916	14,787
Accruals and other	15,598	12,894
Total deferred tax assets	1,051,348	859,641
Right-of-use assets	(23,053)	(15,044)
Fixed assets	(1,546)	(1,212)
Less valuation allowance	(1,026,749)	(843,385)
Net deferred taxes	$ —	$ —

[1] Prior period amounts have been retrospectively adjusted to reflect the effects of the Separation.

A valuation allowance is recorded against deferred tax assets if it is more likely than not that some or all of the deferred tax assets will not be realized. Due to the uncertainty surrounding the realization of the favorable tax attributes in future tax returns, the Company has recorded a full valuation allowance against the Company's otherwise recognizable net deferred tax assets. The valuation allowance increased on a net basis by approximately $183.4 million during the year ended December 31, 2021 due primarily to net operating losses, tax credit carryforwards, and stock-based compensation, offset by the sale of bRT and the Separation. Effective January 1, 2021, the Company adopted ASU 2019-12, which simplifies accounting for income taxes. There was no material impact on the Company's financial position or results of operations upon adoption.

As of December 31, 2021, 2020 and 2019, the Company had U.S. federal net operating loss carryforwards of approximately $2.63 billion, $2.03 billion, and $1.62 billion, respectively, which may be available to offset future income tax liabilities. Of the amount as of December 31, 2021, $1.92 billion will carryforward indefinitely while $711.0 million will expire at various dates through 2037. As of December 31, 2021, 2020 and 2019, the Company also had U.S. state net operating loss

carryforwards of approximately $2.39 billion, $1.89 billion, and $1.56 billion, respectively, which may be available to offset future income tax liabilities and expire at various dates through 2041.

As of December 31, 2021, 2020 and 2019, the Company had federal research and development and orphan drug tax credit carryforwards of approximately $268.3 million, $235.3 million, and $203.1 million, respectively, available to reduce future tax liabilities which expire at various dates through 2041. As of December 31, 2021, 2020 and 2019, the Company had state credit carryforwards of approximately $16.9 million, $14.5 million, and $13.6 million, respectively, available to reduce future tax liabilities which expire at various dates through 2036. During the fourth quarter of 2018, the Company completed an analysis of prior year estimates of U.S. research and development and orphan drug tax credits for the years 2013 through 2017. The analysis resulted in an immaterial adjustment to the Company's income tax benefit, which was offset by an adjustment to the valuation allowance. An analysis of the U.S. research and development and orphan drug credits has not yet been completed for 2019, 2020, or 2021.

In March 2020, the Coronavirus Aid, Relief and Economic Security Act (“CARES Act”) was enacted. This law temporarily suspends and adjusts certain law changes enacted in the Tax Cuts and Jobs Act in 2017. In December 2020, the Consolidated Appropriations Act was enacted. This law modified the employee retention credit under the CARES Act and created credit extenders for certain credits. In March 2021, the American Rescue Plan Act ("ARPA") was enacted and contained extenders to the refundable employee retention credit and provided further limitations to executive compensation effective for tax years beginning after 2026. The Company has concluded that the provisions in the CARES Act, Consolidated Appropriations Act, and ARPA have an immaterial impact on the Company’s income tax expense due to its cumulative losses and full valuation allowance position.

Under the provisions of the Internal Revenue Code, the net operating loss and tax credit carryforwards are subject to review and possible adjustment by the Internal Revenue Service and state tax authorities. Net operating loss and tax credit carryforwards may become subject to an annual limitation in the event of certain cumulative changes in the ownership interest of significant shareholders over a three-year period in excess of 50 percent, as defined under Sections 382 and 383 of the Internal Revenue Code, respectively, as well as similar state provisions. This could limit the amount of tax attributes that can be utilized annually to offset future taxable income or tax liabilities. The amount of the annual limitation is determined based on the value of the Company immediately prior to the ownership change. Subsequent ownership changes may further affect the limitation in future years. The Company has completed several financings since its inception, which it believes has resulted in a change in control as defined by Sections 382 and 383 of the Internal Revenue Code. The Company completed a study through December 2020 confirming no additional ownership changes; any ownership shifts occurring after December 2020 could result in an ownership change under Section 382.

