bluebird bio, Inc.

2022
Annual Report

Fellow Shareholders –

As I wrote this letter last year, bluebird bio was at the precipice of change – just months after the spinoff of our oncology business, and weeks after announcing the most significant restructuring in bluebird's history – one that aimed to right-size our cost structure and sharpen our focus on bringing our three lentiviral vector gene therapies for beta-thalassemia, cerebral adrenoleukodystrophy (CALD) and sickle cell disease to patients in the United States.

We persisted for purpose and following unanimous endorsements from the US Food and Drug Administration's Cellular, Tissue and Gene Therapies Advisory Committee in June, last August and September, we received FDA approval of ZYNTEGLO (betibeglogene autotemcel) for beta-thalassemia and accelerated approval for SKYSONA (elivaldogene autotemcel) for early, active CALD in boys ages 4 to 17.

These approvals -- built on a decade of scientific expertise and a deep commitment to patients and families – launched the next chapter for **bluebird bio, as a commercial gene therapy leader**. Today, as a company dedicated to transformative gene therapies for patients living with serious genetic diseases, we are proving the commercial model for an entire field.

We are establishing a footprint of qualified treatment centers across the US, and the value our therapies offer to patients, the healthcare system and society is being recognized. Informed by payer insights and our deep experience with value-based payment models, we have established an innovative, outcomes-based agreement for ZYNTEGLO, and to date have seen multiple patients initiate therapy, and zero ultimate denials from payers.

We are also living out our promise to families affected by CALD – providing hope to those faced with a devastating diagnosis and limited treatment options. On March 16, 2023, the first patient with CALD to be commercially treated with SKYSONA received their infusion at Boston Children's Hospital – marking a significant milestone not only for one family, but an entire rare disease community.

And, while we deliver for patients today, **we're also paving the road for our largest commercial opportunity**, which is still ahead of us – bringing a transformative gene therapy to individuals living with sickle cell disease (SCD) in the US.

For close to ten years, bluebird bio has been committed to making meaningful progress for SCD and for the SCD community, which has long been overlooked. On April 24, 2023, we announced that bluebird submitted its biologics license application (BLA) for lovo-cel (lovotibeglogene autotemcel) to the FDA for patients with sickle cell disease ages 12 and older who have a history of vaso-occlusive events.

As the most mature gene therapy in development for SCD – with unparalleled breadth of data and duration of follow up -- lovo-cel represents an opportunity to deliver transformational, rather than incremental, benefits that are long overdue, and may reduce the economic and lifelong burden of sickle cell disease as a one-time treatment.

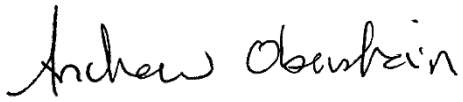
Importantly, the commercial infrastructure we're setting up today is not only enabling us to maximize our opportunity to reach those living with beta-thalassemia with ZYNTEGLO; it also prioritizes proximity to individuals living with SCD in anticipation of an early 2024 commercial launch for lovo-cel, if approved.

Underpinning our success is a commitment to **building our financial strength and fostering our unique culture**. During the five months beginning November 2022, we were able to raise $326 million in net proceeds from the sale of the two priority review vouchers and an equity offering. At the same time, we have stabilized retention and returned to an industry-leading 79 percent employee engagement score, with 90 percent of our flock reporting that they are proud to work for bluebird.

We are grateful to the bluebirds – past and present – who have been committed to this journey; to the patients, caregivers, researchers, and clinicians who have enabled this progress; and to the shareholders who have supported us.

Together, we are giving patients and their families more bluebird days.

Onward,



Forward-Looking Statements

This letter contains "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995. All statements that are not statements of historical facts are, or may be deemed to be, forward-looking statements, including, without limitation, our statements regarding the possible approval of lovo-cel by the FDA, the expected timing relating to such potential regulatory approval and commercial launch of lovo-cel if approved, and the potential benefits of lovo-cel. Such forward-looking statements are based on historical performance and current expectations and projections about our future financial results, goals, plans and objectives and involve inherent risks, assumptions and uncertainties, including internal or external factors that could delay, divert or change any of them in the next several years, that are difficult to predict, may be beyond our control and could cause our future financial results, goals, plans and objectives to differ materially from those expressed in, or implied by, the statements. No forward-looking statement can be guaranteed. Forward-looking statements in this letter should be evaluated together with the many risks and uncertainties that affect bluebird bio's business, particularly those identified in the risk factors discussion in bluebird bio's Annual Report on Form 10-K for the year ended December 31, 2022, as updated by our subsequent Quarterly Reports on Form 10-Q, Current Reports on Form 8-K and other filings with the Securities and Exchange Commission. These risks include, but are not limited to: delays and challenges in obtaining regulatory approval of our product candidates and our commercialization and manufacturing of our products, including risks associated with demonstrating analytical comparability with respect to our lovo-cel program; and we may encounter additional delays in the development of our programs, including the imposition of new clinical holds, that may impact our ability to meet our expected timelines and increase our costs. The forward-looking statements included in this letter are made only as of the date of this letter and except as otherwise required by applicable law, bluebird bio undertakes no obligation to publicly update or revise any forward-looking statement, whether as a result of new information, future events, changed circumstances or otherwise.

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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, 2022
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.)**
455 Grand Union Boulevard Somerville, Massachusetts	**02145**
(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. ☐

If securities are registered pursuant to Section 12(b) of the Act, indicate by check mark whether the financial statements of the registrant included in the filing reflect the correction of an error to previously issued financial statements. ☐

Indicate by check mark whether any of those error corrections are restatements that required a recovery analysis of incentive-based compensation received by any of the registrant's executive officers during the relevant recovery period pursuant to § 240.10D-1(b). ☐

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, 2022, the last business day of the registrant's most recently completed second quarter, was $302,268,804.

As of March 27, 2023, there were 106,370,265 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 2023 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 expectations and projections regarding the sufficiency of our cash, cash equivalents, marketable securities and restricted cash to fund our operations;
- 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, and our plans and expectations regarding our manufacturing activities;
- the timing or likelihood of regulatory filings and marketing approvals for our product candidates and our plans and expectations relating thereto;
- our plans and expectations regarding our commercialization activities for any approved products and the timing or success thereof, including expectations regarding our network of qualified treatment centers;
- 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 general economic conditions and uncertainties, including as a result of COVID-19 pandemic; 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.

- 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 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 commercial programs, product development efforts or other operations.

- Insertional oncogenesis is a significant risk of gene therapies using viral vectors that can integrate into the genome. Any such adverse events may require us to halt or delay further clinical development of our product candidates or to suspend or cease commercialization following marketing approval, and the commercial potential of our products and product candidates may be materially and negatively impacted.

- We rely on a complex supply chain for SKYSONA, ZYNTEGLO, and lovo-cel. The manufacture, testing 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, or timing needed to support our clinical programs and commercialization.

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

- We cannot predict when or if we will obtain marketing approval to commercialize lovo-cel, and the marketing approval of our product candidates may ultimately be for more narrow indications than we expect. If lovo-cel or other 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.

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

- The commercial success of ZYNTEGLO, SKYSONA and of lovo-cel following marketing approval (if and when obtained), will depend upon the degree of market acceptance by physicians, patients, payers and other stakeholders.

- If the market opportunities for our product candidates 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.

- 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 unique and additional challenges in obtaining adequate pricing and reimbursement for our products. 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.

- 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 ZYNTEGLO, SKYSONA and lovo-cel.

PART I

Item 1. Business

Overview

We are a biotechnology company committed to researching, developing, and commercializing potentially curative gene therapies for severe genetic diseases based on our proprietary lentiviral vector ("LVV") gene addition platform. In 2022, following more than a decade of leadership in research and clinical development, we received approval from the US Food and Drug Administration (the "FDA") for two gene therapies: ZYNTEGLO® (betibeglogene autotemcel, also known as beti-cel) and SKYSONA® (elivaldogene autotemcel, also known as eli-cel). Both therapies were launched in the fourth quarter of 2022, and we emerged as a leading commercial gene therapy company.

The FDA approved ZYNTEGLO for the treatment of adult and pediatric patients with ß-thalassemia who require regular red blood cell transfusions on August 17, 2022. The FDA granted accelerated approval of SKYSONA to slow the progression of neurologic dysfunction in boys 4-17 years of age with early active cerebral adrenoleukodystrophy ("CALD") on September 16, 2022. Prior to FDA approval, both ZYNTEGLO and SKYSONA received unanimous favorable votes from the FDA's Cellular, Tissue and Gene Therapy Advisory Committee in June 2022. We intend to submit a biologics licensing application ("BLA") to the FDA for our third gene therapy program -- lovotibeglogene autotemcel - also known as lovo-cel - requesting priority review of the treatment for patients 12 and older with sickle cell disease ("SCD") with a history of vaso-occlusive-events.

We estimate that approximately 22,000 patients living with ß-thalassemia, CALD and SCD in the United States may potentially be addressable by ZYNTEGLO, SKYSONA and, if approved, lovo-cel, with 20,000 of these patients estimated to have SCD, 1,300-1,500 estimated to have ß-thalassemia and 40 estimated to have CALD.

In 2022, fiscal discipline remained a priority for us. Following a corporate restructuring in April 2022, we reduced operating expenses by approximately 30% with a strategic focus on near-term catalysts, while also leveraging opportunities to extend our cash runway, including the sale of two Rare Pediatric Disease Priority Review Vouchers ("PRVs") granted upon the FDA's approval of both ZYNTEGLO and SKYSONA and completion of an equity financing in January 2023.

Our Platform

We believe we have the largest and deepest ex vivo gene therapy data set in the industry, with more than 700 patient years of experience. We custom design each of our products and product candidates to address the underlying cause of disease by introducing a functional copy of a gene to patients' own enriched 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.

Our Programs

ZYNTEGLO® (betibeglogene autotemcel)

On August 17, 2022, the FDA approved ZYNTEGLO, the first gene therapy for people with β-thalassemia who require regular red blood cell transfusions. ZYNTEGLO is approved for patients of all ages and genotypes and offers patients a potentially curative benefit through the achievement of durable transfusion independence and normal or near normal total hemoglobin levels.

β-thalassemia is a rare, genetic blood disease caused by mutations in the beta-globin gene and characterized by significantly reduced or absent adult hemoglobin production. Patients with the most severe form, sometimes called transfusion-dependent β-thalassemia or β-thalassemia major, experience severe anemia and lifelong dependence on regular red blood cell transfusions, a lengthy process that patients typically undergo every 2-5 weeks. Despite advances in treatment and improved transfusion techniques, transfusions only temporarily address symptoms of anemia and people with β-thalassemia who require regular transfusions have an increased risk for morbidity and mortality due to complications from treatment-related iron overload. Data from the Cooley's Anemia Foundation indicate that the median age of death of patients with transfusion-

dependent β-thalassemia in the U.S. who died during the last decade was just 37 years. We estimate that there are approximately 1,300-1,500 individuals with transfusion-dependent β-thalassemia in the U.S.

ZYNTEGLO works by using LVV to add functional copies of a modified form of the beta-globin gene ($\beta^{A\text{-}T87Q}$-globin gene) into a patient's own HSCs, allowing them to make normal to near normal levels of total hemoglobin without regular red blood cell ("RBC") transfusions. The functional beta-globin gene is added into a patient's cells outside of the body (ex-vivo), and the modified genes are then administered to the patient via infusion. The treatment process is comprised of several steps that may take place over the course of several months.

Clinical Development Program

We believe we have the longest and most robust clinical program for β-thalassemia in the field of gene therapy. 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 was a single-dose, open-label, non-randomized, international, multi-site phase 3 clinical study that evaluated the safety and efficacy of beti-cel to treat patients with transfusion-dependent β-thalassemia ("TDT") and non-β^0/β^0 genotypes. This study was completed in March 2022. Twenty-three patients were enrolled and completed dosing in the study, consisting of 15 adolescent and adult patients between 12 and 34 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 had to have received at least 100 mL/kg/year of RBCs or at least eight transfusions per year for the previous two years. All patients must have been eligible for HSCT, but without a known and available matched family HSCT donor. The primary endpoint of this study was the proportion of treated patients who achieved 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 were 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 included monitoring of laboratory parameters, frequency and severity of clinical adverse events, incidence of acute and/or chronic graft versus host disease, 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 remained on study for approximately 24 months post-treatment 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-212 was a single-dose, open-label, non-randomized, international, multi-site phase 3 clinical study that evaluated 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. This study was completed in November 2022. Eighteen patients were enrolled and completed dosing in the study, consisting of ten adolescent and adult patients between twelve and 34 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 previous two years. All patients must have been clinically stable and eligible to undergo HSCT (but without a known and available matched family HSCT donor) 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 was the proportion of treated patients who met the definition of transfusion independence, which was identical to the definition in our HGB-207 study. The secondary endpoints of this study were designed to measure the proportion of patients who meet the definition of transfusion reduction, which was defined as the 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. Safety evaluations performed during the study included monitoring of laboratory parameters, frequency and severity of clinical adverse events, incidence of acute and/or chronic graft versus host disease, 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 remained on study for approximately 24 months post-treatment 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-204 was a single-dose, open-label, non-randomized, international, multi-site phase 1/2 clinical study designed 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 β^{A-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 was a 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.

The approval of ZYNTEGLO was based primarily on data from the phase 3 HGB-207 and HGB-212 studies and the long-term follow-up study LTF-303.

Data from the phase 3 studies (HGB-207 and HGB-212) presented at the American Society of Hematology (ASH) Annual Meeting in December 2022 demonstrated that 90.2% (37/41) of patients treated achieved transfusion independence as of the July 2022 data cut. Transfusion independence is defined as no longer needing red blood cell transfusions for at least 12 months while maintaining a weighted average total hemoglobin of at least 9 g/dL. Patients who achieved transfusion independence produced normal or near normal levels of total hemoglobin and demonstrated improvements in markers of iron overload and markers of ineffective erythropoiesis. Results in these patients were durable as of last follow-up.

Data from all 63 patients treated across our β-thalassemia gene therapy clinical development program have generally continued to demonstrate sustained treatment effect and quality of life improvements in patients with β-thalassemia who require regular red blood cell transfusions following treatment with beti-cel up to 8 years post-treatment (n=3), across ages and genotypes. Based on testimonials collected at month 36 from patients who achieved transfusion independence, the ability to seek employment or be employed increased to 93% of patients (13/14) from 67% (10/15) at baseline. There was also a reduction in the number of absences from school compared with baseline (from 95% (18/19) of impacted patients to 50% (5/10)). In addition, at month 36, 81% (17/21) of patients reported improvement in physical activity, and 100% (20/20) reported that they felt they had benefited from undergoing treatment with beti-cel.

Nineteen percent (12/63) of patients experienced ≥1 adverse event ("AE") considered related or possibly related to beti-cel; the most common beti-cel related AEs were abdominal pain (5/63 [8%]) and thrombocytopenia (3/63 [5%]). Veno-occlusive liver disease, observed in 11% (7/63) of patients, resolved after treatment. Three patients experienced acute events unrelated to their β-thalassemia that required packed red blood cell transfusions (phase 1/2, n=1; phase 3, n=2). No hematologic malignancies, insertional oncogenesis, or vector-derived replication competent lentivirus, was observed.

As part of the FDA approval, we are required to conduct a prospective, multi-center observational study (REG-501) which will evaluate the long-term safety of ZYNTEGLO, including the risk of secondary malignancies occurring after treatment with ZYNTEGLO in at least 150 patients.

SKYSONA® (elivaldogene autotemcel)

On September 16, 2022, the FDA granted accelerated approval of SKYSONA (elivaldogene autotemcel), also known as eli-cel, to slow the progression of neurologic dysfunction in boys 4-17 years of age with early, active CALD. The SKYSONA product label includes a boxed warning for the risk of hematologic malignancy.

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. 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. The disease, which primarily affects young boys, is associated with irreversible neurologic decline, including major functional disabilities such as loss of communication, cortical blindness, requirement for tube feeding, total incontinence, wheelchair dependence, or complete loss of voluntary movement. Nearly half of patients who do not receive treatment die within five years of symptom onset. Prior to the approval of SKYSONA treatment, effective options were limited to allo-HSCT, which is associated with the risk of serious potential complications including death, that can increase dramatically in patients without a human leukocyte antigen matched donor.

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 adrenoleukodystrophy protein ("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.

We have agreed to provide confirmatory long-term clinical data to the FDA as a condition of the SKYSONA accelerated approval, and continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

Clinical Development Program

The approval of SKYSONA was based on data from our phase 2/3 study (ALD-102 (n=32)) and phase 3 study (ALD-104 (n=35)).

Both open-label, single-arm studies enrolled patients with early, active CALD who had elevated very long chain fatty acid (VLCFA) values, a Loes score between 0.5 and 9 (inclusive), and gadolinium enhancement on magnetic resonance imaging (MRI) of demyelinating lesions. Additionally, patients were required to have a neurologic function score ("NFS") of ≤ 1, indicating limited changes in neurologic function. The efficacy of SKYSONA was compared to a natural history population.

Per protocol, patients treated with SKYSONA were assessed using the NFS and monitored for the emergence of six Major Functional Disabilities ("MFDs") associated with CALD progression including loss of communication, cortical blindness, requirement for tube feeding, total incontinence, wheelchair dependence, or complete loss of voluntary movement.

The accelerated approval of SKYSONA was based on an intermediate clinical endpoint of MFD-free survival. A post-hoc enrichment analysis in symptomatic patients assessed MFD-free survival from onset of symptoms (NFS ≥ 1) in SKYSONA treated (N=11) and untreated patients (N=7). SKYSONA treated patients had an estimated 72 percent likelihood of MFD-free survival at 24 months from time of first NFS ≥ 1, compared to untreated patients who had an estimated 43 percent likelihood of MFD-free survival.

The most common adverse events (incidence [$\geq 20\%$]) were mucositis, nausea, vomiting, febrile neutropenia, alopecia, decreased appetite, abdominal pain, constipation, pyrexia, diarrhea, headache and rash. Myelodysplastic syndrome ("MDS"), a hematologic malignancy, has developed in patients treated with SKYSONA in clinical studies and, as of March 2023, MDS had been diagnosed in three patients after administration of SKYSONA. The SKYSONA product label includes a boxed warning for the risk of hematologic malignancy.

Enrollment is complete and all patients have been treated in both studies; follow-up in ALD-104 is ongoing. All patients who complete 24 months of follow-up in studies ALD-102 or ALD-104 are encouraged to participate in a long-term follow-up study (LTF-304) to continue monitoring safety and efficacy outcomes in boys treated with SKYSONA through 15 years post-treatment.

As part of the accelerated approval process with the FDA, we have post-marketing requirements to follow patients who received SKYSONA in studies ALD-102 and ALD-104 for a minimum of ten years to assess event-free survival or need for hematopoietic stem cell transplant. In addition, as a post-marketing requirement, a long-term study is being conducted to assess the safety of SKYSONA and the risk of secondary malignancies occurring after treatment with SKYSONA. We plan to fulfill this latter post-marketing requirement through an observational study (REG-502) which will enroll at least 120 patients followed for 15 years who receive SKYSONA in the commercial setting, which will include studying the effectiveness and safety in 24 boys with more advanced early active CALD for at least five years who are newly treated with SKYSONA.

The eli-cel program was subject to a clinical hold beginning in August 2021, when we received the first report of MDS. On September 15, 2022, the FDA lifted the clinical hold, prior to the completion of its review, and approval, of the SKYSONA BLA.

Lovotibeglogene autotemcel

We are developing (lovotibeglogene autotemcel), also known as lovo-cel, as a one-time treatment for patients with SCD, a serious, progressive and debilitating genetic disease caused by a single mutation in the beta-globin gene that leads to the production of abnormal sickle hemoglobin ("HbS"). HbS causes RBCs to become sickled and fragile, resulting in chronic hemolytic anemia, vasculopathy and unpredictable, vaso-occlusive events ("VOEs"), requiring frequent hospitalization. In the United States, more than 100,000 people are believed to have SCD, and the median age of death for a person living with the disease is 45 years. One in four people living with SCD experience a stroke by age 45, and 75 percent of people living with SCD report difficulty completing daily tasks.

We intend to submit a BLA to the FDA for lovo-cel requesting priority review of the treatment for patients 12 and older with SCD with a history of vaso-occlusive events. The BLA submission will be based on efficacy results from 36 patients in the HGB-206 Group C cohort and include a median of 32 months of follow up. We anticipate that the BLA submission will also include efficacy results from two patients with 18 months of follow up in the HGB-210 study. Efficacy endpoints in the clinical studies focused on the resolution of severe vaso-occlusive events (sVOEs) and VOEs, as well as globin response based on β^{A-T87Q} expression, total hemoglobin and health related quality of life measures. A vaso-occlusive event was defined as an episode of acute pain with no medically determined cause other than a vaso-occlusion, including acute episodes of pain, acute chest syndrome, acute hepatic sequestration, acute splenic sequestration, and acute priapism. A severe vaso-occlusive event was defined as such an event leading to a visit to a hospital or emergency department lasting for at least 24 hours, at least two visits to a day unit or emergency department during a 72-hour period (with both visits requiring intravenous treatment), or an episode of priapism lasting more than 2 hours and resulting in a visit to a medical facility.

Data from the August 2022 BLA data cut, which will be used for the BLA submission, showed similar rates of complete resolution of sVOE and VOE (97% and 90%, respectively) as previously published data from the Group C pivotal cohort of HGB-206 through 24 months of follow-up. Moreover, in such August 2022 data cut, maintenance of complete VOE resolution in the majority of patients through long-term follow-up, combined with stable production of HbA^{T87Q}, suggest outcomes have remained durable effect. We anticipate that the BLA submission will also include safety data from 50 patients treated across the entire lovo-cel program, including six patients with $\geq$ 6 years of follow-up.

We anticipate that the BLA submission will also include safety data as of August 2022 from 50 patients treated across the entire lovo-cel program, with 6 patients having $\geq$ 6 years of follow-up. The majority of adverse events in treated patients were attributed to underlying sickle cell disease or conditioning with busulfan. Nonserious adverse events related to lovo-cel included infusion reactions (hot flush and decreased blood pressure) in 2 patients (4%). Serious adverse events related to lovo-cel included anemia in 2 patients (4%) with alpha-thalassemia, and leukemia in 2 patients (4%), not resulting from insertional oncogenesis. Three of 50 patients (6%) died, 1 due to sudden cardiac death and 2 due to leukemia. Additional data from the BLA data package is anticipated to be published or presented at a medical congress in 2023.

If approved by the FDA, we intend to launch lovo-cel using third-party commercial manufacturing facilities for both the vector and drug product, using a suspension lentiviral vector process. We believe this approach supports the potential commercialization of lovo-cel with a robust and scalable manufacturing process to meet patient demand. We have completed manufacturing of commercial drug product validation lots, and in December 2022 we submitted vector and drug product comparability analyses to the FDA, which included data from the HGB-210 study. In mid-February 2023, we received feedback from the FDA and subsequently submitted additional analyses supporting comparability of the proposed commercial process to the FDA, as further described below under "Manufacturing activities".

In December 2022, the FDA lifted a partial clinical hold on our clinical program for lovo-cel for patients under the age of 18, which had been in place since December 2021.

Lovo-cel is designed to work by using LVV to add functional copies of a modified form of the beta-globin gene (β^{A-T87Q}-globin gene) into the patient's own HSCs, potentially allowing them to make normally functioning hemoglobin A and normal RBCs. The functional beta-globin gene is added into a patient's cells outside of the body (ex-vivo), and the modified genes are then administered to the patient via infusion. The treatment process is comprised of several steps that may take place over the course of several months. β^{A-T87Q}-globin is designed to become part of the hemoglobin that the patient produces and HbA^{T87Q} reduces the sickling of red blood cells in patients and may serve as a distinct biomarker used to quantify expression levels of the

transgenic beta-globin protein in lovo-cel treated patients with SCD. By reducing the amount of red blood cell sickling, we believe the risk of vaso-occlusive events in patients should be reduced.

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 FDA.