The Company files Federal income tax returns in the United States, and various state and foreign jurisdictions. The federal, state and foreign income tax returns are generally subject to tax examinations for the tax years ended December 31, 2018 through December 31, 2020. To the extent the Company has tax attribute carryforwards, the tax years in which the attribute was generated may still be adjusted upon examination by the Internal Revenue Service, or state or foreign tax authorities to the extent utilized in a future period.

A reconciliation of the beginning and ending amount of unrecognized tax benefits is as follows (in thousands):

	Unrecognized tax benefits
Balance as of December 31, 2019	$ 15,945
Increases (decreases) for tax positions related to current period	3,149
Increases (decreases) for tax positions related to prior periods	(100)
Balance as of December 31, 2020	18,994
Increases (decreases) for tax positions related to current period	2,949
Increases (decreases) for tax positions related to prior periods	17
Balance as of December 31, 2021	21,960

The unrecognized tax benefits at December 31, 2021, if recognized, would not affect the Company’s effective tax rate due to its full valuation allowance position. The Company does not anticipate that the amount of existing unrecognized tax benefits will significantly increase or decrease within the next 12 months. The Company has elected to include interest and penalties related to uncertain tax positions as a component of its provision for income taxes. For the years ended December 31, 2021, 2020 and 2019, the Company’s accrued interest and penalties related to uncertain tax positions were not material.

17. Reduction in workforce

In April 2021, the Company announced its decision to withdraw ZYNTEGLO from the German market because reimbursement negotiations in Germany did not result in a price for ZYNTEGLO that reflects the value of the one-time gene therapy with potential life-long benefit for people living with β-thalassemia requiring regular transfusions. A total of approximately 50 employees were impacted by this reduction. During the three months ended June 30, 2021, the Company substantially completed the implementation of this reduction and, in accordance with ASC 420, *Exit and Disposal Activities,* and ASC 712, *Nonretirement Postemployment Benefits*, recorded approximately $4.6 million of costs including severance, the portion of the employees' 2021 retention bonuses to be paid in cash, and the pro rata portion of the employees' 2021 performance bonus.

In July 2021, the Company made the decision to focus its efforts on the U.S. market for beti-cel, eli-cel, and lovo-cel and is executing an orderly wind down of its European operations. A total of approximately 90 employees were impacted by the reduction in workforce associated with this decision. The Company recorded $21.2 million of expense, in accordance with the related accounting standards mentioned above, for the affected employees. This amount includes expense for severance, the pro rata portion of the employees' 2021 performance bonus, the portion of the European employees' 2021 retention bonuses to be paid in cash, and the portion of retention bonuses to be paid in unrestricted stock awards, which were granted on September 30, 2021. As described in Note 14, *Stock-based compensation*, the Company recorded $2.5 million of costs associated with the grant of unrestricted stock awards to affected employees as a one-time payment. All costs associated with the April 2021 and July 2021 reductions are reflected within restructuring expense in the Company's consolidated statements of operations and comprehensive loss.

The Company expects that substantially all accrued restructuring charges will be paid in cash by March 31, 2022.

The following table summarizes the accrued liabilities activity recorded in connection with the reduction in workforce for the year ended December 31, 2021 (in thousands):

	Charges	Amount paid	Amounts accrued at December 31, 2021
April 2021 reduction	$ 4,625	$ (4,625)	$ —
July 2021 reduction	21,176	(16,503)	4,673
Total	$ 25,801	$ (21,128)	$ 4,673

During the year ended December 31, 2021, the Company recorded approximately $25.8 million in restructuring expenses. During the year ended December 31, 2021, the Company recorded $2.5 million in research and development expenses and selling, general and administrative expenses related to the grant of unrestricted stock awards to affected employees.

18. Net loss per share

The following common stock equivalents were excluded from the calculation of diluted net loss per share for the periods indicated because including them would have had an anti-dilutive effect (in thousands):

	Year ended December 31,		
	2021	2020	2019
Outstanding stock options [(1)]	5,534	6,262	5,483
Restricted stock units [(1)]	3,427	1,495	1,127
ESPP shares and other	—	326	19
	8,961	8,083	6,629

[(1)] Outstanding stock options and restricted stock units include awards outstanding to employees of 2seventy bio.

19. Selected quarterly financial data (unaudited)

The following table contains quarterly financial information for 2021 and 2020. The Company believes that the following information reflects all normal recurring adjustments necessary for a fair presentation of the information for the periods presented. The operating results for any quarter are not necessarily indicative of results for any future period.

	2021				
	First quarter	Second quarter	Third quarter	Fourth quarter	Total
	(in thousands, except per share data)				
Total revenues	$ 894	$ 143	$ 1,019	$ 1,606	$ 3,662
Total operating expenses	146,988	154,844	155,468	137,273	594,573
Loss from operations	(146,094)	(154,701)	(154,449)	(135,667)	(590,911)
Net loss from continuing operations	(121,504)	(155,973)	(152,834)	(132,327)	(562,638)
Net loss from discontinued operations	(84,304)	(85,729)	(63,982)	(22,725)	(256,740)
Net loss	(205,808)	(241,702)	(216,816)	(155,052)	(819,378)
Net loss per share from continuing operations —basic and diluted	(1.81)	(2.31)	(2.23)	(1.83)	(8.16)
Net loss per share from discontinued operations—basic and diluted	(1.26)	(1.27)	(0.93)	(0.31)	(3.73)
Net loss per share—basic and diluted	$ (3.07)	$ (3.58)	$ (3.16)	$ (2.14)	$ (11.89)

	2020				
	First quarter	Second quarter	Third quarter	Fourth quarter	Total
	(in thousands, except per share data)				
Total revenues	$ —	$ —	$ —	$ —	$ —
Total operating expenses	144,479	143,650	131,743	139,387	559,259
Loss from operations	(144,479)	(143,650)	(131,743)	(139,387)	(559,259)
Net loss from continuing operations	(146,392)	(140,665)	(137,678)	(136,321)	(561,056)
Net income (loss) from discontinued operations	(56,219)	119,200	(57,067)	(63,553)	(57,639)
Net loss	(202,611)	(21,465)	(194,745)	(199,874)	(618,695)
Net loss per share from continuing operations —basic and diluted	(2.63)	(2.33)	(2.08)	(2.05)	(9.02)
Net income (loss) per share from discontinued operations—basic and diluted	(1.01)	1.97	(0.86)	(0.96)	(0.93)
Net loss per share—basic and diluted	$ (3.64)	$ (0.36)	$ (2.94)	$ (3.01)	$ (9.95)