Clinical Development Program

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:

- HGB-206 is a single-dose, open-label, non-randomized, multi-site phase 1/2 clinical study in the United States evaluating 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, $\beta^S/\beta+$ 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 used for Group B and Group C. The primary efficacy endpoint for this study is the percentage of patients with complete resolution of all VOEs, between six- and 18-months post-treatment, and the secondary efficacy endpoints for this study includes the percentage of patients with complete resolution of severe VOEs and globin response based on $\beta^{A\text{-}T87Q}$ expression and total hemoglobin. Safety endpoints includes 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 oligoclonality, or leukemia. Each patient remains on study for approximately 24 months post-treatment and is then 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 designed 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. Patients must be at least two years of age at enrollment with a diagnosis of sickle cell disease, with β^S/β^S, $\beta^S/\beta+$ or β^S/β^0 genotype. Patients must have recurrent VOEs and must have failed to achieve clinical benefit from treatment with hydroxyurea. The primary efficacy endpoint for this study is complete resolution of VOEs, between six- and 18-months post-treatment, and the secondary efficacy endpoint for this study includes the percentage of patients with complete resolution of severe VOEs and 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 oligoclonality or leukemia. Each patient remains on study for approximately 24 months post-treatment and is then invited to enroll in LTF-307, a long-term follow-up protocol that will assess safety and efficacy for an additional 13 years. Data from drug product manufactured at our commercial manufacturing facility for the HGB-210 study are included in the lovo-cel BLA submission to demonstrate analytical comparability and support validation of our commercial manufacturing process.

- HGB-205 was a 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.

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. We use an adherent cell culture process at SAFC to manufacture LVV for ZYNTEGLO and SKYSONA. In addition, we have entered into multi-year agreements with Lonza Houston, Inc. to produce clinical and commercial drug product for ZYNTEGLO and SKYSONA and Minaris Regenerative Medicine ("Minaris") to produce drug product for lovo-cel. We also rely on specialized third-party testing organizations to confirm the quality of LVV and drug product prior to their use in clinical trials and commercial sales.

Over the course of the clinical development program for lovo-cel, we transitioned the lovo-cel LVV manufacturing process from an adherent cell culture process to a suspension process in order to meet anticipated commercial demand and potentially lower our cost of goods. Additionally, we transitioned lovo-cel drug product manufacturing from a clinical manufacturing site to a commercial manufacturing site. Our registrational clinical study for lovo-cel (which we refer to as HGB-206 Group C) was supplied primarily with LVV manufactured with the adherent process and drug product manufactured at both our clinical and commercial manufacturing sites; however, we plan to commercially launch utilizing the suspension process and commercial drug product manufacturing, if approved. To support these changes in manufacturing, in December 2022 we completed planned analytical analyses to demonstrate comparability between the two processes. In mid-February 2023, we received feedback from the FDA regarding comparability of lovo-cel using the proposed commercial process. We have submitted additional analyses to address the FDA's questions. The FDA is reviewing the analyses prior to our submission of the BLA and we plan to move quickly to submit the BLA upon resolution of the FDA's comparability questions. Please see Part I, Item 1A. "Risk Factors—Changes in our manufacturing processes may cause delays in our clinical development and commercialization plans" of this Annual Report on Form 10-K for further information.

We believe our team of technical personnel has extensive manufacturing, analytical and quality experience as well as strong project management discipline to 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 treatment centers in the United States, which we refer to as qualified treatment centers ("QTCs"), to be centers for collection of HSCs from the patient and for infusion of drug product to the patient.

In 2022, we paused efforts to demonstrate comparability of using cryopreserved patient starting material versus fresh patient starting material for the manufacture of lovo-cel drug product to focus our resources on BLA approvals and product launches. We are evaluating plans to reinitiate and advance cryopreserved starting material. If these efforts are successful, including if cryopreservation is determined to be technically feasible and is approved by the FDA and implemented with respect to our lovo-cel program, we believe cryopreservation could (i) expand the patient population that our therapies could potentially serve by improving patient and QTC experience by reducing the number of mobilization cycles, and (ii) lower our cost of goods by reducing the need for multiple manufacturing runs per patient.

Commercial operations

Throughout the course of 2022, we established commercial capabilities by adding employees with established experience in quality assurance and compliance, medical education, marketing, supply chain, sales, public policy, patient services, market access and product reimbursement.

Our commercial strategy centers on three key components:

- A qualified treatment center network
- Quality access and reimbursement
- Patient support

As of March 27, 2023, ZYNTEGLO is commercially available to patients in the US through a network of 12 QTCs (defined as having a signed services agreement). Each ZYNTEGLO QTC has been selected based on their expertise in areas such as transplant, cell, and gene therapy, and is trained to administer ZYNTEGLO. We expect to scale to between 40 to 50 centers by the end of 2023. Five commercial patient starts (which we define as patients who have had their cells collected) have occurred for ZYNTEGLO, as of March 27, 2023. Following cell collection, the patient's cells are shipped to a manufacturing facility where they are transduced with the appropriate LVV and tested to ensure they meet stringent release specification criteria. They are then frozen and shipped back to the QTC where the patient receives treatment via IV infusion. It is estimated to take between 70 – 90 days from apheresis (cell collection) to when manufactured drug product is ready to be shipped back to the QTC for patient infusion.

We have set a wholesale acquisition cost of $2.8M for ZYNTEGLO. To help enable timely and quality access for patients, we are offering payers an outcomes-based agreement, under which we will reimburse contracted commercial and government payers up to 80% of the cost of the therapy if a patient fails to achieve and maintain transfusion independence up to two years following infusion. All patients in ZYNTEGLO phase 3 studies who achieved transfusion independence have remained transfusion free as of March 2023. As of March 2023, more than 190 million US lives are covered by a favorable coverage policy for ZYNTEGLO.

ZYNTEGLO commercial launch operations are expected to enable a smooth transition to a potential lovo-cel commercial launch if and when it is approved by the FDA for the treatment of patients with SCD. The planned QTC footprint is designed to rapidly reach SCD patients, and the established QTC ZYNTEGLO contract is expected to allow for a simplified activation process for lovo-cel. We estimate that 65% of SCD patients will live within 50 miles of a planned QTC at launch.

SKYSONA is currently available through a network of three activated QTCs. Cell collection has been completed for two commercial SKYSONA patients as of March 2023 and on March 16, 2023 the first SKYSONA commercial infusion was completed. We believe payers recognize the value and urgency to treat these patients, and to date there have been no ultimate denials by payers for the therapy. We have set a wholesale acquisition cost of $3 million for SKYSONA.

For our approved therapies, we have established mybluebirdsupport, a patient support program that provides education, insurance and treatment support using patient navigators.

While we believe we have largely established 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, plan for the scale needed for the potential launch of lovo-cel, establish patient-focused programs, educate healthcare professionals, and secure additional 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.

European withdrawal

In August 2021, we announced our intent to wind down our operations in Europe and to focus on the US 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. Accordingly, we withdrew the regulatory marketing authorizations for SKYSONA and ZYNTEGLO from the European Union and withdrew 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. We maintain rights to all three therapies in all global markets and continue to consider options, including possible collaboration with third-parties, to attempt to bring our therapies to market outside the US.

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 certain non-U.S. patents and patent applications that we own lapse by ceasing further prosecution of certain pending ex-U.S. patent applications and not paying future maintenance fees for certain ex-U.S. patents when due. As of March 8, 2023, our patent portfolio includes the following:

- approximately 21 patents or patent applications that we own or have exclusively in-licensed from third parties, including 5 that are co-owned with MIT, related to LVVs and vector systems;
- approximately 115 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
- approximately 8 U.S. patents or patent applications that we own or have exclusively in-licensed from third parties related to therapeutic cellular product candidates.

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 and 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.

ZYNTEGLO and lovo-cel

The ZYNTEGLO 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 ZYNTEGLO and lovo-cel. As of March 8, 2023, we had an exclusive license to one issued U.S. patent. We expect the issued composition of matter patent to expire in 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 ZYNTEGLO and lovo-cel. As of March 8, 2023, we had an exclusive license (from RDF) to five issued U.S. patents related to our LVV platform. We expect the issued composition of matter patents to expire from 2023-2027 in the United States.
- **MIT/bluebird bio.** This co-owned patent portfolio contains patents and patent applications directed to certain specific compositions of matter for lentiviral beta-globin expression vectors. As of March 8, 2023, we co-owned four issued U.S. patents and one pending U.S. patent application. We expect the issued composition of matter patents to expire in 2023 (excluding possible patent term extensions). Further, 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 (excluding possible patent term extensions). We note that we have an exclusive license to MIT's interest in this co-owned intellectual property.

SKYSONA

The SKYSONA 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 SKYSONA.

- **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 SKYSONA.

- **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 March 8, 2023, we owned three U.S. patents and 7 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 March 8, 2023, we had an exclusive license to three issued U.S. patents, one pending U.S. patent application, 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 March 8, 2023, we owned four issued U.S. patents, two pending U.S. patent applications and seven corresponding foreign patent applications and 41 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 March 8, 2023, we had a non-exclusive license to four patent families that include two pending U.S. patent applications, seven 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. 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 lovo-cel 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 SA, referred to hereafter as "Inserm", 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. The last patent in the Inserm licensed patent portfolio expired in February of 2016.

We are obligated to pay Inserm a percentage of net sales as a royalty on any of our products that use the in-licensed intellectual property for the longer of the life of any patents covering the product or 10 years from first commercial sale. Any net sales of SKYSONA will be subject to this royalty which 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.

We are obligated to pay Institut Pasteur a percentage of net sales as a royalty on any of our commercialized products covered by the in-licensed intellectual property, which include ZYNTEGLO and SKYSONA, and will likely include lovo-cel, if and when approved. 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 have been required to make an annual maintenance payment, 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).

We are obligated to pay Stanford a percentage of net sales as a royalty on any of our commercialized products covered by the in-licensed intellectual property, which include ZYNTEGLO and SKYSONA, and will likely include lovo-cel, when and if approved. 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.

We are obligated to pay MIT a percentage of net sales as a royalty on any of our commercialized products covered by the in-licensed intellectual property which includes ZYNTEGLO and will likely include lovo-cel in the future, if and when approved. 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 Research Development Foundation, which we refer to as "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.

We are obligated to pay RDF a percentage of net sales as a royalty on any of our commercialized products covered by the in-licensed intellectual property which include ZYNTEGLO and SKYSONA, and will likely include lovo-cel, when and if approved. 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.

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. We are obligated to pay SIRION a percentage of net sales as a royalty on any of our commercialized products covered by the in-licensed intellectual property which includes ZYNTEGLO and will likely include lovo-cel when and if approved. These royalties are 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, which we refer to as 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. Financial terms of the agreement included an upfront payment to us as well as potential development and regulatory milestone payments and potential 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 commercialize will 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 / European Medicines Agency 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, in a phase 2/3 trial supported by Agios Pharmaceuticals, Inc.; another pyruvate kinase receptor activator, FT-4202, in a phase 2/3 study supported by Novo Nordisk (through its subsidiary, Forma Therapeutics); 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 gene therapy options in development for sickle cell disease. These include: CTX-001, which is being developed by CRISPR Therapeutics AG's in collaboration with Vertex Pharmaceuticals Incorporated with an ongoing phase 2/3 study and a rolling BLA submission in progress, and which leverages the CRISPR/Cas9 gene editing platform to disrupt the BCL11A erythroid enhancer; and 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. There are several other groups developing gene therapy approaches for SCD in early phases of development, including Beam Therapeutics 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. Reblozyl (luspatercept), a subcutaneously-delivered protein therapeutic marketed by Merck and Bristol Myers Squibb that targets molecules in the TGF-β superfamily, has been approved in the United States for the treatment of anemia in adult patients with β-thalassemia who require regular red blood cell transfusions, and was approved in the European Union for the treatment of adult patients with transfusion-dependent anemia associated with β-thalassemia. Additionally, Agios is developing mitapivat for both transfusion-dependent and non-transfusion-dependent β-thalassemia, with two phase 3 studies in progress. 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, including CRISPR Therapeutics AG (in collaboration with Vertex Pharmaceuticals Incorporated) which is conducting an ongoing phase 2/3 study for its CTX-001, which leverages the CRISPR/Cas9 gene editing platform to disrupt the BCL11A erythroid enhancer and for which a rolling BLA submission has been initiated.

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. Other possible treatments being investigated include 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 certain biological products, including our products and product candidates. 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, a proposed clinical protocol and investigator information, 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 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, among other things, 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. The FDA may also require, or sponsors may voluntarily decide, to continue evaluating patients in ongoing clinical trials to gather additional information regarding the long-term effects of any approved products. 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 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 initial receipt of the information. 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 may suspend, or its data safety monitoring board may recommend suspension of 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

FDA approval of a BLA must be obtained before commercial marketing of the biological product candidate. 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. Data can come from company-sponsored clinical studies intended to test the safety and effectiveness of a use of the product, or from a number of alternative sources, including studies initiated by independent investigators. 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 of the PREA requirements. Unless otherwise required by regulation, PREA does not apply to any biological product for an indication for which orphan designation has been granted.

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, pure 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's goal is to review standard applications within ten months after the filing date, or, if the application qualifies for priority review, six months after the FDA accepts the application for filing. In both standard and priority reviews, the review process may also be extended by FDA requests for additional information or clarification.

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 GTP regulations applicable to the operations that it performs. 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.

After the FDA evaluates a BLA and conducts inspections of manufacturing facilities where the investigational product and/or its drug substance will be produced, the FDA may issue an approval letter or a Complete Response Letter ("CRL"). An approval letter authorizes commercial marketing of the product with specific prescribing information for specific indications. A CRL will describe all of the deficiencies that the FDA has identified in the BLA, except that where the FDA determines that the data supporting the application are inadequate to support approval, the FDA may issue the CRL without first conducting required inspections, testing submitted product lots, and/or reviewing proposed labeling. In issuing the CRL, the FDA may recommend actions that the applicant might take to place the BLA in condition for approval, including requests for additional

information or clarification. The FDA may delay or refuse approval of a BLA if applicable regulatory criteria are not satisfied, require additional testing or information and/or require post-marketing testing and surveillance to monitor safety or efficacy of a product.

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 REMS, 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.

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 a 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 disease or condition for seven years, except in limited circumstances, such as a showing of clinical superiority to the product with orphan exclusivity. The designation of such drug also entitles a party to financial incentives such as opportunities for grant funding towards clinical trial costs, tax advantages, exemptions from PREA requirements and BLA user-fee waivers. Competitors, however, may receive approval of different products for the disease or condition for which the orphan product has exclusivity or obtain approval for the same product but for a different disease or condition for which the orphan product has exclusivity. Orphan product exclusivity also could block the approval of a product 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 condition or disease. If a drug or biological product designated as an orphan product receives marketing approval for a disease or condition 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 drugs and biological products that meet certain criteria. Specifically, drugs and biological product candidates 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 candidate and the specific indication for which it is being studied. The product candidate sponsor 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. Fast Track designation provides opportunities for more frequent interactions with the FDA, and with regard to a Fast Track product candidate, 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.

A biological product candidate intended to treat a serious or life-threatening disease or condition may also be eligible for Breakthrough Therapy designation to expedite its development and review. A product candidate can receive Breakthrough Therapy designation if preliminary clinical evidence indicates that the product candidate, alone or in combination with one or more other drugs or biologics, may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. The designation includes all of the Fast Track designation features, as well as more intensive FDA interaction and guidance beginning as early as Phase 1 and an organizational commitment to expedite the development and review of the product candidate, including involvement of senior managers. Moreover in 2017, the FDA established the Regenerative Medicine Advanced Therapy ("RMAT"), designation as part of its implementation of the 21st Century Cures Act. An investigational drug is eligible for RMAT

designation if: (1) it meets the definition of a regenerative medicine therapy, which is defined as a cell therapy, therapeutic tissue engineering product, human cell and tissue product, or any combination product using such therapies or products, with limited exceptions; (2) it is intended to treat, modify, reverse, or cure a serious disease or condition; and (3) preliminary clinical evidence indicates that the investigational drug has the potential to address unmet medical needs for such disease or condition. In a February 2019 final guidance, the FDA also stated that certain gene therapies that lead to a sustained effect on cells or tissues may meet the definition of a regenerative medicine therapy. RMAT designation provides potential benefits that include more frequent meetings with FDA to discuss the development plan for the product candidate, and eligibility for rolling review of BLAs and priority review.

Any product candidate submitted to the FDA for marketing, including those receiving Fast Track designation, Breakthrough Therapy designation or RMAT designation, may be eligible for other types of FDA programs intended to expedite development and review, such as priority review. A BLA is eligible for priority review if the product candidate is designed to treat a serious condition, and if approved would provide a significant improvement safety or effectiveness compared to marketed products. The FDA will attempt to direct additional resources to the evaluation of an application for designated for priority review in an effort to facilitate the review. Additionally, a product candidate 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 the FDA's determination that the product candidate has an effect on a surrogate endpoint that is reasonably likely to predict a clinical benefit, or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, such as an intermediate endpoint, that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments.

As a condition of approval, the FDA generally requires that a sponsor of a drug or biological product receiving accelerated approval perform adequate and well-controlled confirmatory clinical studies. Failure to conduct required confirmatory trials in a timely manner, or to verify a clinical benefit during such confirmatory trials, will allow the FDA to withdraw the approved biologic product from the market on an expedited basis. In addition, the FDA currently requires as a condition for accelerated approval pre-submission of promotional materials, which could adversely impact the timing of the commercial launch of the product.

Fast Track designation, Breakthrough Therapy designation, RMAT designation priority review and accelerated approval do not change the standards for approval but may expedite the development or approval process. Even if a product candidate qualifies for one or more of these programs, the FDA may later decide that the product no longer meets the conditions for qualification or decide that the time period for FDA review or approval will not be shortened.

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. Manufacturers of approved 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 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.

Manufacturers 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

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.

Biosimilars and Exclusivity

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 (the "BPCIA") 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.

Under the BPCIA, an application for a biosimilar product may not be submitted to the FDA until four years following the date that the reference product was first licensed by the FDA. In addition, the approval of a biosimilar product may not be made effective by the FDA until 12 years from the date on which the reference product was first licensed. During this 12-year period of exclusivity, another company may still market a competing version of the reference product if the FDA approves a full BLA

for the competing product containing the sponsor's own preclinical data and data from adequate and well-controlled clinical trials to demonstrate the safety, purity and potency of their product. The BPCIA also created certain exclusivity periods for biosimilars approved as interchangeable products. At this juncture, it is unclear whether products deemed "interchangeable" by the FDA will, in fact, be readily substituted by pharmacies, which are governed by state pharmacy law.

Healthcare 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 without limitation, state and federal anti-kickback, fraud and abuse, false claims, data privacy and security and transparency laws and regulations with respect to drug pricing and payments and other transfers of value made to healthcare professionals.

The U.S. federal 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. 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.

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 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 federal Civil Monetary Penalties Law prohibits, among other things, the offering or transferring of remuneration to a Medicare or Medicaid beneficiary that the person knows or should know is likely to influence the beneficiary's selection of a particular supplier of Medicare or Medicaid payable items or services.

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 physicians (defined to include doctors, dentists, optometrists, podiatrists, chiropractors, certain non-physician

practitioners (physician assistants, nurse practitioners, clinical nurse specialists, certified registered nurse anesthetists and anesthesiologist assistants, and certified nurse midwives) and teaching hospitals, including physician ownership and investment interests, and public reporting of such data. 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.

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 also 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.

Violations of any of these laws or other applicable governmental regulations may result in significant penalties, including civil monetary penalties, damages, exclusion of an entity or individual from participation in government healthcare programs, additional reporting obligations and oversight if the government requires a corporate integrity agreement or other agreement to resolve allegations of non-compliance with these laws, 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.

Data Privacy and Security Laws

Numerous state, federal and foreign laws, regulations and standards govern the collection, use, access to, confidentiality and security of health-related and other personal information, and could apply now or in the future to our operations or the operations of our partners. In the United States, numerous federal and state laws and regulations, including data breach notification laws, health information privacy and security laws and consumer protection laws and regulations govern the collection, use, disclosure, and protection of health-related and other personal information. In addition, certain foreign laws govern the privacy and security of personal data, including health-related data. Privacy and security laws, regulations, and other obligations are constantly evolving, may conflict with each other to complicate compliance efforts, and can result in investigations, proceedings, or actions that lead to significant civil and/or criminal penalties and restrictions on data processing.

Pricing, Coverage and Reimbursement

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. Moreover, these processes vary in length and may take several weeks, months, or longer to conclude depending on the individual payer. 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.

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 contracts and the option for payers to pay in installments over time, to assist with realizing the value and sharing the risk of a potential one-time treatment, such as for ZYNTEGLO. While we have signed outcomes-based contracts with several pharmacy benefit managers (PBMs) representing dozens of downstream insurance plans and are engaged in discussions with additional PBMs and national payers, there is no assurance that these payment models will be widely adopted. 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 (though based on the structure of our contracts, this risk is quantifiable and relatively predictable). These factors could affect our ability to successfully commercialize our products and adversely impact our business, financial condition, results of operations and prospects.

Government Price Reporting

Medicaid is a joint federal and state program administered by the states for low income and disabled beneficiaries. Medicare is a federal program that is administered by the federal government covering individuals aged 65 and over as well as those with certain disabilities. We are enrolled in the Medicaid Drug Rebate Program ("MDRP"). Under the MDRP, as a condition of federal funds being made available for our covered outpatient drugs under Medicaid and for certain drugs or biologicals under Medicare Part B, we pay a rebate to state Medicaid programs for each unit of our covered outpatient drugs dispensed to a Medicaid beneficiary and paid for by the state Medicaid program. Medicaid rebates are based on pricing data that we report on a monthly and quarterly basis to the U.S. Centers for Medicare & Medicaid Services ("CMS"), the federal agency that administers the MDRP and Medicare programs. For the MDRP, these data include the average manufacturer price ("AMP") for each drug and, in the case of innovator products, best price. In connection with Medicare Part B, a pharmaceutical manufacturer must provide CMS with average sales price ("ASP") information for certain drugs or biologicals on a quarterly basis. ASP is calculated based on a statutorily defined formula, as well as regulations and interpretations of the statute by CMS. This information is used to compute Medicare Part B payment rates, which consist of ASP plus a specified percentage. If we become aware that our MDRP price reporting submission for a prior period was incorrect or has changed as a result of recalculation of the pricing data, we must resubmit the revised data for up to three years after those data originally were due. If we fail to provide information timely or are found to have knowingly submitted false information to the government, we may be subject to civil monetary penalties and other sanctions, including termination from the MDRP, in which case payment would not be available for our covered outpatient drugs under Medicaid or, if applicable, Medicare Part B.

Federal law requires that a manufacturer that participates in the MDRP also participate in the Public Health Service's 340B drug pricing program (the "340B program") in order for federal funds to be available for the manufacturer's drugs under Medicaid and Medicare Part B. The 340B program is administered by the Health Resources and Services Administration ("HRSA") and requires us, as a participating manufacturer, to agree to charge statutorily defined covered entities no more than the 340B "ceiling price" for our covered outpatient drugs when used in an outpatient setting. These 340B covered entities include a variety of community health clinics and other entities that receive health services grants from the Public Health

Service, as well as hospitals that serve a disproportionate share of low income patients. A drug that is designated for a rare disease or condition by the Secretary of Health and Human Services is not subject to the 340B ceiling price requirement with regard to the following types of covered entities: rural referral centers, sole community hospitals, critical access hospitals, and free standing cancer hospitals. The 340B ceiling price is calculated using a statutory formula, which is based on the AMP and rebate amount for the covered outpatient drug as calculated under the MDRP. In general, products subject to Medicaid price reporting and rebate liability are also subject to the 340B ceiling price calculation and discount requirement. We must report 340B ceiling prices to HRSA on a quarterly basis, and HRSA publishes them to 340B covered entities. HRSA has finalized regulations regarding the calculation of the 340B ceiling price and the imposition of civil monetary penalties on manufacturers that knowingly and intentionally overcharge covered entities for 340B eligible drugs. HRSA has also finalized an administrative dispute resolution process through which 340B covered entities may pursue claims against participating manufacturers for overcharges, and through which manufacturers may pursue claims against 340B covered entities for engaging in unlawful diversion or duplicate discounting of 340B drugs. In addition, legislation may be introduced that, if passed, would further expand the 340B program, such as adding further covered entities or requiring participating manufacturers to agree to provide 340B discounted pricing on drugs used in an inpatient setting.

In order to be eligible to have drug products paid for with federal funds under Medicaid and Medicare Part B and purchased by certain federal agencies and grantees, we must also participate in the U.S. Department of Veterans Affairs ("VA") Federal Supply Schedule ("FSS") pricing program. Under the VA/FSS program, we must report the Non-Federal Average Manufacturer Price ("Non-FAMP") for our covered drugs to the VA and charge certain federal agencies no more than the Federal Ceiling Price, which is calculated based on Non-FAMP using a statutory formula. These four agencies are the VA, the U.S. Department of Defense, the U.S. Coast Guard, and the U.S. Public Health Service (including the Indian Health Service). We must also pay rebates on products purchased by military personnel and dependents through the TRICARE retail pharmacy program. If we fail to provide timely information or are found to have knowingly submitted false information, we may be subject to civil monetary penalties.

Individual states continue to consider and have enacted legislation to limit the growth of healthcare costs, including the cost of prescription drugs and combination products. A number of states have either implemented or are considering implementation of drug price transparency legislation. Requirements under such laws include advance notice of planned price increases, reporting price increase amounts and factors considered in taking such increases, wholesale acquisition cost information disclosure to prescribers, purchasers, and state agencies, and new product notice and reporting. Such legislation could limit the price or payment for certain drugs, and a number of states may impose civil monetary penalties or pursue other enforcement mechanisms against manufacturers who fail to comply with drug price transparency requirements.

Healthcare Reform and Potential Changes to Healthcare Laws

A primary trend in the U.S. healthcare industry and elsewhere is cost containment. Government authorities and other third party payers have attempted to control costs by limiting coverage and the level of reimbursement for particular medical products and services, implementing reductions in Medicare and other healthcare funding and applying new payment methodologies. For example, in March 2010, the Affordable Care Act ("ACA") was enacted, which, among other things, increased the minimum Medicaid rebates owed by most manufacturers under the Medicaid Drug Rebate Program; introduced 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; extended manufacturer Medicaid rebate obligations to utilization by individuals enrolled in Medicaid managed care plans; established a new Medicare Part D coverage gap discount program; subjected drug manufacturers to new annual fees based on pharmaceutical companies' share of sales to federal healthcare programs; imposed a new federal excise tax on the sale of certain medical devices; created a new Patient Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research; and established a Center for Medicare Innovation at the CMS to test innovative payment and service delivery models to lower Medicare and Medicaid spending.

Since its enactment, there have been judicial, executive and Congressional challenges to certain aspects of the ACA. On June 17, 2021, the U.S. Supreme Court dismissed the most recent judicial challenge to the ACA brought by several states without specifically ruling on the constitutionality of the ACA. In addition, other legislative changes have been proposed and adopted in the United States since the ACA was enacted. The Budget Control Act of 2011, among other things, led to reductions of Medicare payments to providers, which will remain in effect through 2031 unless additional Congressional action is taken. More recently, in March 2021, President Biden signed into law the American Rescue Plan Act of 2021, which eliminates the statutory cap on the Medicaid drug rebate, currently set at 100% of a drug's AMP, beginning January 1, 2024.

Most significantly, in August 2022, President Biden signed the Inflation Reduction Act of 2022 (IRA) into law. This statute marks the most significant action by Congress with respect to the pharmaceutical industry since adoption of the ACA in 2010.

Among other things, the IRA requires manufacturers of certain drugs to engage in price negotiations with Medicare (beginning in 2026), with prices that can be negotiated subject to a cap; imposes rebates under Medicare Part B and Medicare Part D to penalize price increases that outpace inflation (first due in 2023); and replaces the Part D coverage gap discount program with a new discounting program (beginning in 2025). The IRA permits the Secretary of the Department of Health and Human Services (HHS) to implement many of these provisions through guidance, as opposed to regulation, for the initial years. For that and other reasons, it is currently unclear how the IRA will be effectuated, and while the impact of the IRA on our business and the pharmaceutical industry cannot yet be fully determined, it is likely to be significant.

Additionally, 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 Congressional inquiries and proposed and enacted federal and state legislation designed to, among other things, bring more transparency to drug and biologic pricing, reduce the cost of prescription drugs and biologics under Medicare, review the relationship between pricing and manufacturer patient programs and reform government program reimbursement methodologies for drugs and biologics.

Individual states in the United States have also become increasingly active in passing legislation and implementing regulations designed to control pharmaceutical and biological product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access, marketing cost disclosure and other transparency measures, and, in some cases, measures designed to encourage importation from other countries and bulk purchasing.

We cannot predict the likelihood, nature or extent of government regulation that may arise from future legislation or administrative or executive action, either in the United States or abroad. We expect that additional state and federal healthcare reform measures will be adopted in the future, any of which could limit the amounts that governments and third-party payers will pay for healthcare products and services.

COVID-19

As a result of the COVID-19 pandemic, we have adopted a hybrid work environment for our office staff. Our laboratory staff have some flexibility to work remotely; however, their core job functions require physical presence at our laboratory location to perform the duties of their roles. Further, we continue to evaluate any impact of COVID-19 on our business, including but not limited to our QTC network, our supply chain, and any potential future clinical trials. 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 2022 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 and any potential resurgence; 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, 2023, we had 323 full-time employees, 47 of whom have Ph.D., M.D. or Pharm.D. degrees. Of these full-time employees, 199 employees are engaged in research and development activities and 124 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 are an organization committed to creating an inclusive and engaged culture that meets the needs of the whole employee, through competitive total rewards and retention efforts and commitment to Diversity, Equity, Inclusion and Belonging.

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. Our 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 and benefits 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. Through our pay-for-performance culture, 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 are building 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, to improve performance and retention, increase our organizational learning and support the promotion of our current employees.

Diversity

We believe Diversity, Equity, Inclusion and Belonging ("DEIB") are the cornerstone to an engaged, successful, and innovative organization. We are committed to taking action to help address racial injustice and inequality. We established our DEIB steering committee that includes employees at all levels to provide oversight and guidance to establishing meaningful measures and actions to continue to increase DEIB at all levels and experiences. 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 455 Grand Union Boulevard, Somerville, Massachusetts and our telephone number at that address is (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 $266.6 million for the year ended December 31, 2022. As of December 31, 2022, we had an accumulated deficit of $3.99 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 directionally decrease as we focus on bringing our therapies to patients in the commercial setting. To date, we have financed our operations primarily through the sale of equity securities and priority review vouchers, and, to a lesser extent, through collaboration agreements and grants from governmental agencies and charitable foundations. We did not generate material revenues from the sale of ZYNTEGLO in the European Union and only recently launched ZYNTEGLO and SKYSONA in the US. Our future revenues will depend upon the size of any markets in which our products and product candidates 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 to invest in lovo-cel in anticipation of the submission of our BLA and subsequent FDA review;
- grow our capabilities to support our commercialization efforts for ZYNTEGLO and SKYSONA, including continuing to establish a sales, marketing and distribution infrastructure in the United States;
- obtain, build and expand manufacturing capacity, including capacity at third-party manufacturers;
- attract and retain skilled personnel;
- 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; 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 commercial programs, product development efforts or other operations.

Developing and commercializing gene therapy products is expensive, and we do not expect to generate meaningful product revenues in the foreseeable future. Based on our current business plan as of the date of our consolidated financial statements appearing elsewhere in this Annual Report on Form 10-K, there is substantial doubt regarding our ability to continue as a going concern. See Part II, Item 7. "Management's Discussion and Analysis of Financial Condition and Results of Operations—Liquidity and Capital Resources" of this Annual Report on Form 10-K for a discussion of our expected cash runway both including our restricted cash of $45.4 million and excluding this restricted cash. Our restricted cash is currently unavailable for use, and there is no assurance as to when or if our restricted cash will become available for use. Furthermore, pursuant to the terms of certain agreements we have in place, we could be required to further increase our restricted cash due, in part, to recent concerns related to the stability of the banking sector, which would consequently reduce the amount of cash available to fund our operations. Accordingly, we will need to raise additional funding in order to execute on our current business plans and strategy, including prior to becoming profitable.

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 products. 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.

Moreover, as a result of recent volatile market conditions, the cost and availability of capital has been and may continue to be adversely affected. Concern about the stability of the banking sector has generally led many lenders and institutional investors to reduce, and in some cases, cease to provide credit to businesses and consumers. Continued turbulence in the U.S. market and economy may adversely affect our liquidity and financial condition, including our ability to access the capital markets to meet liquidity needs. In addition, we maintain the majority of our cash and cash equivalents in accounts with major financial institutions, and our deposits at these institutions exceed insured limits. Market conditions can impact the viability of these institutions. In the event of failure of any of the financial institutions where we maintain our cash and cash equivalents, there can be no assurance that we would be able to access uninsured funds in a timely manner or at all. Any inability to access or delay in accessing these funds could adversely affect our business and financial position.

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.

Insertional oncogenesis is a significant risk of gene therapies using viral vectors that can integrate into the genome. Any such adverse events may require us to halt or delay further clinical development of our product candidates or to suspend or cease commercialization following marketing approval, and the commercial potential of our products and product candidates may be materially and negatively impacted.

Adverse events or other undesirable side effects caused by our product or product candidates could cause us or regulatory authorities to interrupt, delay or halt clinical trials and could result in a more restrictive label or the delay, denial or withdrawal of regulatory approval by the FDA or other comparable foreign regulatory authorities. 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 could cause cancer in the patient, known as insertional oncogenesis. For instance, three patients with CALD treated with eli-cel (now SKYSONA) in our clinical studies have been diagnosed with myelodysplastic syndrome ("MDS") likely mediated by Lenti-D LVV insertion. We cannot make assurances that additional patients treated with SKYSONA, ZYNTEGLO or lovo-cel in the clinical or commercial setting will not be diagnosed with MDS, leukemia or lymphoma.

Moreover, in December 2021, the FDA placed the lovo-cel clinical development program under a partial clinical hold for patients under the age of 18. The hold related to a case persistent anemia in an adolescent patient with two α-globin gene deletions (−α3.7/−α3.7), also known as alpha-thalassemia trait, who was treated with lovo-cel. In December 2022, the FDA lifted its partial clinical hold for patients under the age of 18 in studies evaluating lovo-cel for SCD. Notwithstanding the lifting of this partial clinical hold, additional adverse events or new data or analyses regarding previously reported events may indicate significant safety issues, and the FDA could potentially impose or reimpose a clinical hold in the future on studies evaluating lovo-cel. Moreover, laboratory results following gene therapy can be difficult to interpret resulting in different or changing diagnoses by treating physicians. For instance, on January 31, 2023, we received a physician diagnosis of MDS in a patient treated with lovo-cel, in response to lab results obtained through routine monitoring of the same adolescent patient with two α-globin gene deletions subject to the partial clinical hold noted above. Consistent with established safety protocols, the information was reviewed by an independent Data Monitoring Committee which concluded that available evidence did not support a diagnosis of MDS and additional data would be needed to confirm such diagnosis, and that lovo-cel clinical studies should continue. Test results received since the investigator's initial report (including integration site analysis) demonstrated no evidence of insertional oncogenesis and the patient continues to be clinically stable and is not undergoing treatment for an MDS diagnosis. Study investigators and the FDA have been informed and we will continue to monitor additional analyses as further test results are received. We maintain dialogue with the FDA and, from time to time, as required or requested by the FDA, update the FDA on additional adverse events or new data or analyses regarding previously reported events.

Furthermore, treatment with our products and product candidates involve chemotherapy or myeloablative treatments which can cause side effects or adverse events that may impact the perception of the potential benefits of our products and product candidates. For instance, MDS leading to acute myeloid leukemia is a known risk of certain myeloablative regimens. Accordingly, it is possible that the events of MDS and acute myeloid leukemia previously reported in our HGB-206 clinical study were caused by underlying SCD, transplant procedure, and stress on the bone marrow following drug product infusion in connection with the lovo-cel treatment. Additionally, the procedures associated with the administration or collection of cells for ZYNTEGLO, SKYSONA, or lovo-cel, 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.

Moreover, patients treated with our therapies, including lovo-cel, have exhibited persistent oligoclonality, which we define as two consecutive instances of (i) any LVV insertion site observed at >=10% relative frequency, or (ii) two or more insertion sites observed at >= to 5% relative frequency, as measured by integration site analysis. Based on our clinical protocols, we increase monitoring of patients who exhibit persistent oligoclonality. It is not clear at this time whether persistent oligoclonality represents an increased risk of developing MDS, leukemia, or lymphoma in the future, but it is a criterion used by the FDA to evaluate the safety of gene therapies over time.

Additionally, there is the potential risk of other 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 LVVs possess characteristics that may pose high risks of delayed adverse events.

If any such adverse events occur, including insertional oncogenesis, 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 our approved products in the manner we expect, or at all. 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 of our approved products. If any of these were to occur, the commercial potential of our programs may be materially and negatively impacted.

Even if a product candidate such as lovo-cel is ultimately approved and, although ZYNTEGLO and SKYSONA have been approved by the FDA, serious safety events may result in the product being removed from the market or its market opportunity being significantly reduced. For instance, it is possible that as we commercialize our products or test our product candidates in larger, longer and more extensive clinical trials, or as use of these products and product candidates (if approved) becomes more widespread, illnesses, injuries, discomforts and other adverse events that were observed in previous trials, as well as conditions that did not occur or went undetected in previous trials, will be reported by patients. Many times, side effects (that may or may not be related to our products or product candidates) are only detectable after investigational products are tested in large-scale clinical trials or, in some cases, after they are made available to patients on a commercial scale following approval. Other patients receiving our products and product candidates may develop cancers, including leukemia, lymphoma, or MDS in the future, which may negatively impact the commercial prospects of our products and product candidates. We or others may later identify undesirable side effects or adverse events caused by such products, and a number of potentially significant negative consequences could result, including but not limited to:

- regulatory authorities may suspend, limit or withdraw approvals of such product, or seek an injunction against its manufacture or distribution;
- regulatory authorities may require additional warnings on the label, including “boxed” warnings, or issue safety alerts, "Dear Healthcare Provider" or "Dear Doctor" letters, press releases or other communications containing warnings or other safety information about the product;
- we may be required to change the way the product is administered or conduct additional clinical trials or post-marketing studies;
- we may be required to create a risk evaluation and mitigation strategy, or REMS which could include elements to assure safe use, or a medication guide outlining the risks of such side effects for distribution to patients;
- we may be subject to fines, injunctions or the imposition of criminal penalties;
- we could be sued and held liable for harm caused to patients; and
- our reputation may suffer.

Any of these events could impair our ability to develop or commercialize our products and product candidates, and their commercial potential may be materially and negatively impacted.

We rely on a complex supply chain for SKYSONA, ZYNTEGLO, and lovo-cel. The manufacture, testing 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, or timing needed to support our clinical programs and commercialization.

We rely on third parties to manufacture the LVV and the drug product for ZYNTEGLO and SKYSONA, our two commercial products, and for our clinical trials, including the ongoing phase 3 clinical study evaluating the efficacy and safety of lovo-cel in the treatment of patients with SCD. Although we continue to advance plans to make additional investment in manufacturing to expand capacity, we, to date, 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 first year of anticipated sales. 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, we may be unable to execute on our 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, scarcity of qualified personnel, shortages of any production raw materials 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 requires a lengthy technology transfer process and regulatory review and approval, which often takes significant time 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 SKYSONA, ZYNTEGLO, 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 products and product candidates may be materially harmed, result in delays in our plans or increased capital expenditures.

In addition, we currently have only one drug product supplier for ZYNTEGLO and SKYSONA and one drug product supplier anticipated for commercial distribution for lovo-cel and, accordingly, 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 SKYSONA, ZYNTEGLO, 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 have initially established transduction facilities in areas which we believe can adequately service patients from regions where we are commercializing SKYSONA, ZYNTEGLO, and where we anticipate commercializing lovo-cel, if and when approved. However, we cannot ensure that such facilities will enable us to produce and deliver drug product in a timely manner; any issues with production and delivery of drug product could have a material adverse effect on our successful commercialization of our product and product candidates. Moreover, establishing additional facilities in appropriate regions 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.

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, in our lovo-cel program, 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 drug product manufactured a commercial, rather than a clinical, manufacturing facility. Such transitions require regulatory review and approval including reaching agreement with the FDA on an acceptable comparability data package. Based on feedback recently received from the FDA and related questions regarding the sufficiency of such comparability data, we have submitted a comprehensive data package to the FDA in effort to demonstrate comparability between the two processes, which the FDA is reviewing prior to the submission of the BLA. The FDA may require us to conduct additional clinical studies, collect additional data, develop additional assays, or modify product specifications relating to such comparability analysis prior to the FDA accepting BLA for filing or potentially approving the application which may delay or prevent our plans for commercialization. Any such requests or delays may have a material adverse effect on our forecasted timelines for approval of lovo-cel and may require substantial additional funds.

We are evaluating plans to transition our drug product manufacturing process for lovo-cel, if approval is obtained, to utilize cryopreserved apheresis patient starting material in order to expand the potential reach of our therapy and to provide manufacturing flexibility. Such changes to our drug manufacturing process will similarly require comparability and process validation data to support such transition and, therefore, may not be approved in a timely manner, if at all.

We cannot predict when or if we will obtain marketing approval to commercialize lovo-cel, and the marketing approval of our product candidates may ultimately be for more narrow indications than we expect. If lovo-cel or other 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.

The 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 are limited data concerning long-term safety and efficacy following treatment with our product candidates. These data, or other positive data, may not continue to 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 marketed products or 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, such as using lovo-cel for treatment for children under the age of 18, our business may suffer.

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, comparability and/or quality perspective, to support the approval of the BLA. Based on our discussions with the FDA, we are seeking 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, the FDA may require that we conduct additional or larger pivotal trials before we can obtain approval of a BLA for lovo-cel, if ever. Please also see risk factor above —"Changes in our manufacturing processes may cause delays in our clinical development and commercialization plans".

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

Risks related to commercialization

We have limited experience as a commercial company and the marketing and sale of ZYNTEGLO, SKYSONA and of 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 as we have only recently launched ZYNTEGLO and SKYSONA in the US, our first two commercial products marketed in the US. 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 in the U.S. To execute our business plan, we will need to successfully:

- gain regulatory approval to commercialize lovo-cel in the United States;
- sustain adequate pricing and reimbursement for ZYNTEGLO and SKYSONA, across all U.S. payer segments, and obtain pricing and reimbursement for lovo-cel across payers in the US, when and if approved;
- 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 ZYNTEGLO, SKYSONA, and lovo-cel, when and if approved;
- manage our spending as we seek marketing approvals, and engage in commercialization efforts; and
- initiate, develop and maintain successful strategic alliances.

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

The commercial success of ZYNTEGLO, SKYSONA and of lovo-cel following marketing approval (if and when obtained), will depend upon the degree of market acceptance by physicians, patients, payers and other stakeholders.

The commercial success of ZYNTEGLO, SKYSONA, and of 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 ZYNTEGLO, SKYSONA, and lovo-cel, in particular, as medically useful, cost-effective, and safe. ZYNTEGLO, SKYSONA, and lovo-cel, which we may bring to the market if approved, may not gain market acceptance by physicians, patients, payers and other stakeholders. 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 ZYNTEGLO, SKYSONA, and of lovo-cel, if and when approved, will depend on a number of factors, including:

- the potential and perceived 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; for instance, the SKYSONA product label includes a boxed warning for the risk of hematologic malignancy;
- the prevalence and severity of any side effects resulting from the chemotherapy and myeloablative treatments associated with the procedure by which our products are administered, including the possible prejudicial effects that chemotherapy can have on fertility;
- relative convenience and ease of administration;
- given the complexity of manufacturing product, the perception that issues may arise in the supply of product which could delay treatment;
- 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 products;
- publicity concerning our products, or competing products and treatments;

- sufficient insurance coverage or reimbursement;

- the possible occurrence of adverse clinical findings or decreased effectiveness of a product or product candidate over time identified during continued monitoring and evaluation of patients; and

- the mix of private and governmental payers coverage, particularly if the percentage of patients receiving reimbursement from state Medicaid is high since such process can be slower to reimburse.

Even if a product displays a favorable efficacy and safety profile in clinical studies, market acceptance of the product will not be known until some period after it is launched. Our efforts to educate the medical community and payers on the benefits of our products may require significant resources and may never be successful. For instance, following marketing approval of ZYNTEGLO 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 products and 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 ZYNTEGLO, SKYSONA, or lovo-cel, to be unsuccessful or less successful than anticipated.

Our ability to successfully commercialize our products or product candidates, if approved, including our ability to achieve their widespread market acceptance, is critical to the success of our business.

We dedicate a substantial amount of our resources to the commercialization of ZYNTEGLO and SKYSONA. Our ability to generate revenue in the near-term will depend almost entirely on our ability to execute on our commercialization plans and the level of market adoption for, and the continued use of, ZYNTEGLO and SKYSONA and, if approved, lovo-cel, by physicians, hospitals, patients, and/or healthcare payers, including government payers, consumers, managed care organizations, and retail and specialty pharmacies. If we are not successful in commercializing our products, including achieving and maintaining an adequate level of market adoption, our profitability and our future business prospects will be adversely impacted.

Future expansion of commercial opportunity is dependent upon lifecycle management and access to complementary therapies. Our efforts to reduce cost of goods through efficiencies of scale or new technologies, such as improved mobilization, may not be successful and/or we may not have access to the complementary technologies we need to succeed, which could impact the level of future profitability. For instance, improvements in conditioning regimens (which could increase the patient population who has access to our products), may not be successfully developed and approved, and if they are, we may not have access to those improvements which, in most instances, are technology owned by third-parties. Additionally, the future opportunity to market our therapies in geographies outside the US through partnership or our internal efforts may not materialize.

If the market opportunities for our product candidates 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 product candidates, 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 product candidates may be limited or may not be amenable to treatment with our product candidates. For instance, in our lovo-cel and SKYSONA 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 products and product candidates 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 product candidates and our ability to achieve and maintain profitability and, as a consequence, our business may suffer.

We have limited sales and distribution experience and limited capabilities for marketing and market access. Although we have invested and expect to continue to invest significant financial and management resources, if we are unable to establish and maintain these commercial capabilities and infrastructure, or to enter into agreements with third parties to market and sell our 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 ZYNTEGLO, SKYSONA, 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 further 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 ZYNTEGLO, SKYSONA, 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 will need to rely heavily on third parties for commercializing any products in 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.

We may encounter challenges with engaging or coordinating with qualified treatment centers needed for the ongoing commercialization of ZYNTEGLO and SKYSONA and the potential commercialization of lovo-cel.

Our commercial strategy is to engage apheresis and transplant centers as qualified treatment centers for the collection of patient hematopoietic stem cells ("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. For instance, we have currently signed agreements with twelve such treatment centers and our corporate strategy is to contract with at least 40 such centers by the end of 2023. Any delay or failure to meet these goals may limit patient access to our therapies and, accordingly, have a material adverse effect on our commercial forecasts and business.

Furthermore, 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. Additionally, delays with infusion at the qualified treatment centers, due to, for instance, the patient's schedule or health condition or such center’s capacity, could result in a patient becoming medically ineligible for our treatment, the drug product becoming unusable and loss of medical coverage, which would have a material adverse effect on commercial sales.

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.

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 unique and additional challenges in obtaining adequate pricing and reimbursement for our products. 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 healthcare, and especially expensive medicines, such as gene therapy products. Sales of our products will depend substantially on the extent to which the costs of our 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 payers will be willing to reimburse providers at the company-established list price or reimbursement levels that payers will be willing to pay will be acceptable to us. Moreover, given that our therapies are likely to be administered in the inpatient care setting, it will be important that our products are reimbursed as a separate item from the underlying services incurred during the patient's hospitalization; however, such "separate reimbursement" is not guaranteed by all payers. Accordingly, the estimation of potential revenues will be complex and it is difficult to predict what payers 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.

In the U.S., regional Medicare Administrative Contractors ("MACs") are responsible for making a determination with regard to whether a new therapy meets the Centers for Medicare and Medicaid Services' ("CMS") standard of "reasonable and necessary" such that it is covered and reimbursed by Medicare and Medicaid. Reimbursement methodologies in Medicare and Medicaid vary based on the type of therapeutic agent and setting of care, and in Medicaid, the reimbursement methodologies also vary by state. We anticipate that coverage determinations for our marketed therapies and for lovo-cel, if granted FDA approval in the future, will be made by MAC. While there is uncertainty with this process both in terms of the timing of the decision making process and the decision to cover itself, our exposure to the Medicare program is limited given that only a small percentage of our patient population may be Medicare eligible (i.e., a small percentage of patients may be dually eligible for Medicare and Medicaid, in which case Medicare services as the primary payer and Medicaid as the secondary payer for any service not otherwise covered by Medicare).

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 ZYNTEGLO, SKYSONA, or for lovo-cel following marketing approval, if and when obtained. We expect to experience pricing pressures in connection with the sale of our products due to greater scrutiny on list prices and total prescription drug spending across all payer channels as well additional legislative changes. Net prices for drugs may be reduced by mandatory discounts or rebates required by government or private payers. As a result, increasingly high barriers are being erected to the entry of new products often in the form of limiting the patient population for whom a new therapy is deemed "medically necessary." Even if coverage is provided, the amount payers are willing to reimburse may not be a sufficient return on our investment.