Exhibit Index

Exhibit Number	Exhibit Title	Incorporated by Reference			
		Form	File no.	Exhibit	Filing Date
2.1*	Separation Agreement, dated as of November 3, 2021, by and between the Registrant and 2seventy bio, Inc.	8-K	001-35966	2.1	November 4, 2021
3.1	Amended and Restated Certificate of Incorporation of the Registrant	8-K	001-35966	3.1	June 24, 2013
3.2	Amended and Restated By-laws of the Registrant	10-K	001-35966	3.2	February 23, 2021
4.1	Specimen Common Stock Certificate	S-1/A	333-188605	4.1	June 4, 2013
4.2	Description of the Registrant's Securities	10-K	001-35966	4.2	February 23, 2021
4.3	Form of Pre-Funded Warrant	8-K	001-35966	4.1	September 8, 2021
10.1#	Second Amended and Restated 2002 Employee, Director and Consultant Stock Plan, as amended, and forms of award agreement thereunder	S-1	333-188605	10.1	May 14, 2013
10.2#	2010 Stock Option and Grant Plan, as amended, and forms of award agreement thereunder	S-1	333-188605	10.2	May 14, 2013
10.3#	2013 Stock Option and Incentive Plan and forms of award agreement thereunder	S-1/A	333-188605	10.3	June 4, 2013
10.4	Form of Indemnification Agreement between the Registrant and each of its Executive Officers and Directors	S-1	333-188605	10.4	May 14, 2013
10.5†	Patent License Agreement, dated December 11, 1996, by and between the Registrant (formerly known as Genetix Pharmaceuticals Inc., successor-in-interest to Innogene Pharmaceuticals, Inc.) and Massachusetts Institute of Technology, as amended	S-1	333-188605	10.6	May 14, 2013
10.6†	Fourth Amendment to Patent License Agreement, dated October 28, 2016, by and between the Registrant and Massachusetts Institute of Technology	10-K	001-35966	10.7	February 22, 2017
10.7†	Patent and Know-How License Agreement No. 07554F30, dated May 14, 2009, by and between the Registrant (formerly known as Genetix Pharmaceuticals Inc.) and INSERM-TRANSFERT, as amended	S-1	333-188605	10.7	May 14, 2013
10.8†	License Agreement, dated September 13, 2011, by and between the Registrant and Institut Pasteur, as amended	S-1	333-188605	10.8	May 14, 2013
10.9†	Amendment No. 3 to License Agreement, dated September 10, 2013, by and between the Registrant and Institut Pasteur	10-Q	001-35966	10.2	November 14, 2013
10.10†	Amendment No. 4 to License Agreement, dated April 1, 2015, by and between the Registrant and Institut Pasteur	10-Q	001-35966	10.10	May 6, 2015
10.11†	License Agreement, dated December 7, 2011, by and between the Registrant and Research Development Foundation	S-1	333-188605	10.9	May 14, 2013
10.12†	Novation Agreement, dated April 2, 2012, by and between the Registrant and The Board of Trustees of the Leland Stanford Junior University	S-1	333-188605	10.10	May 14, 2013
10.13††	License Agreement by and between the Registrant and Biogen Idec MA Inc., dated August 13, 2014	10-Q	001-35966	10.21	August 9, 2021
10.14†	Letter Agreement by and between the Registrant and Biogen MA Inc., dated September 29, 2017	10-Q	001-35966	10.21	November 1, 2017
10.15††	Exclusive Patent License Agreement by and between the Registrant and the National Institutes of Health, dated August 31, 2015	10-Q	001-35966	10.23	August 9, 2021
10.16†	License Agreement, dated December 23, 2015, by and between the Registrant and SIRION Biotech GmbH	10-K	001-35966	10.23	February 21, 2019
10.17††	Clinical and Commercial Supply Agreement – Viral Vector Product, dated November 27, 2017, by and between the Registrant and SAFC Carlsbad, Inc., as amended	10-Q	001-35966	10.25	August 1, 2019