Furthermore, because a provider is responsible for costs associated not just with obtaining our medicines but also with the underlying hospital stay in which the administration of our therapies occur, the pricing and reimbursement dynamics that impact patient access are not entirely within our control as providers and payers negotiate separately for the cost of the associated items and services, decisions in which we cannot and do not play a role. These services include the collection of HSCs from the patient, followed by chemotherapy and myeloablative treatments, and inpatient hospital stay following drug product infusion. If we are unable to obtain adequate levels of reimbursement, our ability to successfully market and sell our products will be adversely affected.

We have entered into and continue to engage with payers across all channels around outcomes-based contracts for ZYNTEGLO. We also offer the option to pay for the therapy in installments over time. In the event that a payer opts for the outcomes-based contract, we will need to reserve a certain portion of revenue from each sale to account for the potential that a rebate will be owed if the patient fails to meet the pre-established outcome metric over a one or two year evaluation period following drug product administration. These contracts also may result in the timing of revenue recognition not corresponding to the timing of cash collection. Despite our efforts to engage with CMS and work with experts to ensure all of our payer contracting efforts comply with relevant federal and state regulations, including government price reporting obligations, given the complexity of these arrangements, we may not be able to satisfy the compliance requirements, which may result in significant fines and liability.

Collectively, these factors could affect our ability to successfully commercialize our 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

Clinical drug development involves a lengthy and expensive process, with an uncertain outcome. We may incur additional costs or experience delays in completing, or ultimately be unable to complete, the development and commercialization of lovo-cel or other product candidates.

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 of lovo-cel or any other product candidate include:

- inability to generate sufficient preclinical, toxicology, or other in vivo or in vitro data to support the initiation or continuation of clinical trials;
- delays or failure in obtaining regulatory authorization to commence a trial;
- delays in reaching agreement on acceptable terms with prospective contract research organizations ("CROs"), and clinical trial sites, the terms of which can be subject to extensive negotiation and may vary significantly among different CROs and clinical trial sites;
- delays in identifying, recruiting and training suitable clinical investigators;
- delays in obtaining required IRB or ethics committee approvals at each clinical trial site;
- delays in manufacturing, testing, releasing, validating or importing/exporting sufficient stable quantities of our product candidates for use in clinical trials or the inability to do any of the foregoing;
- insufficient or inadequate supply or quality of product candidates or other materials necessary for use in clinical trials, or delays in sufficiently developing, characterizing or controlling a manufacturing process suitable for clinical trials;
- imposition of a clinical hold by regulatory agencies, including after review of an IND or amendment or equivalent foreign application or amendment, as a result of a new safety finding that presents unreasonable risk to clinical trial participants or after an inspection of our clinical study operations or study sites or due to unforeseen safety issues;
- failure by our CROs, other third parties or us to adhere to clinical trial protocols or failure to perform in accordance with the FDA's or any other regulatory authority's good clinical practice requirements ("GCPs") or applicable regulatory guidelines in other countries;
- occurrence of adverse events associated with the product candidate that are viewed to outweigh its potential benefits, or occurrence of adverse events in trial of the same class of agents conducted by other companies, particularly due to the fact that we are required to follow patients in our clinical studies for an extended period of time (up to 15 years);
- changes to the clinical trial protocols;
- clinical sites deviating from trial protocol or dropping out of a trial;
- changes in the standard of care on which a clinical development plan was based, which may require new or additional trials;
- selection of clinical endpoints that require prolonged periods of observation or analyses of resulting data;

- the cost of clinical trials of our product candidates being greater than we anticipate;

- clinical trials of our product candidates producing negative or inconclusive results, which may result in our deciding, or regulators requiring us, to conduct additional clinical trials or abandon development of such product candidates;

- transfer of manufacturing processes to larger-scale facilities operated by a contract manufacturing organization ("CMO") and delays or failure by our CMOs or us to make any necessary changes to such manufacturing process (please see "Risk Factors—Changes in our manufacturing processes may cause delays in our clinical development and commercialization plans" of this Annual Report on Form 10-K for further information); or

- changes in regulatory requirements and guidance that require amending or submitting new clinical protocols.

Clinical trials must be conducted in accordance with the FDA and other applicable regulatory authorities' legal requirements, regulations or guidelines, and are subject to oversight by these governmental agencies and ethics committees or IRBs at the medical institutions where the clinical trials are conducted.

Further, conducting clinical trials in foreign countries, as we may do for our product candidates, presents additional risks that may delay completion of our clinical trials. These risks include the failure of enrolled patients in foreign countries to adhere to clinical protocol as a result of differences in healthcare services or cultural customs, managing additional administrative burdens associated with foreign regulatory schemes, as well as political and economic risks relevant to such foreign countries.

Moreover, principal investigators for our clinical trials may serve as scientific advisors or consultants to us from time to time and receive compensation in connection with such services. Under certain circumstances, we may be required to report some of these relationships to the FDA or comparable foreign regulatory authorities. The FDA or comparable foreign regulatory authority may conclude that a financial relationship between us and a principal investigator has created a conflict of interest or otherwise affected interpretation of the study. The FDA or comparable foreign regulatory authority may therefore question the integrity of the data generated at the applicable clinical trial site and the utility of the clinical trial itself may be jeopardized. This could result in a delay in approval, or rejection, of our marketing applications by the FDA or comparable foreign regulatory authority, as the case may be, and may ultimately lead to the denial of marketing approval of one or more of our product candidates.

Delays in the completion of any clinical trial of our product candidates will increase our costs, slow down our product candidate development and approval process and delay or potentially jeopardize our ability to commence product sales and generate product revenue. In addition, many of the factors that cause, or lead to, a delay in the commencement or completion of clinical trials may also ultimately lead to the denial of regulatory approval of our product candidates. Any delays to our clinical trials that occur as a result could shorten any period during which we may have the exclusive right to commercialize our product candidates and our competitors may be able to bring products to market before we do, and the commercial viability of our product candidates could be significantly reduced. Any of these occurrences may harm our business, financial condition and prospects significantly.

We depend on enrollment of patients in our clinical trials for our product candidates. If we experience delays or difficulties enrolling in our clinical trials, our research and development efforts and business, financial condition, and results of operations could be materially adversely affected.

Successful and timely completion of clinical trials, including additional trials which the FDA may require we complete prior to or as part of approval of our product and product candidates, will require that we enroll a sufficient number of patient candidates. These trials and other trials we conduct may be subject to delays for a variety of reasons, including as a result of patient enrollment taking longer than anticipated, patient withdrawal or adverse events. These types of developments could cause us to delay the trial or halt further development.

Our clinical trials will compete with other clinical trials that are in the same therapeutic areas as our product candidates, and this competition reduces the number and types of patients available to us, as some patients who might have opted to enroll in our trials may instead opt to enroll in a trial being conducted by one of our competitors. Because the number of qualified clinical investigators and clinical trial sites is limited, we expect to conduct some of our clinical trials at the same clinical trial sites that some of our competitors use, which will reduce the number of patients who are available for our clinical trials at such clinical trial sites. In addition, there may be limited patient pools from which to draw for clinical studies. In addition to the rarity of some diseases, the eligibility criteria of our clinical studies will further limit the pool of available study participants as

we will require that patients have specific characteristics that we can measure or to assure their disease is either severe enough or not too advanced to include them in a study.

Patient enrollment depends on many factors, including:

- the size and nature of the patient population;
- the severity of the disease under investigation;
- eligibility criteria for the trial;
- the proximity of patients to clinical sites;
- the design of the clinical protocol;
- the ability to obtain and maintain patient consents;
- the ability to recruit clinical trial investigators with the appropriate competencies and experience;
- the risk that patients enrolled in clinical trials will drop out of the trials before the administration of our product candidates or trial completion;
- the availability of competing clinical trials;
- the availability of new drugs approved for the indication the clinical trial is investigating; and
- clinicians' and patients' perceptions as to the potential advantages of the drug being studied in relation to other available therapies.

These factors may make it difficult for us to enroll enough patients to complete our clinical trials in a timely and cost-effective manner. Delays in the completion of any clinical trial of our product candidates will increase our costs, slow down our product candidate development and approval process and delay or potentially jeopardize our ability to commence product sales and generate revenue. In addition, some of the factors that cause, or lead to, a delay in the commencement or completion of clinical trials may also ultimately lead to the denial of regulatory approval of our product candidates.

Data from our clinical trials that we announce or publish from time to time may change as more patient data become available either through long-term patient follow-up and/or as such data is audited and verified which could result in material changes to clinical and safety profiles for our products.

From time to time, we may disclose data from our preclinical studies and clinical trials. Such data from clinical trials that we may complete are subject to the risk that one or more of the clinical outcomes may materially change as patient enrollment continues and more patient data become available or as patients from our clinical trials continue other treatments for their disease. In addition, the clinical trials evaluating our products and product candidates generally require that we continue to monitor and evaluate safety and efficacy in patients over an extended period of time following treatment, including for up to fifteen years for some studies, which may result in the safety or efficacy profile to change over time. Changes in the efficacy and safety profile of our product or product candidates over time could significantly harm our business prospects including resulting in volatility in the price of our common stock.

Additionally, from time to time, we may publicly disclose preliminary or top-line data from our preclinical studies and clinical trials, which are based on a preliminary analysis of then-available data, and the results and related findings and conclusions are subject to change following a more comprehensive review of the data related to the particular study or trial. We also make assumptions, estimations, calculations and conclusions as part of our analyses of data, and we may not have received or had the opportunity to fully and carefully evaluate all data. As a result, the top-line or preliminary results that we report may differ from future results of the same studies, or different conclusions or considerations may qualify such results, once additional data have been received and fully evaluated. Top-line data also remain subject to audit and verification procedures

that may result in the final data being materially different from the preliminary data we previously published. As a result, top-line data should be viewed with caution until the final data are available.

Further, others, including regulatory agencies, may not accept or agree with our assumptions, estimates, calculations, conclusions or analyses or may interpret or weigh the importance of data differently, which could impact the value of the particular program, the approvability or commercialization of the particular product candidate or product and our company in general. In addition, the information we choose to publicly disclose regarding a particular study or clinical trial is based on what is typically extensive information, and you or others may not agree with what we determine is material or otherwise appropriate information to include in our disclosure. If others, including regulatory authorities, disagree with the conclusions reached with respect to such information and assessments, our ability to obtain approval for, and commercialize, our product candidates may be harmed, which could harm our business, operating results, prospects or financial condition.

Even if we have received or will receive accelerated approval from the FDA, if our confirmatory trials do not verify clinical benefit, or if we do not comply with rigorous post-marketing requirements, the FDA may seek to withdraw any accelerated approval we have obtained.

In September 2022, SKYSONA received accelerated approval from the FDA, and we may in the future receive accelerated approval for our one or more of our product candidates. Under the accelerated approval program, the FDA may grant accelerated approval to a product candidate designed to treat a serious or life-threatening condition that provides meaningful therapeutic benefit over available therapies upon a determination that the product candidate has an effect on a surrogate endpoint or intermediate clinical endpoint that is reasonably likely to predict clinical benefit. The FDA considers a clinical benefit to be a positive therapeutic effect that is clinically meaningful in the context of a given disease, such as irreversible morbidity or mortality. For the purposes of accelerated approval, a surrogate endpoint is a marker, such as a laboratory measurement, radiographic image, physical sign, or other measure that is thought to predict clinical benefit, but is not itself a measure of clinical benefit. An intermediate clinical endpoint is a clinical endpoint that can be measured earlier than an effect on irreversible morbidity or mortality that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit.

The accelerated approval pathway may be used in cases in which the advantage of a new drug over available therapy may not be a direct therapeutic advantage, but is a clinically important improvement from a patient and public health perspective. If granted, accelerated approval is usually contingent on the sponsor's agreement to conduct, in a diligent manner, one or more additional confirmatory studies to verify and describe the drug's clinical benefit. If such post-approval studies fail to confirm the drug's clinical benefit or are not completed in a timely manner, the FDA may withdraw its approval of the drug on an expedited basis. For example, we agreed to provide confirmatory long-term clinical data to the FDA as a condition of the SKYSONA accelerated approval, and continued approval for the approved indication will be contingent upon verification and description of clinical benefit in a confirmatory trial. Moreover, certain payers, including state medicaid agencies, may scrutinize therapies that reach the market through accelerated approval, which can lead to delays in broader access after approval and require additional company resources to address any concerns.

In addition, in December 2022, President Biden signed an omnibus appropriations bill to fund the U.S. government through fiscal year 2023. Included in the omnibus bill is the Food and Drug Omnibus Reform Act of 2022, which among other things, introduced reforms intended to expand the FDA's ability to regulate products receiving accelerated approval, including by increasing the FDA's oversight over the conduct of confirmatory trials; however, the ultimate impact of these reforms remains unclear.

A Regenerative Medicine Advanced Therapy designation by the FDA, even if granted for any of our product candidates, may not lead to a faster development or regulatory review or approval process and does not increase the likelihood that our product candidates will receive marketing approval.

We have obtained Regenerative Medicine Advanced Therapy ("RMAT") designation for lovo-cel for the treatment of SCD, and we may seek additional RMAT designations for our product candidates. A biological product candidate is eligible for RMAT designation if: (1) it meets the definition of a regenerative medicine therapy, which the FDA defines as a cell therapy, therapeutic tissue engineering product, human cell and tissue product, or any combination product using such therapies or products, with limited exceptions; (2) the candidate is intended to treat, modify, reverse, or cure a serious disease or condition; and (3) preliminary clinical evidence indicates that the candidate has the potential to address unmet medical needs for such disease or condition. RMAT designation provides potential benefits that include more frequent meetings with FDA to discuss the development plan for the product candidate, and eligibility for rolling review o and priority review of BLAs. Product candidates granted RMAT designation may also be eligible for accelerated approval on the basis of a surrogate or intermediate endpoint reasonably likely to predict long-term clinical benefit, or through reliance upon data obtained from a meaningful

number of sites, including through expansion to a sufficient number of sites, as appropriate. RMAT-designated product candidates that receive accelerated approval may, as appropriate, be able to fulfill their post-approval requirements through the submission of clinical evidence, clinical studies, patient registries, or other sources of real-world evidence (such as electronic health records); through the collection of larger confirmatory data sets; or via post-approval monitoring of all patients treated with such therapy prior to approval of the therapy.

RMAT designation is within the sole discretion of the FDA. Accordingly, even if we believe one of our product candidates meets the criteria for RMAT designation, the FDA may disagree and instead determine not to make such designation. RMAT designation does not change the standards for product approval, and there is no assurance that such designation or eligibility for such designation will result in expedited review or approval or that the approved indication will not be narrower than the indication covered by the RMAT designation. Additionally, RMAT designation can be revoked if the product candidate fails to meet the qualifications as clinical data continue to emerge.

We have obtained and may seek orphan drug designation for our product candidates, but we may be unable to obtain such designation or to obtain or maintain the benefits associated with orphan drug designation, including market exclusivity, which may cause our product revenue, if any, to be reduced.

We have obtained orphan drug designations for certain diseases or conditions for beti-cel, lovo-cel and eli-cel. Under the Orphan Drug Act, the FDA may designate a biological product as an orphan drug if it is intended to treat a rare disease or condition, defined as a patient population of fewer than 200,000 in the United States, or a patient population greater than 200,000 in the United States where there is no reasonable expectation that the cost of developing the drug will be recovered from sales in the United States. Orphan drug designation must be requested before submitting a BLA. In the United States, orphan drug designation entitles a party to financial incentives such as opportunities for grant funding towards clinical trial costs, tax advantages, waivers from certain pediatric clinical trial requirements, and application fee waivers. After the FDA grants orphan drug designation, the generic identity of the therapeutic agent and its potential orphan use are disclosed publicly by the FDA.

In addition, if a product candidate receives the first FDA approval for the disease or condition for which it has orphan designation, the product is entitled to orphan drug exclusivity, which means the FDA may not approve any other application to market the same drug for the same disease or condition for a period of seven years, except in limited circumstances, such as a showing of clinical superiority over the product with orphan exclusivity or where the manufacturer is unable to assure sufficient product quantity for the orphan patient population. Exclusive marketing rights in the United States may also be unavailable if we or our collaborators seek approval for a disease or condition broader than the orphan designated disease or condition and may be lost if the FDA later determines that the request for designation was materially defective.

Even if we obtain orphan drug designation, we may not be the first to obtain marketing approval for any particular orphan disease or condition due to the uncertainties associated with developing pharmaceutical products. Further, even if we obtain orphan drug exclusivity for a product candidate, that exclusivity may not effectively protect the product from competition because different drugs can be approved for the same disease condition. Even after an orphan drug is approved, the FDA can subsequently approve the same drug for the same condition if the FDA concludes that the later drug is clinically superior in that it is safer, more effective, or makes a major contribution to patient care. Orphan drug designation neither shortens the development time or regulatory review time of a drug nor gives the drug any advantage in the regulatory review or approval process.

We have obtained a rare pediatric disease designation for lovo-cel for the treatment of SCD; however, there is no guarantee that FDA approval will result in issuance of a priority review voucher.

In 2012, Congress authorized the FDA to award priority review vouchers to sponsors of certain rare pediatric disease product applications. This program is designed to encourage development of new drug and biological products for prevention and treatment of certain rare pediatric diseases. Specifically, under this program, a sponsor who receives an approval for a drug or biologic for a “rare pediatric disease” that meets certain criteria may qualify for a voucher that can be redeemed to receive a priority review of a subsequent marketing application for a different product. The sponsor of a rare pediatric disease drug product receiving a priority review voucher may transfer (including by sale) the voucher to another sponsor. The voucher may be further transferred any number of times before the voucher is used, as long as the sponsor making the transfer has not yet submitted the application. The FDA may also revoke any priority review voucher if the rare pediatric disease drug for which the voucher was awarded is not marketed in the U.S. within one year following the date of approval.

We have obtained a rare pediatric disease designation for lovo-cel for the treatment of SCD. However, there is no guarantee that we will be able to obtain a priority review voucher, even if lovo-cel is approved by the FDA. For example, even though we received priority review vouchers in connection with the approvals of SKYSONA and ZYNTEGLO, the FDA may determine that a BLA for lovo-cel, even if ultimately approved, does not meet the eligibility criteria for a priority review voucher, such as where the FDA limits approval, if ultimately received, to a patient population over 18 years of age. Moreover, Congress included a sunset provision in the statute authorizing the rare pediatric disease priority review voucher program. Under the current statutory sunset provisions, after September 30, 2024, FDA may only award a voucher for an approved rare pediatric disease product application if the sponsor has rare pediatric disease designation for the product candidate, and that designation was granted by September 30, 2024. After September 30, 2026, FDA may not award any rare pediatric disease priority review vouchers.

Our biological products and product candidates may face competition sooner than anticipated.

The Affordable Care Act includes a subtitle called the Biologics Price Competition and Innovation Act of 2009 ("BPCIA"), which created an abbreviated approval pathway for biological products that are biosimilar to or interchangeable with an FDA-licensed reference biological product. Under the BPCIA, an application for a highly similar or "biosimilar" product may not be submitted to the FDA until four years following the date that the reference product was first approved by the FDA. In addition, the approval of a biosimilar product may not be made effective by the FDA until 12 years from the date on which the reference product was first approved. During this 12-year period of exclusivity, another company may still market a competing version of the reference product if the FDA approves a full BLA for the competing product containing the sponsor's own preclinical data and data from adequate and well-controlled clinical trials to demonstrate the safety, purity and potency of their product. We believe that any of our product candidates approved as a biological product under a BLA should qualify for the 12-year period of exclusivity. However, there is a risk that this exclusivity could be shortened due to congressional action or otherwise, or that the FDA will not consider our product candidates to be reference products for competing products, potentially creating the opportunity for competition sooner than anticipated. Moreover, the extent to which a biosimilar, once approved, will be substituted for any one of our reference products in a way that is similar to traditional generic substitution for non-biological products is not yet clear, and will depend on a number of marketplace and regulatory factors that are still developing.

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 ZYNTEGLO, SKYSONA and lovo-cel.

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 products or product candidates uneconomical or obsolete, and we may not be successful in marketing our product candidates against competitors. For additional information regarding our competition, see "Part I, Item 1. Business—Competition".

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, in part, upon our ability to identify, develop and commercialize products based on our platform technologies. 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 any 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 products and product candidates or adversely affect our ability to conduct our business or obtain and maintain marketing approvals for our products and 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 products and 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 product candidates, 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.

Disruptions at the FDA and other government agencies caused by funding shortages or global health concerns could hinder their ability to hire, retain or deploy key leadership and other personnel, prevent new or modified products from being developed, reviewed, approved or commercialized in a timely manner or at all, which could negatively impact our business.

The ability of the FDA and foreign regulatory authorities to review and approve new products can be affected by a variety of factors, including government budget and funding levels, statutory, regulatory, and policy changes, the FDA's or foreign regulatory authorities' ability to hire and retain key personnel and accept the payment of user fees, and other events that may otherwise affect the FDA's or foreign regulatory authorities' ability to perform routine functions. Average review times at the FDA and foreign regulatory authorities have fluctuated in recent years as a result. In addition, government funding of other government agencies that fund research and development activities is subject to the political process, which is inherently fluid and unpredictable. Disruptions at the FDA may also slow the time necessary for new drugs, medical devices and biologics or modifications to approved drugs and biologics to be reviewed and/or approved by necessary government agencies, which would adversely affect our business. For example, over the last several years, the U.S. government has shut down several times and certain regulatory agencies, such as the FDA, have had to furlough critical FDA employees and stop critical activities.

Separately, in response to the global COVID-19 pandemic, the FDA postponed most inspections of domestic and foreign manufacturing facilities at various points. Even though the FDA has since resumed standard inspection operations of domestic facilities where feasible, the FDA has continued to monitor and implement changes to its inspectional activities to ensure the safety of its employees and those of the firms it regulates as it adapts to the evolving COVID-19 pandemic, and any resurgence of the virus or emergence of new variants may lead to further inspectional delays. Regulatory authorities outside the United States have adopted similar policy measures in response to the COVID-19 pandemic. If a prolonged government shutdown occurs, or if global health concerns continue to prevent the FDA or other regulatory authorities from conducting their regular inspections, reviews, or other regulatory activities, it could significantly impact the ability of the FDA or other regulatory authorities to timely review and process our regulatory submissions, which could have a material adverse effect on our business.

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 support commercialization of SKYSONA and ZYNTEGLO and 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, including for lovo-cel. 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, including the inability to negotiate favorable terms to increase capacity to meet future forecasted demand;
- 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 products or product candidates. 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, particularly those we anticipate using for production of lovo-cel (when and if approved) 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 may be required to successfully complete a pre-approval inspection for compliance with GMPs and other applicable regulations as a condition of marketing approval of our product candidates. In addition, the regulatory authorities may, at any time, audit or inspect a manufacturing facility involved with the preparation of our products or product candidates or the associated quality systems for compliance with the regulations applicable to the activities being conducted. If these facilities do not successfully complete a pre-approval plant inspection, it is possible FDA or other marketing approval of the product candidates may be delayed or prevented.

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 products or product candidates, cause us to incur higher costs and prevent us from successfully commercializing our products or product candidates. 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 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 rely on contract research organizations ("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 and in accordance with applicable GCPs, GLPs and other 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. Regulatory authorities enforce these GCPs through periodic inspections of trial sponsors, principal investigators and trial sites. We cannot assure you that upon inspection by a given regulatory authority, such regulatory authority will determine that any of our clinical trials complies with GCP regulations. 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 commercialize ZYNTEGLO and SKYSONA and complete the development of, and obtain the regulatory, pricing and reimbursement approvals necessary to commercialize lovo-cel (if and when approved). 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 our approved products;
- launching and commercializing our approved products with a sustainable field-based team and marketing and distribution infrastructure;
- obtaining sufficient pricing and reimbursement for our approved products from private and governmental payers;
- obtaining market acceptance and adoption of our approved products 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 products and product candidates, 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 products and product candidates is subject to outcomes-based arrangements over time, as it is for ZYNTEGLO, 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. For instance, a portion of our financial runway guidance includes $45.4 million of restricted cash which is currently unavailable for use and there is no assurance as to when or if our restricted cash will become available. Moreover, our future net product revenues will depend upon the size of the markets which the products have received approval, its ability to achieve sufficient market acceptance, reimbursement from third-party payers, adequate market share in those markets and performance of the drug product subject to outcome-based programs. 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 revenues from product sales will be difficult to predict from period to period, given the absence of historical sales data for ZYNTEGLO, SKYSONA, and lovo-cel, if approved.

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 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 has 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.

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.

As a result of the COVID-19 pandemic, we have experienced and may in the future 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, and the treatment of patients in the commercial context. The COVID-19 pandemic has also 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. Furthermore, certain third parties in our supply chain 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. 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 we may continue to experience 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.

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 and any potential resurgence of the pandemic and additional or modified government 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 activities in the United States, healthcare systems or the global economy. For instance, we continue to evaluate any impact of COVID-19 on our QTC network, our supply chain, and any potential future clinical trials. 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. 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.

Our products, whether FDA-approved or investigational, remain subject to regulatory scrutiny.

For any regulatory approvals that we have or may receive, the manufacturing processes, labeling, packaging, distribution, adverse event reporting, storage, advertising, promotion, import, export and recordkeeping for our products and/or product candidates will be subject to extensive and ongoing regulatory requirements. These requirements include submissions of safety and other post-marketing information and reports, registration, as well as ongoing compliance with cGMPs and GCPs for any clinical trials that we may conduct. In addition, manufacturers of drug products and their facilities are subject to continual review and periodic, unannounced inspections by the FDA and other regulatory authorities for compliance with cGMP regulations and standards. Even though we have obtained marketing approval in the U.S. for ZYNTEGLO and SKYSONA and may obtain regulatory approval in the U.S. for lovo-cel, any regulatory approvals we may receive will require the submission of reports to regulatory authorities and surveillance to monitor the safety and efficacy of the product candidates, and such approvals may contain significant limitations related to use restrictions for specified age groups, warnings, precautions or contraindications, and may include burdensome post-approval study or risk management requirements.. 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. Furthermore, we have agreed to provide confirmatory long-term clinical data to the FDA as a condition of the SKYSONA accelerated approval, and continued approval for the approved indication will be contingent upon verification and description of clinical benefit in a confirmatory trial. If our confirmatory trials fail to adequately verify or describe the anticipated clinical benefit of SKYSONA, or if we fail to conduct such trials in a timely manner, the FDA could withdraw its approval for SKYSONA on an expedited basis.

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 clinical programs due to safety concerns arising from our

SKYSONA and lovo-cel programs, and we can make no assurance that we will not experience interruptions in any clinical studies, marketing or other commercialization activities in the future, whether due to safety concerns in any approved or investigational 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.

The FDA's and other regulatory authorities' policies may change and additional government regulations may be promulgated that could prevent, limit or delay marketing authorization of any product candidates we develop. We also cannot predict the likelihood, nature or extent of government regulation that may arise from future legislation or administrative action, either in the United States or abroad. If we are slow or unable to adapt to changes in existing requirements or the adoption of new requirements or policies, or if we are not able to maintain regulatory compliance, we may be subject to enforcement action and we may not achieve or sustain profitability.

The FDA and other regulatory agencies actively enforce the laws and regulations prohibiting the promotion of off-label uses.

The FDA strictly regulates marketing, labeling, advertising and promotion of prescription drugs and biologics. These regulations include standards and restrictions for direct-to-consumer advertising, industry-sponsored scientific and educational activities, promotional activities involving the internet and off-label promotion. Any regulatory approval that the FDA grants is limited to those specific diseases and indications for which a product is deemed to be safe, pure and potent, or effective, by the FDA. For example, the current FDA-approved indication for ZYNTEGLO is limited to the treatment of adult and pediatric patients with β-thalassemia who require regular red blood cell transfusions, and the FDA-approved indication for SKYSONA is limited to slow the progression of neurologic dysfunction in boys 4-17 years of age with early, active CALD, which is defined to include to asymptomatic or mildly symptomatic (neurologic function score, NFS $\leq$ 1) boys who have gadolinium enhancement on brain magnetic resonance imaging and Loes scores of 0.5-9.

While physicians in the United States may choose, and are generally permitted, to prescribe drugs for uses that are not described in the product's labeling and for uses that differ from those tested in clinical trials and approved by the regulatory authorities, our ability to manufacture and promote any products will be narrowly limited to those indications that are specifically approved by the FDA. If we are found to have manufactured and promoted such off-label uses, we may become subject to significant liability. The U.S. federal government has levied large civil and criminal fines against companies for alleged improper promotion of off-label use and has enjoined several companies from engaging in off-label promotion. The

FDA has also requested that companies enter into consent decrees or permanent injunctions under which specified promotional conduct is changed or curtailed. If we cannot successfully manage the promotion any product candidates, if approved, we could become subject to significant liability, which would materially adversely affect our business and financial condition.

We are subject, directly or indirectly, to federal and state healthcare fraud and abuse laws and, false claims 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, patient services 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.

Actual or perceived failures to comply with applicable data protection, privacy and security laws, regulations, standards and other requirements could adversely affect our business, results of operations, and financial condition.

The global data protection landscape is rapidly evolving, and we are or may become subject to numerous state, federal and foreign laws, requirements and regulations governing the collection, use, disclosure, retention, and security of personal information, such as information that we may collect in connection with clinical trials. Implementation standards and enforcement practices are likely to remain uncertain for the foreseeable future, and we cannot yet determine the impact future laws, regulations, standards, or perception of their requirements may have on our business. This evolution may create uncertainty in our business, affect our ability to operate in certain jurisdictions or to collect, store, transfer use and share personal information, necessitate the acceptance of more onerous obligations in our contracts, result in liability or impose additional costs on us. The cost of compliance with these laws, regulations and standards is high and is likely to increase in the future. Any failure or perceived failure by us to comply with federal, state or foreign laws or regulations, our internal policies and procedures or our contracts governing our processing of personal information could result in negative publicity, government investigations and enforcement actions, claims by third parties and damage to our reputation, any of which could have a material adverse effect on our business, results of operation, and financial condition.

In the U.S., HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act of 2009 ("HITECH") and their implementing regulations (collectively, "HIPAA"), 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. Certain states have also adopted comparable privacy and security laws and regulations, which govern the privacy, processing and protection of health-related and other personal information. For example, California 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 CCPA provides for civil penalties for violations, as well as a private right of action for data breaches that has increased the likelihood of, and risks associated with data breach litigation. Further, the California Privacy Rights Act ("CPRA") generally went into effect on January 1, 2023, and significantly amends the CCPA. It imposes additional data protection obligations on covered businesses, including additional consumer rights processes, limitations on data uses, new audit requirements for higher risk data, and opt outs for certain uses of sensitive data. It also creates a new California data protection agency authorized to issue substantive regulations and could result in increased privacy and information security enforcement. Additional compliance investment and potential business process changes may also be required. Similar laws have passed in Virginia, Colorado, Connecticut and Utah, and have been proposed in other states and at the federal level, reflecting a trend toward more stringent privacy legislation in the United States. The enactment of such laws could have potentially conflicting requirements that would make compliance challenging. In the event that we are subject to or affected by HIPAA, the CCPA, the CPRA or other domestic privacy and data protection laws, any liability from failure to comply with the requirements of these laws could adversely affect our financial condition.

Furthermore, the Federal Trade Commission (FTC) and many state Attorneys General continue to enforce federal and state consumer protection laws against companies for online collection, use, dissemination and security practices that appear to be unfair or deceptive. For example, according to the FTC, failing to take appropriate steps to keep consumers' personal information secure can constitute unfair acts or practices in or affecting commerce in violation of Section 5(a) of the Federal Trade Commission Act. The FTC expects a company's data security measures to be reasonable and appropriate in light of the sensitivity and volume of consumer information it holds, the size and complexity of its business, and the cost of available tools to improve security and reduce vulnerabilities.

We are also or may become subject to rapidly evolving data protection laws, rules and regulations in foreign jurisdictions. For example, in Europe, the European Union General Data Protection Regulation ("GDPR") went into effect in May 2018 and imposes strict requirements for processing the personal data of individuals within the European Economic Area ("EEA"). Companies that must comply with the GDPR face increased compliance obligations and risk, including more robust regulatory enforcement of data protection requirements and potential fines for noncompliance of up to €20 million or 4% of the annual global revenues of the noncompliant company, whichever is greater. Among other requirements, the GDPR regulates transfers of personal data subject to the GDPR to third countries that have not been found to provide adequate protection to such personal data, including the United States; in July 2020, the Court of Justice of the EU ("CJEU") limited how organizations could lawfully transfer personal data from the EU/EEA to the United States by invalidating the Privacy Shield for purposes of international transfers and imposing further restrictions on the use of standard contractual clauses ("SCCs"). In March 2022, the US and EU announced a new regulatory regime intended to replace the invalidated regulations; however, this new EU-US Data Privacy Framework has not been implemented beyond an executive order signed by President Biden on October 7, 2022 on Enhancing Safeguards for United States Signals Intelligence Activities. European court and regulatory decisions subsequent to the CJEU decision of July 16, 2020 have taken a restrictive approach to international data transfers. As supervisory authorities issue further guidance on personal data export mechanisms, including circumstances where the SCCs cannot be used, and/or start taking enforcement action, we could suffer additional costs, complaints and/or regulatory investigations or fines, and/or if we are otherwise unable to transfer personal data between and among countries and regions in which we operate, it could affect the manner in which we provide our services, the geographical location or segregation of our relevant systems and operations, and could adversely affect our financial results.

Since the beginning of 2021, after the end of the transition period following the United Kingdom's departure from the European Union, we are also subject to the United Kingdom data protection regime, which imposes separate but similar obligations to those under the GDPR and comparable penalties, including fines of up to £17.5 million or 4% of a noncompliant company's global annual revenue for the preceding financial year, whichever is greater. As we continue to expand into other foreign countries and jurisdictions, we may be subject to additional laws and regulations that may affect how we conduct business.

If we fail to comply with reporting and payment obligations under the Medicaid Drug Rebate Program or other governmental pricing programs, we could be subject to additional reimbursement requirements, penalties, sanctions and

fines, which could have a material adverse effect on our business, financial condition, results of operations and growth prospects.

We participate in governmental programs that impose extensive drug price reporting and payment obligations on pharmaceutical manufacturers. Medicaid is a joint federal and state program that is administered by the states for low income and disabled beneficiaries. Under the Medicaid Drug Rebate Program (the "MDRP"), as a condition of federal funds being made available for our covered outpatient drugs under Medicaid and certain drugs or biologicals under Medicare Part B, we pay a rebate to state Medicaid programs for each unit of our covered outpatient drugs dispensed to a Medicaid beneficiary and paid for by the state Medicaid program. Medicaid rebates are based on pricing data that we report on a monthly and quarterly basis to CMS, the federal agency that administers the MDRP and Medicare programs. For the MDRP, these data include the Average Manufacturer Price ("AMP") for each drug and, in the case of innovator products, best price. In connection with Medicare Part B, a pharmaceutical manufacturer must provide CMS with average sales price ("ASP") information for certain drugs or biologicals on a quarterly basis. ASP is calculated based on a statutorily defined formula, as well as regulations and interpretations of the statute by CMS. If we become aware that our MDRP price reporting submission for a prior period was incorrect or has changed as a result of recalculation of the pricing data, we must resubmit the corrected data for up to three years after those data originally were due. If we fail to provide information timely or are found to have knowingly submitted false information to the government, we may be subject to civil monetary penalties and other sanctions, including termination from the MDRP, in which case payment would not be available for our covered outpatient drugs under Medicaid or, if applicable, Medicare Part B.

Federal law requires that any company that participates in the MDRP also participate in the 340B program in order for federal funds to be available for the manufacturer's drugs under Medicaid and Medicare Part B. The 340B program is administered by HRSA and imposes a statutorily defined "ceiling price" for pharmaceutical products purchased by defined "covered entities" when administered in the outpatient setting. bluebird's therapies are administered in the inpatient setting exclusively and thus, we do not anticipate any 340B claims and requires us, as a participating manufacturer, to agree to charge statutorily defined covered entities no more than the 340B "ceiling price" for our covered drugs used in an outpatient setting. These 340B covered entities include a variety of community health clinics and other entities that receive health services grants from the Public Health Service, as well as hospitals that serve a disproportionate share of low income patients. A drug that is designated for a rare disease or condition by the Secretary of Health and Human Services is not subject to the 340B ceiling price requirement with regard to the following types of covered entities: rural referral centers, sole community hospitals, critical access hospitals, and free standing cancer hospitals. The 340B ceiling price is calculated using a statutory formula, which is based on the AMP and rebate amount for the covered outpatient drug as calculated under the MDRP. In general, products subject to Medicaid price reporting and rebate liability are also subject to the 340B ceiling price calculation and discount requirement. We must report 340B ceiling prices to HRSA on a quarterly basis, and HRSA publishes them to 340B covered entities. HRSA has finalized regulations regarding the calculation of the 340B ceiling price and the imposition of civil monetary penalties on manufacturers that knowingly and intentionally overcharge covered entities for 340B eligible drugs. HRSA has also finalized an administrative dispute resolution process through which 340B covered entities may pursue claims against participating manufacturers for overcharges, and through which manufacturers may pursue claims against 340B covered entities for engaging in unlawful diversion or duplicate discounting of 340B drugs. In addition, legislation may be introduced that, if passed, would further expand the 340B program, such as adding further covered entities or requiring participating manufacturers to agree to provide 340B discounted pricing on drugs used in an inpatient setting.

In order to be eligible to have drug products paid for with federal funds under Medicaid and Medicare Part B and purchased by certain federal agencies and grantees, we must also participate in the VA/FSS pricing program. Under the VA/FSS program, we must report the Non-FAMP for our covered drugs to the VA and charge certain federal agencies no more than the Federal Ceiling Price, which is calculated based on Non FAMP using a statutory formula. These four agencies are the VA, the U.S. Department of Defense, the U.S. Coast Guard, and the U.S. Public Health Service (including the Indian Health Service). We must also pay rebates on products purchased by military personnel and dependents through the TRICARE retail pharmacy program. If we fail to provide timely information or are found to have knowingly submitted false information, we may be subject to civil monetary penalties.

Individual states continue to consider and have enacted legislation to limit the growth of healthcare costs, including the cost of prescription drugs and combination products. A number of states have either implemented or are considering implementation of drug price transparency legislation that may prevent or limit our ability to take price increases at certain rates or frequencies. Requirements under such laws include advance notice of planned price increases, reporting price increase amounts and factors considered in taking such increases, wholesale acquisition cost information disclosure to prescribers, purchasers, and state agencies, and new product notice and reporting. Such legislation could limit the price or payment for certain drugs, and states may impose civil monetary penalties or pursue other enforcement mechanisms against manufacturers who fail to comply with

drug price transparency requirements. If we are found to have violated state law requirements, we may become subject to penalties or other enforcement mechanisms, which could have a material adverse effect on our business.

Pricing and rebate calculations vary across products and programs, are complex, and are often subject to interpretation by us, governmental or regulatory agencies, and the courts, which can change and evolve over time. Such pricing calculations and reporting, along with any necessary restatements and recalculations, could increase our costs for complying with the laws and regulations governing the MDRP and other governmental programs, and under the MDRP could result in an overage or undercharge in Medicaid rebate liability for past quarters. Price recalculations under the MDRP also may affect the ceiling price at which we are required to offer products under the 340B program. Civil monetary penalties can be applied if we are found to have knowingly submitted any false price or product information to the government, if we fail to submit the required price data on a timely basis, or if we are found to have charged 340B covered entities more than the statutorily mandated ceiling price. CMS could also terminate our Medicaid drug rebate agreement, in which case federal payments may not be available under Medicaid or Medicare Part B, if applicable, for our covered outpatient drugs. Pursuant to the Inflation Reduction Act of 2022 (the "IRA"), the AMP figures we report will also be used to compute rebates under Medicare Part D triggered by price increases that outpace inflation. We cannot assure you that our submissions will not be found to be incomplete or incorrect.

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 products or product candidates harm patients, or is perceived to harm patients even when such harm is unrelated to our products or 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 products for which we have obtained 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 products and product candidates. There is a risk that our products and 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 products; 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 products and 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 products and 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 products and 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 our approved products maintain. 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.

The increasing focus on environmental sustainability and social initiatives could increase our costs, harm our reputation and adversely impact our financial results.

There has been increasing public focus by investors, patients, environmental activists, the media and governmental and nongovernmental organizations on a variety of environmental, social and other sustainability matters. We may experience pressure to make commitments relating to sustainability matters that affect us, including the design and implementation of specific risk mitigation strategic initiatives relating to sustainability. If we are not effective in addressing environmental, social and other sustainability matters affecting our business, or setting and meeting relevant sustainability goals, our reputation and financial results may suffer. In addition, even if we are effective at addressing such concerns, we may experience increased costs as a result of executing upon our sustainability goals that may not be offset by any benefit to our reputation, which could have an adverse impact on our business and financial condition.

In addition, this emphasis on environmental, social and other sustainability matters has resulted and may result in the adoption of new laws and regulations, including new reporting requirements. If we fail to comply with new laws, regulations or reporting requirements, our reputation and business could be adversely impacted.

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

The United States has enacted or proposed legislative and regulatory changes affecting the healthcare system that could prevent or delay marketing approval of our product candidates, restrict or regulate post-approval activities and affect our ability to profitably sell products for which we have obtained 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.

A primary trend in the U.S. healthcare industry and elsewhere is cost containment. Government authorities and other third party payers have attempted to control costs by limiting coverage and the level of reimbursement for particular medical products and services, implementing reductions in Medicare and other healthcare funding and applying new payment methodologies. For example, in March 2010, the Affordable Care Act ("ACA") was enacted, which, among other things, increased the minimum Medicaid rebates owed by most manufacturers under the Medicaid Drug Rebate Program; introduced 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; extended manufacturer Medicaid rebate obligations to utilization by individuals enrolled in Medicaid managed care plans; established a new Medicare Part D coverage gap discount program; subjected drug manufacturers to new annual fees based on pharmaceutical companies' share of sales to federal healthcare programs; imposed a new federal excise tax on the sale of certain medical devices; created a new Patient Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research; and established a Center for Medicare Innovation at the CMS to test innovative payment and service delivery models to lower Medicare and Medicaid spending.

Since its enactment, there have been judicial, executive and Congressional challenges to certain aspects of the ACA. On June 17, 2021, the U.S. Supreme Court dismissed the most recent judicial challenge to the ACA brought by several states without specifically ruling on the constitutionality of the ACA. In addition, other legislative changes have been proposed and adopted in the United States since the ACA was enacted. The Budget Control Act of 2011, among other things, led to reductions of Medicare payments to providers, which will remain in effect through 2031 unless additional Congressional action is taken. More recently, in March 2021, President Biden signed into law the American Rescue Plan Act of 2021, which eliminates the statutory cap on the Medicaid drug rebate, currently set at 100% of a drug's AMP, beginning January 1, 2024.

Most significantly, in August 2022, President Biden signed the Inflation Reduction Act of 2022 ("IRA") into law. This statute marks the most significant action by Congress with respect to the pharmaceutical industry since adoption of the ACA in 2010. Among other things, the IRA requires manufacturers of certain drugs to engage in price negotiations with Medicare (beginning in 2026), with prices that can be negotiated subject to a cap; imposes rebates under Medicare Part B and Medicare Part D to penalize price increases that outpace inflation (first due in 2023); and replaces the Part D coverage gap discount program with a new discounting program (beginning in 2025). The IRA permits the Secretary of the Department of Health and Human Services (HHS) to implement many of these provisions through guidance, as opposed to regulation, for the initial years.

For that and other reasons, it is currently unclear how the IRA will be effectuated, and while the impact of the IRA on our business and the pharmaceutical industry cannot yet be fully determined, it is likely to be significant.

At the U.S. 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.

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 products and product candidates. Such reforms could have an adverse effect on anticipated revenue from products and 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 information technology 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 activities related to our approved products and have a material adverse effect on our reputation, business, financial condition or results of operations.

Our information technology systems and those of our current or future third-party collaborators, service providers, contractors and consultants may fail and are vulnerable to attack, damage and interruption from computer viruses and malware (e.g. ransomware), malicious code, natural disasters, terrorism, war, telecommunication and electrical failures, hacking, cyberattacks, phishing attacks and other social engineering schemes, employee theft or misuse, human error, fraud, denial or degradation of service attacks, sophisticated nation-state and nation-state-supported actors or unauthorized access or use by persons inside our organizations, or persons with access to systems inside our organization. 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. The prevalent use of mobile devices and unauthorized applications also increases the risk of data security incidents. As a result of the COVID-19 pandemic, and continued hybrid working environment, we may also face increased cybersecurity risks due to our reliance on internet technology and the number of our employees who are working remotely, which may create additional opportunities for cybercriminals to exploit vulnerabilities. Furthermore, because the techniques used to obtain unauthorized access to, or to sabotage, systems change frequently and often are not recognized until launched against a target, we may be unable to anticipate these techniques or implement adequate preventative measures. We may also experience security breaches that may remain undetected for an extended period. Even if identified, we may be unable to adequately investigate or remediate incidents or breaches due to attackers increasingly using tools and techniques that are designed to circumvent controls, to avoid detection, and to remove or obfuscate forensic evidence.

We and certain of our service providers are from time to time subject to cyberattacks and security incidents. While we do not believe that we have experienced any significant system failure, accident or security breach to date, if we were to experience a 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 our products and 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. 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. Further, our insurance coverage may not be sufficient to cover the financial, legal, business or reputational losses that may result from an interruption or breach of our systems.

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.

If the distribution of shares of 2seventy, 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 of shares of 2seventy was conditioned upon, among other things, our receipt of a private letter ruling from the U.S. Internal Revenue Service (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 U.S. Internal Revenue Code of 1986, as amended (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. This can include events that occur following the distribution such as subsequent public offerings by us or 2seventy or share sales to persons that engaged in negotiations over share purchases prior to the distribution. Subsequent tax opinions have been obtained by us and 2seventy in connection with certain post-distribution sales of 2seventy's shares. The IRS private letter ruling, the opinion of Goodwin Procter LLP and tax opinions related to certain subsequent post-distribution sales of 2seventy shares were based, among other things, on various facts and assumptions, as well as certain representations, statements and undertakings from us and 2seventy (including those relating to the past and future conduct of us and 2seventy) 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 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 at the time of the distribution, 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's distributed common stock in a taxable sale for its fair market value and our stockholders who receive shares of 2seventy 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 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 under Section 355(e) of the Code or an acquisition of 2seventy stock or assets or certain actions by 2seventy, then 2seventy 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 us or 2seventy under Section 355(e) of the Code and both we and 2seventy are responsible for such failure, liability will be shared according to relative fault. If neither we nor 2seventy 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 products and 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 products and 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 products and 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 products and 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 our products and 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, our current and future products. Several patent applications covering our products and 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 or 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 products and 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. For example, as discussed in Part I, Item 3, "Legal Proceedings", San Rocco Therapeutics, LLC, formerly known as Errant Gene Therapeutics, LLC has alleged that our use of the BB305 lentiviral vector in connection with the beti-cel program infringes U.S. Patent Nos. 7,541,179 and 8,058,061, and seeks equitable, injunctive and monetary relief, including royalties, treble damages, attorney fees and costs. 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 products and 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 or 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 or 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 products or 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 attorney's 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 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 products. Because our programs may involve additional technologies 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. For instance, our growth strategy depends in part upon our ability to leverage advancements in complementary technologies such as in reduced toxicity conditioning or in stem cell mobilization. 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 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 products or 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 products, 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 products 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 products and product candidates. 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 products and 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 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, such as the recent volatility and disruption experienced in the global economy and rising interest and inflation rates, 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, either from patients participating in our clinical trials or in connection with sales of our commercial products or other gene therapy products in the market;
- inability to obtain additional funding;
- any delay in filing our BLA for lovo-cel, and any adverse development or perceived adverse development with respect to the regulatory authority's review of such BLA;
- failure to successfully manage the commercial launch of ZYNTEGLO or SKYSONA or of 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 ZYNTEGLO or SKYSONA or for lovo-cel from private and governmental payers;
- failure to obtain market acceptance and adoption of ZYNTEGLO or SKYSONA or of lovo-cel;
- 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 ZYNTEGLO, SKYSONA 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;
- 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, including under our Equity Distribution Agreement with Goldman Sachs & Co. LLC, 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") we are 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. In January 2023, the number of shares of common stock available for issuance under the 2013 Plan was increased by approximately 3.3 million shares as a result of this automatic increase provision. The 2013 Plan will expire in

2023 and we will need to adopt a new plan subject to shareholder approval. We also 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 may be 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 have in the past litigated 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 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 Sections 382 and 383 of the Code, if a corporation undergoes an "ownership change," generally defined as a cumulative change of greater than 50% (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 and development tax credits) to offset its post-change income and taxes may be limited. We have completed several financings since our inception, which we believe have resulted in shifts in our equity ownership. We completed a study through December 2020 confirming no ownership changes have occurred since our initial public offering in 2013. We may have experienced ownership changes since December 2020, and we may also experience ownership changes in the future as a result of subsequent shifts in our equity ownership, some of which are outside our control. If finalized, Treasury Regulations currently proposed under Section 382 of the Code may further limit our ability to utilize our pre-change NOLs or other pre-change tax attributes if we undergo a future ownership change. Accordingly, if we earn net taxable income, our ability to use our pre-change NOLs and other pre-change tax attributes 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 and regulations could adversely affect our business, financial condition and results of operations.