Exhibit Number	Exhibit Title	Incorporated by Reference			
		Form	File no.	Exhibit	Filing Date
10.18††	Amendment No. 2 to Clinical and Commercial Supply Agreement Viral Vector Product by and between bluebird bio (Switzerland) GmbH and SAFC Carlsbad, Inc.	8-K	001-35966	10.1	January 21, 2020
10.19	Amendment No. 3 to Clinical and Commercial Supply Agreement Viral Vector Product by and between bluebird bio (Switzerland) GmbH and SAFC Carlsbad, Inc.	10-K	001-35966	10.28	February 23, 2021
10.20#	Employment Agreement, dated February 3, 2014, by and between the Registrant and Jason F. Cole	10-Q	001-35966	10.18	May 13, 2014
10.21#	Amendment to Employment Agreement, dated March 7, 2016, by and between the Registrant and Jason F. Cole	10-Q	001-35966	10.25	May 4, 2016
10.22#	Amendment No. 2 to Employment Agreement, dated November 3, 2016, by and between the Registrant and Jason F. Cole	10-K	001-35966	10.27	February 22, 2017
10.23#	Employment Agreement, dated January 7, 2021, by and between the Registrant and Andrew Obenshain	—	—	—	Filed herewith
10.24#	Employment Agreement, dated June 1, 2021, by and between the Registrant and Gina Consylman	—	—	—	Filed herewith
10.25#	Employment Agreement, dated April 20, 2021, by and between the Registrant and Thomas Klima	—	—	—	Filed herewith
10.26#	Employment Agreement, dated June 14, 2021, by and between the Registrant and Anne-Virginie Eggimann	—	—	—	Filed herewith
10.27#	Offer Letter, dated October 1, 2019, by and between the Registrant and Jessica Whitten	—	—	—	Filed herewith
10.28#	2013 Employee Stock Purchase Plan	S-1/A	333-188605	10.17	June 4, 2013
10.29#	First Amendment of the Bluebird Bio, Inc. 2013 Employee Stock Purchase Plan	10-K	001-35966	10.38	February 21, 2018
10.30#	Second Amendment of the Bluebird Bio, Inc. 2013 Employee Stock Purchase Plan	S-8	333-257135	99.1	June 15, 2021
10.31#	2021 Inducement Plan and forms of award agreements thereunder	S-8	333-257135	99.2	June 15, 2021
10.32#	Executive Cash Incentive Bonus Plan	S-1	333-188605	10.18	May 14, 2013
10.33††	Sublease, dated April 16, 2019, by and between the Registrant and Aventis Inc.	10-Q	001-35966	10.42	August 1, 2019
10.34	Amendment to Sublease, dated April 19, 2019, by and between the Registrant and Aventis Inc.	10-Q	001-35966	10.43	August 1, 2019
10.35*	Office Lease Agreement, dated November 2, 2021, by and between the Registrant and Assembly Row 5B, LLC	10-Q	001-35966	10.30	November 5, 2021
10.36*	Sub-sublease Agreement, by and between the Registrant and Meta Platforms, Inc.	—	—	—	Filed herewith
10.37††*	Securities Purchase Agreement, dated September 7, 2021, by and among the Registrant and the institutional investors named therein	8-K	001-35966	10.1	September 8, 2021
10.38	Registration Rights Agreement, dated September 7, 2021, by and among the Registrant and the persons listed on the attached Schedule A thereto	8-K	001-35966	10.2	September 8, 2021
10.39	Tax Matters Agreement, dated as of November 3, 2021, by and between the Registrant and 2seventy bio, Inc.	8-K	001-35966	10.1	November 4, 2021
10.40*	Employee Matters Agreement, dated as of November 3, 2021, by and between the Registrant and 2seventy bio, Inc.	8-K	001-35966	10.2	November 4, 2021
10.41*	Intellectual Property License Agreement, dated as of November 3, 2021, by and between the Registrant and 2seventy bio, Inc.	8-K	001-35966	10.3	November 4, 2021
10.42*	Transition Services Agreement, dated as of November 3, 2021, by and between the Registrant and 2seventy bio, Inc.	8-K	001-35966	10.4	November 4, 2021

Exhibit Number	Exhibit Title	Incorporated by Reference			
		Form	File no.	Exhibit	Filing Date
10.43*	Transition Services Agreement, dated as of November 3, 2021, by and between 2seventy bio, Inc. and the Registrant	8-K	001-35966	10.5	November 4, 2021
23.1	Consent of Ernst & Young LLP	—	—	—	Filed herewith
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.	—	—	—	Filed herewith
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.	—	—	—	Filed herewith
32.1	Certification of Principal Executive Officer and Principal Financial Officer pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.	—	—	—	Furnished herewith
101.INS	Inline XBRL Instance Document (the instance document does not appear in the Interactive Data File because its XBRL tags are embedded within the Inline XBRL document)				Filed herewith
101.SCH	Inline XBRL Taxonomy Extension Schema Document.	—	—	—	Filed herewith
101.CAL	Inline XBRL Taxonomy Extension Calculation Linkbase Document.	—	—	—	Filed herewith
101.DEF	Inline XBRL Taxonomy Extension Definition Linkbase Document.	—	—	—	Filed herewith
101.LAB	Inline XBRL Taxonomy Extension Label Linkbase Document.	—	—	—	Filed herewith
101.PRE	Inline XBRL Taxonomy Extension Presentation Linkbase Document.	—	—	—	Filed herewith
104	Cover Page Interactive Data File (formatted as Inline XBRL with applicable taxonomy extension information contained in Exhibits 101)	—	—	—	Filed herewith

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† Portions of this exhibit (indicated by asterisks) have been omitted pursuant to a request for confidential treatment and this exhibit has been submitted separately to the SEC.

†† Portions of this exhibit (indicated by asterisks) have been omitted in accordance with the rules of the SEC.

# Indicates a management contract or any compensatory plan, contract or arrangement.

* Schedules and exhibits have been omitted pursuant to Item 601(b)(2) of Regulation S-K. The Registrant will furnish copies of any such schedules and exhibits to the SEC upon request.