New income, sales, use or other tax laws, statutes, rules, regulations or ordinances could be enacted at any time, which could affect the tax treatment of any of our future earnings. Further, existing tax laws, statutes, rules, regulations or ordinances could be interpreted, changed, modified or applied adversely to us. Generally, future changes in applicable tax laws and regulations, or their interpretation and application, potentially with retroactive effect, could have an adverse effect on our business, financial conditions and results of operations. We are unable to predict whether such changes will occur and, if so, the ultimate impact on our business. 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.

Unstable market and economic conditions may have serious adverse consequences on our business, financial condition and share price.

The global economy, including credit and financial markets, has recently experienced extreme volatility and disruptions, including severely diminished liquidity and credit availability, rising interest and inflation rates, declines in consumer confidence, declines in economic growth, increases in unemployment rates and uncertainty about economic stability. If the equity and credit markets continue to deteriorate or the United States enters a recession, it may make any necessary debt or equity financing more difficult to obtain in a timely manner or on favorable terms, more costly or more dilutive. In addition, there is a risk that one or more of our CROs, suppliers or other third-party providers may not survive an economic downturn or recession. As a result, our business, results of operations and price of our common stock may be adversely affected.

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, 2022:

Massachusetts

Our current corporate headquarters encompasses approximately 61,180 square feet of office space and is located at 455 Grand Union Boulevard, Somerville, Massachusetts. The lease commenced in April 2022 and will continue until December 31, 2032. The lease for our previous headquarters located at 60 Binney Street, Cambridge, Massachusetts was assigned to 2seventy bio, Inc. as of the tax-free spin-off consummated in November 2021. Under the terms of the assignment, we retained access rights to a portion of this office and laboratory space as needed. Currently, we are only using the laboratory space at 60 Binney Street and will discontinue this use as soon as our laboratory space in Charlestown, Massachusetts (as described below) is available for use.

In October 2022, we entered into a sublease with Finch Therapeutics, Inc. ("Finch") for 42,162 square feet of office and laboratory space at Finch's corporate headquarters located at 100 Hood Park Drive, Charlestown, Massachusetts which Finch leases from Hood Park, LLC. This sublease commenced December 15, 2022 and is expected to terminate on December 14, 2025.

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 commenced April 1, 2022, and is expected to terminate on December 31, 2030.

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, 2022, 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 October 21, 2021, San Rocco Therapeutics, LLC, formerly known as 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. Patent Nos. 7,541,179 and 8,058,061. The term of U.S. Patent No. 8,058,061 already expired on November 25, 2022, and U.S. Patent No. 7,541,179 will expire on May 13, 2024. The allegations relate to our use of the BB305 lentiviral vector, including in connection with 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 ("SRT"). 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. On April 6, 2022, we—along with Third Rock Ventures, LLC—filed a motion seeking various relief including to stay the proceedings and compel arbitration on two threshold issues, which we argued warranted complete dismissal of the action as a matter of law, regardless of the merits of SRT's underlying infringement claims. On July 26, 2022, the Court granted our request to stay the proceedings and issued an Order compelling the parties to arbitrate the threshold issues we raised. On February 7, 2023, the Arbitrator issued a final award finding in favor of SRT on both threshold issues, thereby enabling SRT to pursue its claims for alleged infringement. On March 1, 2023, the parties jointly stipulated, subject to the approval of the United States District Court for the District of Delaware, to lift the stay. The Court lifted the stay on March 2, 2023, and our answer to SRT's complaint is due on or before March 31, 2023. We do not believe there is any infringement of the patents-in-suit and that the patents-in-suit are invalid. We have also filed petitions for inter partes review with the Patent Trial & Appeal Board (PTAB) of the United States Patent & Trademark Office, seeking to invalidate the patents. The PTAB is expected to issue its initial decisions in April 2023. We plan to vigorously defend against SRT's claims including by seeking a declaration from the Court that SRT's action is an exceptional case within the meaning of 35 U.S.C. § 285, and by seeking costs, attorney fees, and other relief to which we may be justly entitled.

Item 4. Mine Safety Disclosures

Not applicable.

PART II

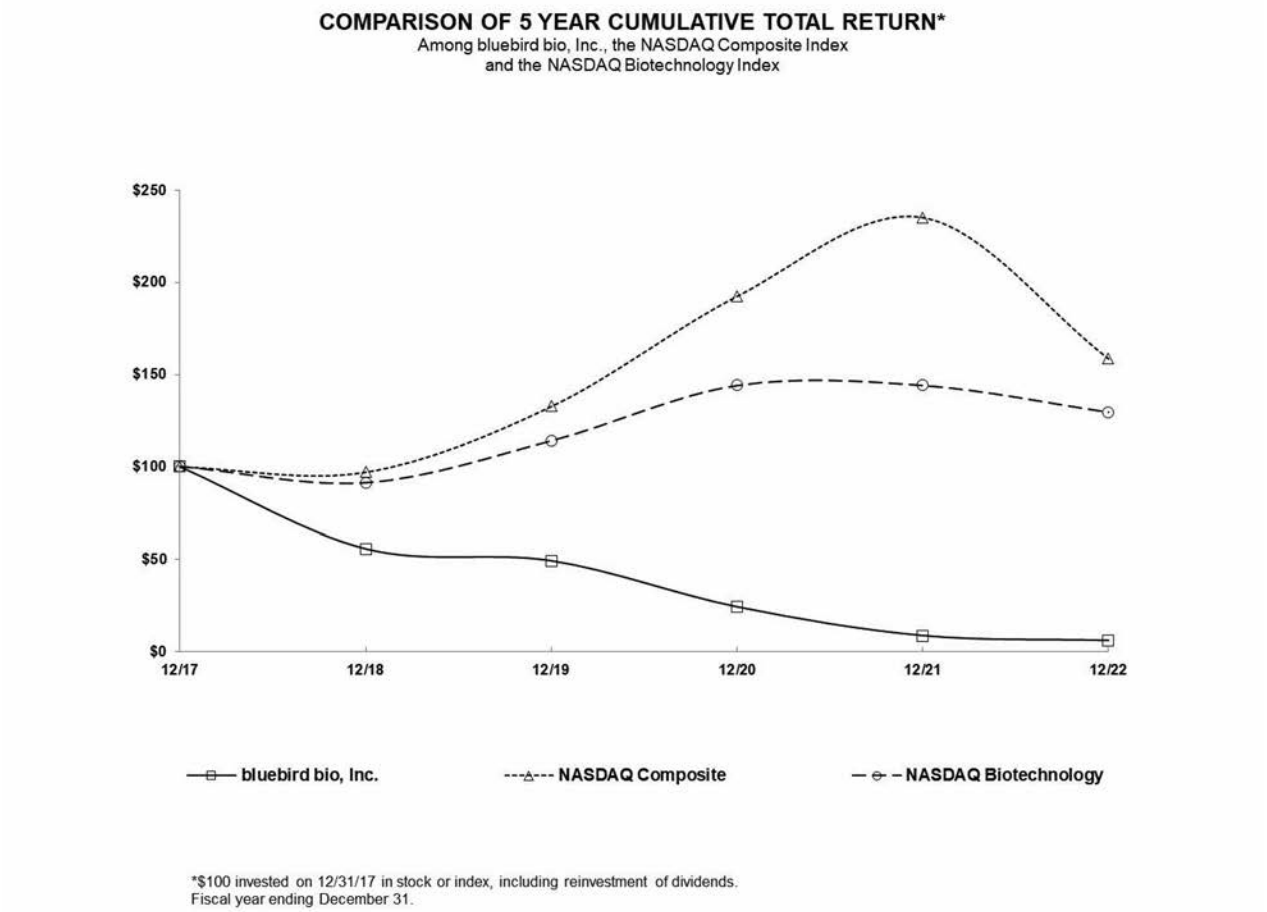
Item 5. Market for Registrant's Common Equity, Related Stockholder Matters and Issuer Purchases of Equity Securities

Our common stock has been traded on the Nasdaq Global Select Market under the symbol "BLUE." On March 27, 2023, the last reported sale price for our common stock on the Nasdaq Global Select Market was $4.51 per share.

Stock Performance Graph

The graph set forth below compares the cumulative total stockholder return on our common stock between December 31, 2017 and December 31, 2022, 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, 2017 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 March 27, 2023, there were approximately 8 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 curative transformative gene therapies for severe genetic diseases based on our lentiviral vector ("LVV") gene addition platform. In 2022, following more than a decade of leadership in research and clinical development, we received approval from the U.S. Food and Drug Administration (the "FDA") for two gene therapies. Both therapies were launched in the fourth quarter of 2022.

On August 17, 2022, ZYNTEGLO (betibeglogene autotemcel, also known as beti-cel), was approved by the FDA for the treatment of adult and pediatric patients with ß-thalassemia who require regular red blood cell transfusions. On September 16, 2022, the FDA granted Accelerated Approval of SKYSONA (elivaldogene autotemcel, also known as eli-cel), to slow the progression of neurologic dysfunction in boys 4-17 years of age with early active cerebral adrenoleukodystrophy ("CALD"). We intend to submit a biologics licensing application ("BLA") to the FDA for our third gene therapy candidate -- lovotibeglogene autotemcel – also known as lovo-cel – requesting priority review of the treatment for patients 12 and older with sickle cell disease ("SCD") with a history of vaso-occlusive-events.

We are focusing our development and commercialization efforts in the U.S. market. We have obtained the withdrawal of the marketing authorization for beti-cel in the European Union, which became effective on March 24, 2022. On November 18, 2021, we obtained the withdrawal of the marketing authorization for eli-cel in the European Union. We withdrew our marketing applications for beti-cel and eli-cel from the 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.

Since our inception in 1992, we have devoted substantially all of our resources to our development and commercialization efforts relating to our products and 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, to market, commercially manufacture and distribute our approved products 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, the sale of two Rare Pediatric Disease Priority Review Vouchers ("PRVs") and through collaborations.

In December 2022, we sold a PRV for aggregate net proceeds of $102.0 million. In January 2023, we sold our second PRV for aggregate net proceeds of $93.0 million. We received the PRVs in August 2022 and September 2022 under a U.S. Food and Drug Administration program intended to encourage the development of treatments for rare pediatric diseases.

In January 2023, we sold 23.0 million shares of common stock (inclusive of shares sold pursuant to an option to the underwriters in connection with the offering) through an underwritten public offering at a price of $6.00 per share for aggregate net proceeds of $131.1 million.

In April 2022, we initiated a comprehensive restructuring plan intended to reduce operating expenses. As part of the restructuring, we reduced our workforce by approximately 30% in the second and third quarters of 2022. See Note 18, Reduction in Workforce, to our consolidated financial statements appearing elsewhere in this Annual Report on Form 10-K for more information on this restructuring plan.

As of December 31, 2022, we had cash, cash equivalents and marketable securities of approximately $181.7 million. We have never been profitable and have incurred net losses in each year since inception. Our net loss from continuing operations was $266.6 million for the year ended December 31, 2022 and our accumulated deficit was $3.99 billion as of December 31, 2022. 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 commercialization of ZYNTEGLO and SKYSONA in the United States;
- seek regulatory approval for lovo-cel and any other product candidates;
- scale our manufacturing capabilities in support of the commercialization of ZYNTEGLO and SKYSONA;
- conduct clinical studies for our clinical program; and
- increase research and development-related activities for 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. We may not be able to generate substantial revenue from the sale of our products, and 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. Until we generate significant revenues from product sales, if ever, we expect to 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.

Business update

We had cash, cash equivalents and marketable securities of approximately $181.7 million as of December 31, 2022. Our expectation is that we will continue to generate operating losses and negative operating cash flows in the foreseeable future as we commercialize ZYNTEGLO and SKYSONA and seek regulatory approval of lovo-cel for SCD and will require the need for additional funding to support our planned operations before becoming profitable.

Although management has concluded that there is substantial doubt regarding our ability to continue as a going concern, this conclusion is based on our analysis under applicable accounting principles. Based on our current business plan, we anticipate our cash, cash equivalents, and marketable securities as of December 31, 2022, along with the $93.0 million net proceeds from the sale of a priority review voucher in January 2023, $131.1 million in net proceeds from a public offering in January 2023, and $45.4 million of restricted cash will be sufficient to fund our operations into the fourth quarter of 2024. Without the release of our restricted cash, however, we estimate our cash, cash equivalents and marketable securities as of December 31, 2022, along with the $93.0 million net proceeds from the sale of a priority review voucher in January 2023 and $131.1 million in net proceeds from a public offering in January 2023, will be sufficient to fund our operations into the second quarter of 2024. We have based these estimates on assumptions of revenues and operating costs that may prove to be wrong. Our restricted cash is currently unavailable for use, and there is no assurance as to when or if our restricted cash will become available for use. Furthermore, pursuant to the terms of certain agreements we have in place, we could be required to further increase our restricted cash due, in part, to recent concerns related to the stability of the banking sector, which would consequently reduce the amount of cash available to fund our operations. In addition, our future net product revenues will depend upon the size of the markets, our ability to obtain regulatory approval of lovo-cel for SCD, our ability to achieve sufficient market acceptance, reimbursement from third-party payers, adequate market share in those markets and the performance of drug product subject to outcome-based programs. As a result, we could deplete our capital resources sooner than we currently expect. If, for any reason, our revenues or our expenses differ materially from our assumptions or we utilize our cash more quickly than anticipated, or if we are unable to obtain funding on a timely basis or access our restricted cash, we may be required to revise our business plan and strategy, which may result in bluebird 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 bluebird 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.

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 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 contract research organizations (“CROs”) and clinical sites that conduct our clinical studies;
- 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; and
- costs associated with our regulatory, quality assurance and quality control operations.

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 to what extent we will generate revenues from the commercialization and sale of our approved products and 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 continue to incur research and development expenses for the foreseeable future as we continue to advance the development of lovo-cel, and conduct research activities for our platform technology. We expect our research and development expenses to decrease in conjunction with an increase in commercial activities and selling, general and administrative expense due to the approvals of ZYNTEGLO and SKYSONA. Our research and development expenses include expenses associated with the following activities:

- for the long-term follow-up protocol associated with the clinical studies of ZYNTEGLO;
- for the long-term follow-up protocol associated with the clinical studies of SKYSONA;
- for the clinical studies of lovo-cel, consisting of HGB-206, HGB-210 study, and the associated long-term follow-up protocol;
- research and development activities for our platform technology; and
- for the manufacture of clinical study materials in support of our clinical 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,		
	2022	2021	2020 [1]
	(in thousands)		
ZYNTEGLO (beti-cel)	$ 43,093	$ 53,292	$ 66,141
lovo-cel (formerly LentiGlobin for SCD)	80,307	64,861	58,862
SKYSONA (eli-cel)	30,979	54,581	48,028
Preclinical programs	7,277	7,252	6,644
Total direct research and development expense	161,656	179,986	179,675
Employee- and contractor-related expenses	29,933	48,297	39,255
Stock-based compensation expense	19,259	42,989	49,766
Laboratory and related expenses	776	5,466	8,956
License and other collaboration expenses	—	—	40
Facility expenses	29,140	41,898	37,377
Other expenses	—	1,310	4,240
Total other research and development expenses	79,108	139,960	139,634
Total research and development expense	$ 240,764	$ 319,946	$ 319,309

(1) 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 continue commercialization activities for ZYNTEGLO and SKYSONA in the United States and perform commercial readiness activities in the United States for lovo-cel, in anticipation of potential approval.

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.

Gain from sale of priority review voucher, net.

Gain from sale of priority review voucher, net consists of gain from sale of priority review voucher. In December 2022, we sold our first PRV for $102.0 million. We received the PRV in August 2022 under a U.S. Food and Drug Administration program intended to encourage the development of treatments for rare pediatric diseases.

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*. In 2022, product revenue represents sales of 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. To date there have been no product sales of ZYNTEGLO or SKYSONA in the U.S. market.

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, 2022 and 2021:

	Year ended December 31,		
	2022	2021	Change
		(in thousands)	
Revenue:			
Product revenue	$ 2,739	$ 2,850	$ (111)
Other revenue	858	812	46
Total revenues	3,597	3,662	(65)
Operating expenses:			
Research and development	240,764	319,946	(79,182)
Selling, general and administrative	136,908	209,969	(73,061)
Cost of product revenue	10,077	38,857	(28,780)
Restructuring expense	4,940	25,801	(20,861)
Total operating expenses	392,689	594,573	(201,884)
Gain from sale of priority review voucher, net	102,000	—	102,000
Loss from operations	(287,092)	(590,911)	303,819
Interest income, net	1,032	879	153
Other income (expense), net	19,599	27,652	(8,053)
Loss before income taxes	(266,461)	(562,380)	295,919
Income tax (expense) benefit	(117)	(258)	141
Net loss from continuing operations	$ (266,578)	$ (562,638)	$ 296,060
Net loss from discontinued operations	$ —	$ (256,740)	$ 256,740
Net loss	$ (266,578)	$ (819,378)	$ 552,800

Revenue. Total revenue was $3.6 million for the year ended December 31, 2022, compared to $3.7 million for the year ended December 31, 2021, and is comprised primarily of product revenue from sales of ZYNTEGLO in Germany.

Research and development expenses. Research and development expenses were $240.8 million for the year ended December 31, 2022, compared to $319.9 million for the year ended December 31, 2021. The decrease of $79.2 million was primarily attributable to the following:

- $58.7 million of decreased net employee compensation, benefit, and other headcount related expenses, including a decrease of $23.7 million in stock-based compensation expense due to an overall decrease in the value of awards, and reduced headcount in 2022;
- $12.0 million of decreased clinical trial costs primarily driven by the completion of certain clinical trials in late 2021;
- $7.7 million of decreased information technology and facility-related costs; and
- $7.5 million of decreased laboratory costs.

These decreased costs were partially offset by $6.8 million of increased manufacturing costs.

Selling, general and administrative expenses. Selling, general and administrative expenses were $136.9 million for the year ended December 31, 2022, compared to $210.0 million for the year ended December 31, 2021. The decrease of $73.1 million was primarily due to the following:

- $75.6 million of decreased employee compensation, benefit, and other headcount related expenses, including a decrease of $39.8 million in stock-based compensation expense due to an overall decrease in the value of awards, and reduced headcount in 2022;
- $9.7 million of decreased costs related to commercial readiness activities due to our decision to focus our efforts on the U.S. market for ZYNTEGLO, SKYSONA, and lovo-cel only;

- $2.1 million of decreased professional service fees; and
- $1.2 million of decreased costs related to medical affairs costs.

These decreased costs were partially offset by $15.6 million of increased costs attributable to information technology and facility-related costs.

Cost of product revenue. Cost of product revenue was $10.1 million for the year ended December 31, 2022, compared to $38.9 million for the year ended December 31, 2021. The decrease is attributable to reserves for excess inventory recognized during the second and third quarter of 2021 as a result of the exit from the European market.

Restructuring expenses. Restructuring expenses were $4.9 million for the year ended December 31, 2022, compared to $25.8 million for the year ended December 31, 2021. The decrease 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 in 2021.

Gain from sale of priority review voucher, net. The increase in gain from sale of priority review voucher, net was related to the sale of a priority review voucher in the fourth quarter of 2022.

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

Other income (expense), net. The change in other income (expense), net was primarily related to the gain recognized on equity securities in 2021, offset by rental income in 2022.

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 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 non-clinical services;
- $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 approximately $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 attributable 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 wind down 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 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, 2022, we had cash, cash equivalents and marketable securities of approximately $181.7 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, 2022, our funds are primarily held in U.S. government agency securities and treasuries, corporate bonds, 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, 2022, we had an accumulated deficit of $3.99 billion. We expect our research and development expenses to decrease in conjunction with an increase in commercial activities and selling, general and administrative expense due to the approvals of ZYNTEGLO and SKYSONA.

Although management has concluded that there is substantial doubt regarding our ability to continue as a going concern, this conclusion is based on our analysis under applicable accounting principles. Based on our current business plan, we anticipate our cash, cash equivalents, and marketable securities as of December 31, 2022, along with the $93.0 million in net proceeds from the sale of a priority review voucher in January 2023, $131.1 million in net proceeds from a public offering in January 2023 and $45.4 million of restricted cash will be sufficient to fund our operations into the fourth quarter of 2024. Without the release of our restricted cash, however, we estimate our cash, cash equivalents and marketable securities as of December 31, 2022, along with the $93.0 million net proceeds from the sale of a priority review voucher in January 2023 and $131.1 million in net proceeds from a public offering in January 2023, will be sufficient to fund our operations into second quarter of 2024. We have based these estimates on assumptions of revenues and operating costs that may prove to be wrong. Our restricted cash is currently unavailable for use, and there is no assurance as to when or if our restricted cash will become available for use. Furthermore, pursuant to the terms of certain agreements we have in place, we could be required to further increase our restricted cash due, in part, to recent concerns related to the stability of the banking sector, which would consequently reduce the amount of cash available to fund our operations. However, we have based this estimate on assumptions of revenues and operating costs that may prove to be wrong. Our future net product revenues will depend upon the size of the markets, our ability to obtain regulatory approval of lovo-cel for SCD, our ability to achieve sufficient market acceptance, reimbursement from third-party payers, adequate market share in those markets and the performance of drug product subject to outcome-based programs. As a result, we could deplete our capital resources sooner than we currently expect. If, for any reason, our revenues or our expenses differ materially from our assumptions or we utilize our cash more quickly than anticipated, or if we are unable to obtain funding on a timely basis we may be required to revise our business plan and strategy, which may result in bluebird 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 bluebird 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.

We have funded our operations principally from the sale of common stock in public offerings, our collaboration with BMS and the sale of the two PRVs. The following is a summary of the financing transactions:

- 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.

- In 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.

- In June 2022, we entered into an Equity Distribution Agreement with Goldman Sachs & Co. LLC ("Goldman") to sell shares of our common stock up to $75.0 million, from time to time, through an “at the market” equity offering program under which Goldman will act as manager. As of December 31, 2022, we sold 10.7 million shares of common stock at-the-market under the Equity Distribution Agreement, resulting in gross proceeds to us of approximately $56.2 million ($54.1 million net of offering costs).

- In December 2022, we sold a PRV for aggregate net proceeds of $102.0 million.

- In January 2023, we sold our second PRV for aggregate net proceeds of $93.0 million.
- In January 2023, we sold 23.0 million shares of common stock (inclusive of shares sold pursuant to an option to the underwriters in connection with the offering) in an underwritten public offering at a price of $6.00 per share for aggregate net proceeds of $131.1 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,		
	2022	2021	2020
	(in thousands)		
Net cash used in operating activities	$ (352,953)	$ (635,639)	$ (470,351)
Net cash provided by (used in) investing activities	250,453	562,557	(84,345)
Net cash (used in) provided by financing activities	54,253	(93,954)	546,715
Decrease in cash, cash equivalents and restricted cash	$ (48,247)	$ (167,036)	$ (7,981)

Operating Activities. The net cash used in operating activities was $353.0 million for the year ended December 31, 2022 and primarily consisted of a net loss of $266.6 million adjusted for non-cash items including a gain from the sale of priority review voucher of $102.0 million, change in net working capital of $39.1 million, stock-based compensation of $35.2 million, the recognition of a reserve for excess inventories of $7.5 million, depreciation and amortization of $5.0 million, other non-cash items of $3.9 million, and unrealized loss on equity securities of $3.1 million.

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.

Discontinued operations contributed net losses of $0.0 million, $256.7 million and $57.6 million for the years ended December 31, 2022, 2021 and 2020, respectively.

Investing Activities. Net cash provided by investing activities for the year ended December 31, 2022 was $250.5 million and was primarily due to proceeds from the maturities of available-for-sale marketable securities of $131.4 million, sale of priority review voucher of $102.0 million, and proceeds from sales of marketable securities of $30.2 million, offset by the purchase of $8.2 million of property, plant and equipment and the capitalization of two FDA approval milestones related to SKYSONA and ZYNTEGLO of $5.0 million.

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.

Financing Activities: Net cash provided by financing activities for the year ended December 31, 2022 was $54.3 million and was primarily due to net cash proceeds from our At The Market ("ATM") equity offering program, net of issuance costs.

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.

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. The lease was modified in July 2022 to reflect the decreased use of the office and lab space. Under the terms of the 60 Binney Street Sublease, we leased 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 July 2022. Beginning in July 2022, due to the modification, we will pay $0.3 million monthly until no later than December 2023. 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 least commenced in April 2022. 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. We made another $7.3 million payment under the Furniture Purchase Agreement upon lease commencement.

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 ("Landlord") for office space located at 455 Grand Union Boulevard in Somerville, Massachusetts to serve as our future corporate 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 are eligible to receive a tenant work allowance of $160 per rentable square foot of the premises. The lease commenced on March 1, 2022, 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. Since the lease commencement date, we have recognized rent expense of $0.3 million monthly.

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.

In August 2022, we entered into another agreement reserving manufacturing capacity with a contract manufacturing organization. We concluded that this agreement contains an embedded operating lease as a controlled environment room at the facility is designated for our exclusive use during the term of the agreement. Under the terms of the agreement, we will utilize an existing deposit with the contract manufacturing organization to cover monthly lease payments through September 2023, with lease prepayments and the deposit equal to $10.8 million. The term of the agreement is 14 months, with the option to extend. The agreement commenced in August 2022 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.

R&D costs are expensed as incurred. These expenses include the costs of our proprietary R&D efforts, as well as costs incurred in connection with certain licensing arrangements. Before a compound receives regulatory approval, we record upfront and milestone payments we make to third parties under licensing arrangements as expense. Upfront payments are recorded when incurred, and milestone payments are recorded when the specific milestone has been achieved. Once a compound receives regulatory approval, we record any milestone payments in Identifiable intangible assets, less accumulated amortization and, unless the asset is determined to have an indefinite life, we typically amortize the payments on a straight-line basis over the remaining agreement term or the expected product life cycle, whichever is shorter.

Based on our development plans as of December 31, 2022, 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, 2022, 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. To date, we have paid €0.5 million pursuant to the terms of such license agreement and we may be obligated to pay up to €1.6 million for future commercial milestones. 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.

- 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 that involve transfusion-dependent β-thalassemia and sickle cell disease therapies, 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 $99.0 million, with $39.5 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, 2022 and 2021, we had cash, cash equivalents and marketable securities of $181.7 million and $396.6 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, 2022, the net fair value of our interest-sensitive marketable securities would have resulted in a hypothetical decline of $0.4 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. Our 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. 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.

Management conducted an evaluation of the effectiveness of our internal control over financial reporting as of December 31, 2022 based on the framework in *Internal Control-Integrated Framework* (2013) issued by the Committee of Sponsoring Organizations of the Treadway Commission (COSO). Based on that evaluation, management has concluded that the Company's internal control over financial reporting was effective as of December 31, 2022.

Attestation Report on Internal Control over Financial Reporting

As a "non-accelerated filer", we are not required to provide an attestation report of our registered public accounting firm on the effectiveness of our internal control over financial reporting.

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 2022 that have materially affected, or are reasonably likely to materially affect, our internal control over financial reporting.

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 2023 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 2023 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 2023 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 2023 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 2023 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.

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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, 2022 and 2021, 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, 2022, 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, 2022 and 2021, and the results of its operations and its cash flows for each of the three years in the period ended December 31, 2022, in conformity with U.S. generally accepted accounting principles.

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 Matter

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 $19.6 million at December 31, 2022.

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 directly 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 29, 2023

bluebird bio, Inc.

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

	As of December 31,	
	2022	2021
Assets		
Current assets:		
Cash and cash equivalents	$ 113,006	$ 161,160
Marketable securities	67,321	138,343
Prepaid expenses	8,374	25,628
Receivables and other current assets	10,787	11,389
Total current assets	199,488	336,520
Marketable securities	1,414	97,114
Property, plant and equipment, net	9,362	9,706
Intangible assets, net	4,868	—
Goodwill	5,646	5,646
Operating lease right-of-use assets	281,996	91,532
Restricted cash and other non-current assets	52,128	53,277
Total assets	$ 554,902	$ 593,795
Liabilities and Stockholders' Equity		
Current liabilities:		
Accounts payable	$ 25,092	$ 25,883
Accrued expenses and other current liabilities	51,985	103,958
Operating lease liability, current portion	51,160	23,152
Total current liabilities	128,237	152,993
Operating lease liability, net of current portion	230,230	66,432
Other non-current liabilities	92	93
Total liabilities	$ 358,559	$ 219,518
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, 2022 and December 31, 2021	$ —	$ —
Common stock, $0.01 par value, 125,000 shares authorized; 82,923 and 71,115 shares issued and outstanding at December 31, 2022 and December 31, 2021, respectively	830	711
Additional paid-in capital	4,186,086	4,096,402
Accumulated other comprehensive loss	(4,070)	(2,911)
Accumulated deficit	(3,986,503)	(3,719,925)
Total stockholders' equity	196,343	374,277
Total liabilities and stockholders' equity	$ 554,902	$ 593,795

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,		
	2022	2021	2020
Revenue:			
Product revenue	$ 2,739	$ 2,850	$ —
Other revenue	858	812	—
Total revenues	3,597	3,662	—
Operating expenses:			
Research and development	240,764	319,946	319,309
Selling, general and administrative	136,908	209,969	239,950
Cost of product revenue	10,077	38,857	—
Restructuring expense	4,940	25,801	—
Total operating expenses	392,689	594,573	559,259
Gain from sale of priority review voucher, net	102,000	—	—
Loss from operations	(287,092)	(590,911)	(559,259)
Interest income, net	1,032	879	5,770
Other income (expense), net	19,599	27,652	(6,881)
Loss before income taxes	(266,461)	(562,380)	(560,370)
Income tax (expense) benefit	(117)	(258)	(686)
Net loss from continuing operations	(266,578)	(562,638)	(561,056)
Net loss from discontinued operations	—	(256,740)	(57,639)
Net loss	$ (266,578)	$ (819,378)	$ (618,695)
Net loss per share from continuing operations—basic and diluted	$ (3.39)	$ (8.16)	$ (9.02)
Net loss per share from discontinued operations—basic and diluted	$ —	$ (3.73)	$ (0.93)
Net loss per share—basic and diluted	$ (3.39)	$ (11.89)	$ (9.95)
Weighted-average number of common shares used in computing net loss per share—basic and diluted	78,585	68,910	62,178
Other comprehensive income (loss):			
Other comprehensive income (loss), net of tax benefit (expense) of $0.0 million, $0.0 million and $0.0 million for the years ended December 31, 2022, 2021 and 2020, respectively	(1,159)	2,364	(3,612)
Total other comprehensive income (loss)	(1,159)	2,364	(3,612)
Comprehensive loss	$ (267,737)	$ (817,014)	$ (622,307)

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, 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
Stock-based compensation	—	—	110,260	—	—	110,260
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
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
Vesting of restricted stock units	979	10	(10)	—	—	—
Exercise of stock options	7	—	16	—	—	16
Purchase of common stock under ESPP	68	1	238	—	—	239
Issuance of common stock for private equity placement	10,742	107	53,960	—	—	54,067
Issuance of unrestricted stock awards to settle accrued employee compensation	12	1	—	—	—	1
Stock-based compensation	—	—	35,480	—	—	35,480
Other comprehensive loss	—	—	—	(1,159)	—	(1,159)
Net loss	—	—	—	—	(266,578)	(266,578)
Balances at December 31, 2022	82,923	$ 830	$ 4,186,086	$ (4,070)	$ (3,986,503)	$ 196,343

See accompanying notes to consolidated financial statements.

bluebird bio, Inc.

Consolidated Statements of Cash Flows
(in thousands)

	Year ended December 31,		
	2022	**2021**	**2020**
Cash flows from operating activities:			
Net loss	$ (266,578)	$ (819,378)	$ (618,695)
Adjustments to reconcile net loss to net cash used in operating activities:			
Change in fair value of contingent consideration	—	387	(6,468)
Depreciation and amortization	5,001	19,649	19,356
Stock-based compensation expense	35,188	127,915	156,631
Gain from sale of priority review voucher	(102,000)	—	—
Unrealized loss (gain) on equity securities	3,135	(29,356)	7,217
Excess inventory reserve	7,519	29,924	—
Other non-cash items	3,904	17,235	458
Changes in operating assets and liabilities:			
Prepaid expenses and other assets	3,260	(5,289)	(10,089)
Inventory	(7,227)	(18,447)	—
Operating lease right-of-use assets	42,706	30,148	21,281
Accounts payable	(920)	9,286	(20,100)
Accrued expenses and other liabilities	(51,228)	40,025	4,835
Operating lease liabilities	(25,713)	(32,142)	(17,380)
Collaboration research advancement	—	(5,596)	(7,397)
Net cash used in operating activities	(352,953)	(635,639)	(470,351)
Cash flows from investing activities:			
Purchase of property, plant and equipment	(8,208)	(14,503)	(28,986)
Purchases of marketable securities	—	(451,391)	(1,003,525)
Proceeds from maturities of marketable securities	131,445	895,333	918,288
Proceeds from sales of marketable securities	30,216	31,318	29,878
Proceeds from sale of Durham, North Carolina manufacturing facility	—	110,300	—
Purchase of intangible assets	(5,000)	(8,500)	—
Proceeds from sale of priority review voucher	102,000	—	—
Net cash provided by (used in) investing activities	250,453	562,557	(84,345)
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	54,237	—	541,536
Proceeds from issuance of common stock and warrants	—	74,975	—
Proceeds from exercise of stock options and ESPP contributions	16	5,355	5,179
Net cash provided by (used in) financing activities	54,253	(93,954)	546,715
Decrease in cash, cash equivalents and restricted cash	(48,247)	(167,036)	(7,981)
Cash, cash equivalents and restricted cash at beginning of year	206,692	373,728	381,709
Cash, cash equivalents and restricted cash at end of year	$ 158,445	$ 206,692	$ 373,728
Reconciliation of cash, cash equivalents and restricted cash:			
Cash and cash equivalents	$ 113,006	$ 161,160	$ 317,705
Restricted cash included in receivables and other current assets	$ 1,502	$ 2,282	$ 1,500
Restricted cash included in restricted cash and other non-current assets	$ 43,937	$ 43,250	$ 54,523
Total cash, cash equivalents and restricted cash	$ 158,445	$ 206,692	$ 373,728
Supplemental cash flow disclosures:			
Purchases of property, plant and equipment included in accounts payable and accrued expenses	$ (3)	$ 411	$ 2,854
Right-of-use assets obtained in exchange for operating lease liabilities	$ 236,003	$ 202,221	$ 19,414
Reduction of right of use asset and associated lease liability due to lease reassessment	$ (2,833)	$ (9,004)	$ —
Issuance of unrestricted stock awards to settle accrued employee compensation	$ —	$ 25,074	$ —
Offering expenses included in accounts payable and accrued expenses	$ 170	$ —	$ —
Cash paid during the period for income taxes	$ 253	$ 617	$ 361

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 Somerville, 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, and commercialization of its approved products, including activities to manufacture product candidates, conduct clinical studies of its product candidates, perform preclinical research to identify new product candidates, provide selling, general and administrative support for these operations and market and commercially manufacture and distribute its approved products.

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.

In April 2022, the Board of Directors of the Company approved a comprehensive restructuring plan intended to reduce operating expenses and enhance the Company's focus on achieving U.S. Food and Drug Administration ("FDA") approval for its programs in the U.S. As part of the restructuring, the Company reduced its workforce by approximately 30% across the second and third quarters of 2022. Refer to Note 18, *Reduction in workforce*, for more information on this restructuring.

In June 2022, the Company entered into an Equity Distribution Agreement (the "Equity Distribution Agreement") with Goldman Sachs & Co. LLC ("Goldman") to sell shares of the Company's common stock up to $75.0 million, from time to time, through an "at the market" equity offering program under which Goldman will act as manager. The Equity Distribution Agreement also provides for the sale of shares to Goldman directly as principal, in which case the Company and Goldman will enter into a separate terms agreement. The Company will pay Goldman a commission equal to up to 3.0% of the gross proceeds of any Common Stock sold through Goldman under the Equity Distribution Agreement. As of December 31, 2022, the Company sold 10.7 million shares of common stock at-the-market under the Equity Distribution Agreement, resulting in gross proceeds to the Company of approximately $56.2 million ($54.1 million net of offering costs). Refer to Note 12, *Equity*, for more information.

The Company's programs in severe genetic diseases include ZYNTEGLO (betibeglogene autotemcel, also known as beti-cel) as a treatment for β-thalassemia; lovotibeglogene autotemcel ("lovo-cel") as a treatment for SCD; and SKYSONA (elivaldogene autotemcel, also known as eli-cel) as a treatment for CALD. On August 17, 2022, ZYNTEGLO was approved by the FDA for the treatment of adult and pediatric patients with ß-thalassemia who require regular red blood cell transfusions. On September 16, 2022, the FDA granted Accelerated Approval of SKYSONA to slow the progression of neurologic dysfunction in boys 4-17 years of age with early active CALD.

In accordance with Accounting Standards Codification ("ASC") 205-40, Going Concern, the Company has evaluated whether there are conditions and events, considered in the aggregate, that raise substantial doubt about the Company's ability to continue as a going concern within one year after the date the financial statements are issued. As of December 31, 2022, the Company had an accumulated deficit of $3.99 billion. During the twelve months ended December 31, 2022, the Company incurred a net loss of $266.6 million and used $353.0 million of cash in operations. As of December 31, 2022, the Company had cash, cash equivalents and marketable securities of $181.7 million.

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 and the release of restricted cash related to the Company's 50 Binney Street sublease 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 maintaining low 2023 spending, including realized savings through the move of the Company's headquarters to Assembly Row in Somerville, Massachusetts, 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 Company will assess on a quarterly basis whether the determination for estimates remain appropriate based on actual data observed. However, the Company has based this estimate on assumptions that may prove to be wrong, and its operating plan may change as a result of many factors currently unknown to it. As a result, the Company could deplete its capital resources sooner than it currently expects. The Company expects to finance its future cash needs through the issuance of equity, or debt, or other alternative means. If the Company is unable to obtain funding on a timely basis, or if revenues from collaboration arrangements or product sales are less than it has projected, the Company may be required to further revise its business plan and strategy, which may result in the Company 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 the Company being unable to expand its operations or otherwise capitalize on its business opportunities. As a result, the Company's business, financial condition and results of operations could be materially affected.

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 Company's consolidated financial statements have been prepared in accordance with accounting principles generally accepted in the United States ("GAAP"). The accompanying consolidated financial statements include the accounts of the Company and its wholly owned or controlled subsidiaries. All intercompany accounts and transactions have been eliminated. 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").

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.

Bank concentration

As a result of volatile market conditions, the cost and availability of capital has been and may continue to be adversely affected by illiquid capital markets. Concern about the stability of the markets generally and the strength of counterparties specifically has led many lenders and institutional investors to reduce, and in some cases, cease to provide credit to businesses and consumers. Continued turbulence in the U.S. and international markets and economies and prolonged declines in business consumer spending may adversely affect our liquidity and financial condition, including our ability to access the capital markets to meet liquidity needs.

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.

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

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, lentiviral vector ("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 a license 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.

In 2022, the Company received approval of ZYNTEGLO and SKYSONA from the FDA. The amount of revenue recognized by the Company is equal to the amount of consideration that is expected to be received from the sale of product to its customers. The Company has Specialty Distributors ("SD") and Specialty Pharmacies ("SP") that deliver product to the Qualified Treatment Centers ("QTC"). Revenue is only recognized when the performance obligation is satisfied. The Company will recognize revenue upon delivery to the SD or SP. To determine whether a significant reversal will occur in future periods, the Company will assess both the likelihood and magnitude of any such potential reversal of revenue.

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. In 2023, the Company ceased further research work and is in the process of winding down such collaboration.

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") and Topic 712, *Compensation - Nonretirement Postemployment Benefits* ("ASC 712"). 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

Not yet adopted

ASU No. 2022-02, Financial Instruments – Credit Losses (Topic 326): Troubled Debt Restructurings and Vintage Disclosures

In March 2022, the FASB issued ASU 2022-02, *Financial Instruments – Credit Losses (Topic 326): Troubled Debt Restructurings and Vintage Disclosures* (“ASU 2022-02”), which eliminates the recognition and measurement guidance on troubled debt restructurings for creditors that have adopted ASC 326 and requires enhanced disclosure of loan modifications for borrowers experiencing financial difficulty. ASU 2022-02 amends the guidance on vintage disclosures to require disclosure of current-period gross write-offs by year of origination. The new standard is effective beginning January 1, 2023. The adoption of ASU 2022-02 is not expected to have a material impact on the Company's financial position or results of operations.

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 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 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.

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. In addition, 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"). As the Company has completed construction of its new office space and recently subleased laboratory space, the Company anticipates that it will be vacating the 60 Binney Street location during 2023.

During the years ended December 31, 2022 and 2021, the Company incurred $8.8 million and $0.7 million, respectively of net expense for transactions with 2seventy bio within research and development and selling, general and administrative expense in the condensed consolidated statements of operations and comprehensive loss, including $4.0 million and $0.8 million, respectively of net expense related to the 60 Binney Street Sublease. As of December 31, 2022, the Company had an immaterial amount of accounts receivable due from and $1.9 million of accounts payable due to 2seventy bio. As of December 31, 2021, the Company had an immaterial amount of accounts receivable and accounts payable due from and due 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 and 2020 (in thousands):

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

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 and 2020 (in thousands):

	Year ended December 31,	
	2021	2020
Operating activities:		
Change in fair value of contingent consideration	$ 387	$ (6,468)
Depreciation and amortization	14,195	13,730
Stock-based compensation expense	29,175	34,036
Loss on fixed assets disposal	569	146
Loss on sale of Durham, North Carolina manufacturing facility	1,986	—
Investing activities:		
Purchase of property, plant and equipment	$ (11,256)	$ (23,159)
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
Right-of-use assets obtained in exchange for operating lease liabilities	151,520	4,989

4. Marketable securities

The following table summarizes the marketable securities held at December 31, 2022 and 2021 (in thousands):

	Amortized cost / cost	Unrealized gains	Unrealized losses	Fair value
December 31, 2022				
U.S. government agency securities and treasuries	$ 67,970	$ —	$ (1,733)	$ 66,237
Corporate bonds	2,524	—	(26)	2,498
Total	$ 70,494	$ —	$ (1,759)	$ 68,735
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

No available-for-sale debt securities held as of December 31, 2022 or 2021 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, 2022 and 2021 (in thousands):

	Total	Quoted prices in active markets (Level 1)	Significant other observable inputs (Level 2)	Significant unobservable inputs (Level 3)
December 31, 2022				
Assets:				
Cash and cash equivalents	$ 113,006	$ 113,006	$ —	$ —
Marketable securities:				
U.S. government agency securities and treasuries	66,237	—	66,237	—
Corporate bonds	2,498	—	2,498	—
Total assets	$ 181,741	$ 113,006	$ 68,735	$ —
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	$ —

Cash and cash equivalents

As of December 31, 2022, 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, 2022 and 2021, 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, 2022 or 2021.

Accrued interest receivable on the Company's available-for-sale debt securities totaled $0.1 million and $0.3 million as of December 31, 2022 and 2021, respectively. No accrued interest receivable was written off during the twelve months ended December 31, 2022 or 2021.

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, 2022 and 2021 (in thousands):

Description	Less than 12 months		12 months or greater		Total	
	Fair value	Unrealized losses	Fair value	Unrealized losses	Fair value	Unrealized losses
December 31, 2022						
U.S. government agency securities and treasuries	$ —	$ —	$ 66,237	$ (1,733)	$ 66,237	$ (1,733)
Corporate bonds	—	—	2,498	(26)	2,498	(26)
Total	$ —	$ —	$ 68,735	$ (1,759)	$ 68,735	$ (1,759)
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)

The Company determined that there was no material change in the credit risk of the above investments during the twelve months ended December 31, 2022. As such, an allowance for credit losses was not recognized. As of December 31, 2022, 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 $0.0 million and $3.7 million at December 31, 2022 and 2021, 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. In May 2022, the Company sold the remainder of its equity securities for proceeds of $0.6 million. The Company recorded losses of $3.1 million, gains of $29.4 million and losses of $7.2 million related to its equity securities during the years ended December 31, 2022, 2021 and 2020, 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

During the year ended December 31, 2022, and 2021, the Company recorded a reserve for excess inventories of $7.5 million, and $29.9 million, respectively, which is included within cost of product revenue in the consolidated statements of operations and comprehensive loss. Following the product approvals by the FDA in the third quarter of 2022, any inventory produced after that date will be capitalized going forward.

7. Property, plant and equipment, net

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

	As of December 31,	
	2022	2021
Laboratory equipment	$ 25,092	$ 29,061
Computer equipment and software	1,854	421
Office equipment	4,348	117
Leasehold improvements	—	12
Construction-in-progress	—	501
Total property, plant and equipment	31,294	30,112
Less accumulated depreciation and amortization	(21,932)	(20,406)
Property, plant and equipment, net	$ 9,362	$ 9,706

Depreciation and amortization expense related to property, plant and equipment was $4.9 million, $4.9 million, and $5.1 million for the years ended December 31, 2022, 2021, and 2020, respectively.

8. Restricted cash

As of December 31, 2022 and 2021, the Company maintained letters of credit of $43.9 million and $43.2 million, respectively, which are collateralized with bank accounts at financial institutions in accordance with the agreements. Total restricted cash as of December 31, 2022 and 2021 consisted of the following (in thousands):

	As of December 31,	
	2022	2021
50 Binney Street lease	$ 40,072	$ 40,072
Assembly Row lease	2,753	2,753
Other	2,614	2,675
Total restricted cash	$ 45,439	$ 45,500

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,	
	2022	2021
Employee compensation	$ 20,095	$ 41,095
Accrued goods and services	8,134	24,273
Accrued clinical and contract research organization costs	12,368	17,769
Accrued manufacturing costs	7,199	15,722
Accrued professional fees	1,939	1,665
Deferred revenue, current portion	1,502	2,282
Other	748	1,152
Total accrued expenses and other current liabilities	$ 51,985	$ 103,958

Accrued employee compensation includes severance costs associated with the Company's orderly wind down of its European operations. As of December 31, 2022 and 2021, the Company had accrued expenses of $0.0 million and $4.7 million, respectively, related to these restructuring costs. Please refer to Note 18, *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 the later of (i) the date that the Company has completely vacated the premises and (ii) the date that 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. The lease was modified on July 28, 2022, to reflect the decreased use of the office and lab space. Under the terms of the 60 Binney Street Sublease, the Company leased 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 June 2022. Beginning in July 2022, due to the modification, the Company will pay $0.3 million monthly until no later than December 2023. 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 commenced in April 2022 and lease payments began in July 2022. The lease term will end on December 31, 2030, unless other specific circumstances specified in the 50 Binney Street Sublease occur.

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.

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 made another $7.3 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 $7.3 million deposit related to the Furniture Purchase Agreement paid in 2022. The fair value of the furniture is $2.4 million, and the remaining excess of the $7.3 million payment over fair value will be recognized as expense over the life of the lease. The Company recognizes monthly sublease income of $2.3 million in Other Income for the sub-subleased space.

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 is eligible for a tenant work allowance of $160 per rentable square foot of the premises. The lease commenced on March 1, 2022, 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. Since the lease commencement date, the Company has recognized rent expense of $0.3 million monthly.

Hood Park lease

In October 2022, the Company entered into a sublease with Finch Therapeutics, Inc. ("Finch") for office and laboratory space at Finch's corporate headquarters located at 100 Hood Park Drive, Charlestown, Massachusetts which Finch leases from Hood Park, LLC. Under the terms of the arrangement, the Company will lease 42,261 square feet for $55 per square foot, subject to annual increases of 3.0%, plus operating expenses and taxes. This sublease commenced December 15, 2022, the date on which the Landlord tenders possession of the premises to the Company, and is expected to terminate on December 14, 2025. The Company has recognized rent expense of $0.1 million for 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 paid 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. The lease is terminated as of December 31, 2022.

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.