SIGNATURES

Pursuant 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.

bluebird bio, Inc.

By: /s/ Andrew Obenshain

Andrew Obenshain
President, Chief Executive Officer and Director

SIGNATURES AND POWER OF ATTORNEY

We, the undersigned directors and officers of bluebird bio, Inc. (the "Company"), hereby severally constitute and appoint Andrew Obenshain and Gina Consylman, and each of them singly, our true and lawful attorneys, with full power to them, and to each of them singly, to sign for us and in our names in the capacities indicated below, any and all amendments to this Annual Report on Form 10-K, and to file or cause to be filed the same, with all exhibits thereto and other documents in connection therewith, with the Securities and Exchange Commission, granting unto said attorneys, and each of them, full power and authority to do and perform each and every act and thing requisite and necessary to be done in connection therewith, as fully to all intents and purposes as each of us might or could do in person, and hereby ratifying and confirming all that said attorneys, and each of them, or their substitute or substitutes, shall do or cause to be done by virtue of this Power of Attorney.

Pursuant 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.

Name	Title	Date
/s/ Andrew Obenshain Andrew Obenshain	President, Chief Executive Officer and Director *(Principal Executive Officer and Duly Authorized Officer)*	March 4, 2022
/s/ Gina Consylman Gina Consylman	Chief Financial Officer *(Principal Financial Officer and Duly Authorized Officer)*	March 4, 2022
/s/ Jessica Whitten Jessica Whitten	Vice President, Global Controller and Chief Accounting Officer *(Principal Accounting Officer)*	March 4, 2022
/s/ Mark Vachon Mark Vachon	Director	March 4, 2022
/s/ John O. Agwunobi, M.D. John O. Agwunobi, M.D.	Director	March 4, 2022
/s/ Lis Leiderman, M.D. Lis Leiderman, M.D.	Director	March 4, 2022
/s/ Nick Leschly Nick. Leschly	Director	March 4, 2022
/s/ Najoh Tita-Reid Najoh Tita-Reid	Director	March 4, 2022

CORPORATE AND STOCKHOLDER INFORMATION

Board of Directors

Mark Vachon [1, 2]
Chairman – Independent
Formerly of GE

John O. Agwunobi, MD [1, 3]
Chairman & Chief Executive Officer, Herbalife Nutrition

Charlotte Jones-Burton, MD, MS [3]
SVP, Product Development & Strategy, Chinook Therapeutics;
Founder, Women of Color in Pharma (WOCIP)

Elisabeth Leiderman, MD [1, 2]
Chief Financial Officer & Head of Corporate Development, Decibel Therapeutics

Nick Leschly
President and Chief Kairos Officer, 2seventy bio

Andrew Obenshain
President and Chief Executive Officer, bluebird bio

Najoh Tita-Reid [2, 3]
Global Chief Marketing Officer, Logitech

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[1] *Audit Committee*
[2] *Compensation Committee*
[3] *Nominating and Corporate Governance Committee*

Executive Officers

Jason F. Cole, Esq.
Chief Strategy and Financial Officer

Anne-Virginie Eggimann
Chief Regulatory Officer

Thomas J. Klima
Chief Commercial Officer

Andrew Obenshain
President and Chief Executive Officer

Independent Registered Public Accounting Firm

Ernst & Young LLP
200 Clarendon Street
Boston, MA 02116
www.ey.com

Annual Meeting of Stockholders

The 2022 Annual Meeting of Stockholders will be held on June 22, 2022, at 8:30 a.m. Eastern Time, at 455 Grand Union Boulevard, Somerville, MA 02145.

Common Stock Listing

NASDAQ: BLUE

Corporate Counsel

Latham & Watkins LLP
200 Clarendon Street
Boston, MA 02116
Phone: 617.948.6000
www.lw.com

Transfer Agent / Registrar

American Stock Transfer & Trust Company, LLC
6201 15th Avenue
Brooklyn, NY 11219
Phone: 800.937.5449
www.astfinancial.com

Investor Relations

Courtney O'Leary
Phone: 978.621.7347