In August 2022, the Company entered into an agreement reserving manufacturing capacity with a contract manufacturing organization. The Company concluded that this agreement contains an embedded operating lease as a controlled environment room at the facility is designated for the Company's exclusive use during the term of the agreement. Under the terms of the agreement, the Company will utilize an existing deposit with the contract manufacturing organization to cover monthly lease payments through September 2023, with lease prepayments and the deposit equal to $10.8 million. The term of the agreement is

14 months, with the option to extend. The Company recorded a right-of-use asset for this operating lease upon lease commencement in August 2022 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, 2022 and 2021 (in thousands):

	For the year ended December 31,		
	2022	2021 [2]	2020 [2]
Lease cost [1]			
Operating lease cost	$ 56,100	$ 25,067	$ 18,660
Total lease cost	$ 56,100	$ 25,067	$ 18,660
Other information			
Operating cash flows used for operating leases	$ 51,376	$ 22,805	$ 17,780
Weighted average remaining lease term	7.2 years	4.7 years	6.3 years
Weighted average discount rate	6.54 %	5.02 %	5.98 %

[1] Short-term lease costs and variable lease costs incurred by the Company for the twelve months ended December 31, 2022, 2021 and 2020 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 $58.6 million, $36.2 million, and $24.2 million for the years ended December 31, 2022, 2021 and 2020, respectively.

As of December 31, 2022, 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, 2022
2023	$ 52,311
2024	50,062
2025	48,743
2026	41,281
2027	40,805
2028 and thereafter	119,220
Total lease payments	352,422
Less: imputed interest	(71,032)
Total operating lease liabilities	$ 281,390

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, 2022, 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
2023	$ 39,484
2024	34,759
2025 and thereafter	24,780
Total purchase commitments	$ 99,023

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, 2022 and 2021, the Company had 82.9 million and 71.1 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.

In June 2022, the Company entered into the Equity Distribution Agreement with Goldman to sell shares of the Company's common stock, with aggregate gross sales proceeds of up to $75.0 million, from time to time, through an "at the market" equity offering program under which Goldman will act as manager. The Equity Distribution Agreement also provides for the sale of shares to Goldman directly as principal, in which case the Company and Goldman will enter into a separate term agreement.

Under the Equity Distribution Agreement, the Company will set the parameters for the sale of shares, including any price, time or size limits or other customary parameters or conditions. The Company intends to sell shares pursuant to the Equity Distribution Agreement from time to time in varying amounts, which may be limited, based upon factors including (among others) market conditions, trading liquidity, the trading price of the Company's common stock, and determinations by the Company of its need for, and appropriate sources of, additional capital. Subject to the terms and conditions of the Equity Distribution Agreement, Goldman may sell the shares by any method permitted by law, including without limitation (i) by means of ordinary brokers' transactions (whether or not solicited), (ii) to or through a market maker, (iii) directly on or through any national securities exchange or facility thereof, a trading facility of a national securities association, an alternative trading system, or any other market venue, (iv) in the over-the-counter market, (v) in privately negotiated transactions, or (vi) through a combination of any such methods. The Company will pay Goldman a commission equal to up to 3.0% of the gross proceeds of any common stock sold through Goldman under the Equity Distribution Agreement, and also has provided Goldman with customary representations, warranties, covenants and indemnification rights. The Equity Distribution Agreement may be terminated by the Company upon written notice to Goldman or by Goldman upon written notice to the Company. In the case of any purchase of shares by Goldman directly as principal pursuant to a Terms Agreement, such Terms Agreement may be terminated by Goldman upon notice to the Company under certain circumstances, including but not limited to the occurrence of a material adverse effect in the Company. For the year ended December 31, 2022, the Company sold 10.7 million shares of common stock for gross proceeds of $56.2 million ($54.1 million net of offering costs). On February 18, 2023, the shelf registration statement on Form S-3 pursuant to which sales under the Equity Distribution Agreement were made expired and there are no longer shares available for the "at the market" equity offering.

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, 2022 and 2021, 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,	
	2022	2021
Options to purchase common stock [(1)]	4,429	5,534
Restricted stock units [(1)]	2,524	3,427
2013 Stock Option and Incentive Plan	6,538	2,250
Pre-funded warrants	2,273	2,273
2013 Employee Stock Purchase Plan	1,279	1,347
	17,043	14,831

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

Subsequent events

On January 18, 2023, the Company entered into an underwriting agreement (the "Underwriting Agreement") with Goldman Sachs & Co. LLC and J.P. Morgan Securities LLC, in connection with the public offering, issuance and sale by the Company of 20,000,000 shares of the Company's common stock, $0.01 par value per share, at a public offering price of $6.00 per share, less underwriting discounts and commissions, pursuant to an effective shelf registration statement on Form S-3 and a related prospectus supplement filed with the Securities and Exchange Commission. Under the terms of the Underwriting Agreement, the Company also granted the underwriters an option exercisable for 30 days to purchase up to an additional 3,000,000 shares of Common Stock at the public offering price, less underwriting discounts and commissions, which option the underwriters exercised in full. The offering closed on January 23, 2023. The Company received aggregate net proceeds of $131.1 million.

13. Sale of Priority Review Voucher

On November 29, 2022, the Company entered into an asset purchase agreement with argenx BV ("argenx"), pursuant to which the Company agreed to sell a Rare Pediatric Disease Priority Review Voucher ("PRV") to argenx. The Company was awarded the voucher under an FDA program intended to encourage the development of certain rare pediatric disease product applications. The Company received the PRV when SKYSONA received accelerated approval by the FDA for the treatment of early, active cerebral adrenoleukodystrophy. Pursuant to the agreement, argenx agreed to pay the Company $102 million, payable in cash, upon the closing of the sale. The Company received cash payment of $102 million upon closing on December 29, 2022, and there were no transaction costs associated with the sale.

Subsequent events

On January 5, 2023, the Company entered into an asset purchase agreement with Bristol-Myers Squibb Company ("BMS"), pursuant to which the Company agreed to sell a PRV to BMS. The Company was awarded the voucher under the FDA program described above. The Company received the PRV when ZYNTEGLO was approved by the FDA for the treatment of ß-thalassemia in adult and pediatric patients who require regular red blood cell transfusions. Pursuant to the agreement, BMS agreed to pay the Company $95 million, payable in cash, upon the closing of the sale, which occurred simultaneously with the parties entering into the agreement. The Company received cash of $95 million and recognized $2 million in transaction costs.

14. Intangible assets

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

	As of December 31, 2022			
	Cost	Accumulated amortization	Impairment	Net
In-licensed rights	5,000	(132)	—	4,868
Total	$ 5,000	$ (132)	$ —	$ 4,868

	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)	$ —

Amortization expense for intangible assets was $0.1 million, $0.4 million, and $0.5 million for the years ended December 31, 2022, 2021 and 2020, 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.

In-licensed rights

In-licensed rights consist of capitalized milestone payments made to third parties upon receiving regulatory approval of ZYNTEGLO and SKYSONA in the U.S. The in-licensed rights are being amortized on a straight-line bases over the remaining life of the product exclusivity period in the U.S. of approximately twelve years, as the life of the product exclusivity reflects the expected time period that the Company will benefit from the in-licensed rights.

The following table summarizes the estimated future amortization for intangible assets for the next five years and thereafter (in thousands):

	As of December 31, 2022
2023	$ 417
2024	417
2025	417
2026	417
2027	417
2028 and thereafter	$ 2,783
Total	$ 4,868

15. Stock-based compensation

2013 Stock Option and Incentive Plan

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 replaced 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 approximately 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 2022 and January 2023, the number of common stock available for issuance under the 2013 Plan was increased by approximately 2.8 million and 3.3 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 remained 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. The 2013 Plan will expire in 2023 and the Company will need to adopt a new plan subject to shareholder approval. As of December 31, 2022, the total number of common stock that may be issued under all plans is 6.5 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 $35.2 million, $98.7 million, and $122.6 million during the years ended December 31, 2022, 2021 and 2020, respectively. Stock-based compensation expense recognized by award type is as follows (in thousands):

	Year ended December 31,		
	2022	2021	2020
Stock options	$ 14,211	$ 54,660	$ 75,837
Restricted stock units	20,193	30,767	38,123
Employee stock purchase plan and other	784	13,313	8,636
	$ 35,188	$ 98,740	$ 122,596

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,		
	2022	2021	2020
Research and development	$ 19,259	$ 42,989	$ 49,766
Selling, general and administrative	15,929	55,751	72,830
	$ 35,188	$ 98,740	$ 122,596

Stock-based compensation of $0.3 million was capitalized into inventory during the year ended December 31, 2022. At December 31, 2022 the balance of stock-based compensation in inventory was $0 as inventory is fully reserved. Stock-based compensation of $1.0 million was capitalized into inventory during the year ended December 31, 2021.

As of December 31, 2022, the Company had $9.7 million and $19.9 million of unrecognized compensation expense related to unvested stock options and restricted stock units (exclusive of those with both service and performance conditions that have not yet been achieved), respectively, that is expected to be recognized over a weighted-average period of 2.93 years and 3.00 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,		
	2022	2021	2020
Expected volatility	66.4 %	66.7 %	69.5 %
Expected term (in years)	6.0	6.0	6.0
Risk-free interest rate	1.9 %	0.8 %	1.4 %
Expected dividend yield	0.0 %	0.0 %	0.0 %

The following table summarizes the stock option activity under the Company's equity awards plans excluding awards held by employees of 2seventy bio:

	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, 2021	3,586	$ 39.23		
Granted	1,194	$ 7.37		
Exercised	(7)	$ 2.22		
Canceled or forfeited	(2,105)	$ 41.52		
Outstanding at December 31, 2022	2,668	$ 24.38	7.9	$ 294
Exercisable at December 31, 2022	1,123	$ 42.00	6.4	$ 11
Vested and expected to vest at December 31, 2022	2,668	$ 24.38	7.9	$ 294

(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, 2022.

The weighted-average fair values of options granted during the years ended December 31, 2022, 2021 and 2020 was $4.46, $16.32, and $43.24, respectively. The intrinsic value of options exercised during the years ended December 31, 2022, 2021 and 2020 was $0.0 million, $5.1 million and $4.0 million, respectively.

Restricted stock units

The following table summarizes the restricted stock unit activity under the Company's equity award plans excluding awards held by employees of 2seventy bio:

	Shares (in thousands)	Weighted-average grant date fair value
Unvested balance at December 31, 2021	3,193	$ 16.21
Granted	1,712	7.38
Vested	(887)	15.83
Forfeited	(1,603)	12.24
Unvested balance at December 31, 2022	2,415	$ 11.44

The intrinsic value of restricted stock units, including shares held by employees of 2seventy bio, vested during the years ended December 31, 2022, 2021 and 2020 was $6.0 million, $44.0 million and $30.9 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 approximately 1.4 million shares of the Company's common stock available to participating employees. During each of the years ended December 31, 2022 and 2021, approximately 0.1 million shares of common stock were issued under the 2013 ESPP.

16. 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 2023, the Company expects to make matching contributions of approximately $1.9 million related to employee contributions made during 2022. The match contribution is included in accrued expenses and other current liabilities as of December 31, 2022 and 2021. Expense related to the 401(k) Plan from continuing operations totaled $2.7 million, $2.8 million, $3.0 million for the years ended December 31, 2022, 2021, and 2020, respectively.

17. Income taxes

The components of loss before income taxes were as follows (in thousands):

	Year ended December 31,		
	2022	2021	2020
U.S.	$ (266,396)	$ (487,404)	$ (431,452)
Foreign	(65)	(74,976)	(128,918)
Total	$ (266,461)	$ (562,380)	$ (560,370)

The provision for (benefit from) income taxes were as follows (in thousands):

	Year ended December 31,		
	2022	2021	2020
Current:			
Federal	$ —	$ —	$ —
State	—	—	2
Foreign	117	258	684
Deferred:			
Federal	—	—	—
State	—	—	—
Foreign	—	—	—
Total income tax expense (benefit)	$ 117	$ 258	$ 686

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,		
	2022	2021	2020
Federal income tax expense at statutory rate	21.0 %	21.0 %	21.0 %
State income tax, net of federal benefit	5.0 %	3.9 %	3.1 %
Permanent differences	(0.1)%	(0.6)%	(0.6)%
Stock-based compensation	(6.2)%	(3.1)%	(2.4)%
Research and development credit	7.9 %	4.3 %	6.0 %
Foreign differential	0.3 %	(1.9)%	(4.6)%
Other	(1.0)%	— %	(0.3)%
Change in valuation allowance	(26.9)%	(23.6)%	(22.3)%
Effective income tax rate (expense) benefit	— %	— %	(0.1)%

For the years ended December 31, 2022, 2021 and 2020, the Company recognized an income tax expense (benefit) of $0.1 million or 0.0%, $0.3 million or 0.0%, and $0.7 million or (0.1)%, respectively. The Company did not recognize any significant tax expense for the years ended December 31, 2022, 2021, or 2020 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 or 2020 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,	
	2022	2021
Deferred tax assets:		
U.S. net operating loss carryforwards (federal and state)	$ 710,828	$ 703,125
Tax credit carryforwards (federal and state)	302,273	281,687
Capitalized license fees and research and development expenses	1,805	2,237
Capitalized research and development expenses under Section 174	51,510	—
Deferred revenue	394	604
Stock-based compensation	15,981	25,181
Lease liabilities	73,764	22,916
Accruals and other	16,161	15,598
Total deferred tax assets	1,172,716	1,051,348
Right-of-use assets	(72,088)	(23,053)
Fixed assets	(1,990)	(1,546)
Less valuation allowance	(1,098,638)	(1,026,749)
Net deferred taxes	$ —	$ —

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 $71.9 million during the year ended December 31, 2022 due primarily to the capitalization of research and development credits that became effective in the 2022 tax year under the Tax Cuts and Jobs Act, net operating losses, and tax credit carryforwards. 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, 2022, 2021 and 2020, the Company had U.S. federal net operating loss carryforwards of approximately $2.66 billion, $2.63 billion, and $2.03 billion, respectively, which may be available to offset future income tax liabilities. Of the amount as of December 31, 2022, $1.95 billion will carryforward indefinitely while $711.0 million will expire at various dates through 2037. As of December 31, 2022, 2021 and 2020, the Company also had U.S. state net operating loss carryforwards of approximately $2.41 billion, $2.39 billion, and $1.89 billion, respectively, which may be available to offset future income tax liabilities and expire at various dates through 2042.

As of December 31, 2022, 2021 and 2020, the Company had federal research and development and orphan drug tax credit carryforwards of approximately $287.8 million, $268.3 million, and $235.3 million, respectively, available to reduce future tax liabilities which expire at various dates through 2042. As of December 31, 2022, 2021 and 2020, the Company had state credit carryforwards of approximately $18.3 million, $16.9 million, and $14.5 million, respectively, available to reduce future tax liabilities which expire at various dates through 2037. 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 years 2018 through 2022. As of December 31, 2022, 2021 and 2020, the Company had capital loss carryforwards of approximately $4.2 million, $0.00 million , and $0.00 million, respectively, which may be available to offset future capital gains and will begin to expire in 2027.

In March 2020, the Coronavirus Aid, Relief and Economic Security Act ("CARES Act") was enacted. In December 2020, the Consolidated Appropriations Act was enacted. 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. In August 2022, the Inflation Reduction Act ("IRA") was enacted and introduced a 15% corporate alternative minimum tax ("CAMT") for corporations with average annual adjusted financial statement income for any three-year tax period ending after December 31, 2021 and preceding tax year exceeding $1 billion, effective for tax years beginning after December 31, 2021, as well as a 1% excise tax on stock repurchases made by public companies, climate and energy provisions, and extensions to the Affordable Care Act subsidies. The Company has concluded that the provisions in the CARES Act, Consolidated Appropriations Act, ARPA, and IRA 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, 2019 through December 31, 2021. 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, 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
Increases (decreases) for tax positions related to current period	1,748
Increases (decreases) for tax positions related to prior periods	(46)
Balance as of December 31, 2022	23,662

The unrecognized tax benefits at December 31, 2022, 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, 2022, 2021 and 2020, the Company's accrued interest and penalties related to uncertain tax positions were not material.

18. Reduction in workforce

In April 2022, the Board of Directors of the Company approved a comprehensive restructuring plan intended to reduce operating expenses. As part of the restructuring, the Company reduced its workforce by approximately 30% across the second and third quarters of 2022. The Company incurred approximately $4.9 million in costs to implement the restructuring, comprised primarily of severance payments and continuing health care coverage over the severance period. The restructuring actions associated with these charges commenced in April 2022, and were completed by September 30, 2022.

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. 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 following tables summarizes the accrued liabilities activity recorded in connection with the reduction in workforce for the year ended December 31, 2022 and 2021 (in thousands):

	Restructuring Expenses in 2021	Amounts paid in 2021	Amounts accrued at December 31, 2021	Restructuring Expenses in 2022	Amounts paid in 2022	Amounts accrued at December 31, 2022
April 2021 reduction	4,625	(4,625)	—	—	—	—
July 2021 reduction	21,176	(16,503)	4,673	—	(4,673)	—
April 2022 reduction	—	—	—	4,940	(4,940)	—
Total	25,801	(21,128)	4,673	4,940	(9,613)	—

The Company recorded approximately $4.9 million and $25.8 million in restructuring expenses as of December 31, 2022 and 2021, respectively.

19. 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,		
	2022	2021	2020
Outstanding stock options [(1)]	4,429	5,534	6,262
Restricted stock units [(1)]	2,524	3,427	1,495
ESPP shares and other	63	—	326
	7,016	8,961	8,083

[(1)] Outstanding stock options and restricted stock units include awards outstanding to employees of 2seventy bio.

Net loss per share for the years ended December, 31, 2022, 2021, and 2020 were $3.39, $11.89, and $9.95, respectively.

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
2.2**	Asset Purchase Agreement, dated as of November 29, 2022, by and between bluebird bio, Inc. and argenx BV	8-K	001-35966	2.1	November 30, 2022
2.3**	Asset Purchase Agreement, dated as of January 5, 2023, by and between bluebird bio, Inc. and Bristol-Myers Squibb Company	8-K	001-35966	2.1	January 6, 2023
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

Exhibit Number	Exhibit Title	Incorporated by Reference			
		Form	File no.	Exhibit	Filing Date
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
10.18††	Amendment No. 2 to Clinical and Commercial Supply Agreement Viral Vector Product by and between the Registrant 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 the Registrant and SAFC Carlsbad, Inc.	10-K	001-35966	10.28	February 23, 2021
10.20	Amendment No. 4 to Clinical and Commercial Supply Agreement Viral Vector Product by and between the Registrant and SAFC Carlsbad, Inc.	10-Q	001-35966	10.1	August 4, 2022
10.21	Amendment No. 5 to Clinical and Commercial Supply Agreement Viral Vector Product by and between the Registrant and SAFC Carlsbad, Inc.	10-Q	001-35966	10.1	November 7, 2022
10.22††	Master Manufacturing Services Agreement, dated June 3, 2016, by and between the Registrant and Lonza Houston, Inc.	—	—	—	Filed herewith
10.23††	Amendment to Master Manufacturing Services Agreement, dated October 23, 2017, by and between the Registrant and Lonza Houston, Inc.	—	—	—	Filed herewith
10.24#	Employment Agreement, dated February 3, 2014, by and between the Registrant and Jason F. Cole	10-Q	001-35966	10.18	May 13, 2014
10.25#	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
10.26#	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
10.27#	Separation Agreement, dated September 12, 2022, by and between bluebird bio, Inc. and Jason F. Cole	10-Q	001-35966	10.3	November 7, 2022
10.28*#	Consulting Agreement, dated September 12, 2022, by and between bluebird bio, Inc. and Jason F. Cole	10-Q	001-35966	10.4	November 7, 2022
10.29#†	Consulting Agreement, dated May 26, 2022, by and between bluebird bio, Inc. and Danforth Advisors, LLC, as amended	10-Q	001-35966	10.5	November 7, 2022
10.30#	Employment Agreement, dated January 7, 2021, by and between the Registrant and Andrew Obenshain	10-K	001-35966	10.23	March 4, 2022
10.31#	Employment Agreement, dated June 1, 2021, by and between the Registrant and Gina Consylman	10-K	001-35966	10.24	March 4, 2022
10.32#	Employment Agreement, dated April 20, 2021, by and between the Registrant and Thomas Klima	10-K	001-35966	10.25	March 4, 2022
10.33#	Employment Agreement, dated June 14, 2021, by and between the Registrant and Anne-Virginie Eggimann	10-K	001-35966	10.26	March 4, 2022
10.34#	Offer Letter, dated October 1, 2019, by and between the Registrant and Jessica Whitten	10-K	001-35966	10.27	March 4, 2022
10.35#	Employment Agreement, dated October 17, 2022, by and between the Registrant and Christopher Krawtschuk	8-K	001-35966	10.1	November 7, 2022
10.36#	Employment Agreement, dated October 31, 2022, by and between the Registrant and Richard Colvin	—	—	—	Filed herewith
10.37#	Employment Agreement, dated January 1, 2023, by and between the Registrant and Joseph Vittiglio	—	—	—	Filed herewith
10.38#	2013 Employee Stock Purchase Plan	S-1/A	333-188605	10.17	June 4, 2013
10.39#	First Amendment of the Bluebird Bio, Inc. 2013 Employee Stock Purchase Plan	10-K	001-35966	10.38	February 21, 2018

Exhibit Number	Exhibit Title	Incorporated by Reference			
		Form	File no.	Exhibit	Filing Date
10.40#	Second Amendment of the Bluebird Bio, Inc. 2013 Employee Stock Purchase Plan	S-8	333-257135	99.1	June 15, 2021
10.41#	2021 Inducement Plan and forms of award agreements thereunder	S-8	333-257135	99.2	June 15, 2021
10.42#	First Amendment to the bluebird bio, Inc. 2021 Inducement Plan	S-8	333-257135	99.3	March 4, 2022
10.43#	Executive Cash Incentive Bonus Plan	S-1	333-188605	10.18	May 14, 2013
10.44#	Non-Employee Director Compensation Policy	—	—	—	Filed herewith
10.45††	Sublease, dated April 16, 2019, by and between the Registrant and Aventis Inc.	10-Q	001-35966	10.42	August 1, 2019
10.46	Amendment to Sublease, dated April 19, 2019, by and between the Registrant and Aventis Inc.	10-Q	001-35966	10.43	August 1, 2019
10.47*	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
10.48*	Sub-sublease Agreement, by and between the Registrant and Meta Platforms, Inc.	10-K	001-35966	10.36	March 4, 2022
10.49*	Sublease, dated October 31, 2022, by and between Finch Therapeutics, Inc. and bluebird bio, Inc.	10-Q	001-35966	10.6	November 7, 2022
10.50††*	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
10.51	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
10.52	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
10.53*	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
10.54*	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
10.55*	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
10.56*	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
10.57*	Amendment to the Transition Services Agreement, by and between 2seventy bio, Inc. and the Registrant	10-Q	001-35966	10.2	August 4, 2022
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

Exhibit Number	Exhibit Title	Incorporated by Reference			
		Form	File no.	Exhibit	Filing Date
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.

** Exhibits have been omitted pursuant to Item 601(a)(5) of Regulation S-K. The Registrant will furnish copies of any such 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 Christopher Krawtschuk, 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 29, 2023
/s/ Christopher Krawtschuk Christopher Krawtschuk	Chief Financial Officer *(Principal Financial Officer, Principal Accounting Officer and Duly Authorized Officer)*	March 29, 2023
/s/ Mark Vachon Mark Vachon	Director	March 29, 2023
/s/ John O. Agwunobi, M.D. John O. Agwunobi, M.D.	Director	March 29, 2023
/s/ Charlotte Jones-Burton, M.D. Charlotte Jones-Burton, M.D.	Director	March 29, 2023
/s/ Lis Leiderman, M.D. Lis Leiderman, M.D.	Director	March 29, 2023
/s/ Nick Leschly Nick Leschly	Director	March 29, 2023
/s/ Najoh Tita-Reid Najoh Tita-Reid	Director	March 29, 2023

CORPORATE AND STOCKHOLDER INFORMATION

Board of Directors

Mark Vachon [1, 2]
Chairman – Independent
Formerly of GE

John O. Agwunobi, MD [1, 3]
Former 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, Atsena Therapeutics

Nick Leschly
Chief Kairos Officer, 2seventy bio

Andrew Obenshain
Chief Executive Officer, bluebird bio

Richard Paulson
President and Chief Executive Officer, Karyopharm Therapeutics

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

Richard A. Colvin, PhD, MD
Chief Medical Officer

Thomas J. Klima
Chief Commercial and Operating Officer

Andrew Obenshain
President and Chief Executive Officer

Joseph Vittiglio
Chief Legal and Business Officer

Independent Registered Public Accounting Firm

Ernst & Young LLP
200 Clarendon Street
Boston, MA 02116
www.ey.com

Annual Meeting of Stockholders

The 2023 Annual Meeting of Stockholders will be held on June 16, 2023, 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