Global Blood Therapeutics, Inc.
Form 10-K
February 27, 2019
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UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

Form 10-K

(Mark One)

ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934
For the fiscal year ended December 31, 2018

Or

TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934
For the transition period from to .

Commission file number: 001-37539

Global Blood Therapeutics, Inc.

(Exact name of registrant as specified in its charter)

Delaware	**27-4825712**
(State of other jurisdiction of incorporation or organization)	**(I.R.S. Employer Identification No.)**
171 Oyster Point Boulevard, Suite 300	
South San Francisco, California	**94080**
(Address of principal executive offices)	**(Zip Code)**

Registrant s telephone number, including area code: (650) 741-7700

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

Title of Each Class	Name of Each Exchange on Which Registered
Common Stock, $.001 par value	The NASDAQ Global Select Market

Securities registered under Section 12(g) of the Act:

None

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

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

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

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

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K (§ 229.405 of this chapter) is not contained herein, and will not be contained, to the best of registrant s knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K.

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

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

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

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

The aggregate market value of the common stock held by non-affiliates of the registrant was approximately $2,286,912,803 as of June 30, 2018 based upon the closing sale price on the NASDAQ Global Select Market reported for such date. Shares of common stock held by each executive officer and director and certain holders of more than 10% of the outstanding shares of the registrant s common stock have been excluded in that such persons may be deemed to be affiliates of the registrant. Shares of common stock held by other persons, including certain other holders of more than 10% of the outstanding shares of common stock, have not been excluded in that such persons are not deemed to be affiliates. This determination of affiliate status is not necessarily a conclusive determination for other purposes.

As of February 22, 2019, the registrant had 56,322,257 shares of common stock, par value $0.001, outstanding.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant s definitive Proxy Statement for the registrant s 2019 Annual Meeting of Stockholders, to be filed subsequent to the date hereof with the Securities and Exchange Commission (SEC), are incorporated by reference into Part III of this report. Such proxy statement will be filed with the SEC not later than 120 days after the end of the registrant s fiscal year ended December 31, 2018.

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CAUTIONARY NOTE REGARDING FORWARD-LOOKING STATEMENTS

Statements made in this Annual Report on Form 10-K that are not statements of historical information are forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended and Section 21E of the Securities Exchange Act of 1934, as amended, or the Exchange Act. These forward-looking statements include, but are not limited to, statements regarding:

- the timing and the success of the Phase 3 and the Phase 2a HOPE-KIDS 1 Study, our clinical trials of voxelotor (previously known as GBT440) in adult and adolescent patients with sickle cell disease, or SCD;
- the timing and success of our additional clinical trials of voxelotor, including in pediatric patients with SCD, and of inclacumab and any other product candidates we may develop in our target indications;
- our plans and ability to submit, and the sufficiency of our data to support, a new drug application, or NDA, with the U.S. Food and Drug Administration, or FDA, for accelerated regulatory approval of voxelotor for SCD;
- the potential outcomes of our pre-NDA meeting with the FDA for an NDA for accelerated regulatory approval of voxelotor for SCD;
- our ability to leverage the safety data from prior clinical studies of inclacumab, which were not in patients with SCD, in our development of inclacumab;
- our ability to enroll patients in and complete our clinical trials at the pace that we project;
- whether the results of our trials will be sufficient to support domestic or foreign regulatory approvals for voxelotor or any other product candidates we may develop in our target indications;
- our ability to obtain, including under any expedited development or review programs, and maintain regulatory approval of voxelotor or any other product candidates we may develop;
- our ability to advance any other programs through preclinical and clinical development, and the timing and scope of these development activities;
- the limitations of current treatment options for SCD;

the benefits of the use of voxelotor, inclacumab or any other product candidates we may identify and develop;

our plans for potential commercial launch of voxelotor, including the expected size of the potential sales force;

our ability to successfully commercialize voxelotor, inclacumab or any other product candidates we may identify and pursue, if approved;

the potential market opportunity for, and rate and degree of market acceptance of, voxelotor or any other product candidates we may identify and pursue;

our ability to maintain, or to recognize the anticipated benefits of, orphan drug designation for voxelotor or to obtain orphan drug designation for any other product candidates we may identify and pursue in the United States, Europe or any other jurisdiction;

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our ability to maintain, or to recognize the anticipated benefits of, access to accelerated development and review programs through the FDA, such as the fast track and breakthrough therapy programs, or through the EMA s PRIME program, for voxelotor or any other product candidates we may identify and pursue;

our expectations regarding government and third-party payor coverage and reimbursement;

our ability to manufacture voxelotor in conformity with the FDA s requirements and to scale up manufacturing of voxelotor to commercial scale;

our ability to successfully build a specialty sales force and commercial infrastructure;

our ability to compete with companies currently producing or engaged in the clinical development of treatments for the disease indications that we pursue;

our reliance on third parties to conduct our clinical trials;

our reliance on third-party contract manufacturers to manufacture and supply our product candidates for us;

our ability to retain and recruit key personnel;

our ability to obtain and maintain intellectual property protection for voxelotor or any other product candidates we may identify and pursue;

our estimates of our expenses, ongoing losses, future revenue, capital requirements, sufficiency of capital resources and our needs for or ability to obtain additional financing;

our financial performance;

developments and projections relating to our competitors or our industry;

our plans to explore strategic transactions to broaden our pipeline; and

our ability to implement our strategic plans for our business and technology.

We have made these statements in reliance on the safe harbor provisions of the Private Securities Litigation Reform Act of 1995. These statements are subject to certain risks and uncertainties, which could cause actual results to differ materially from those projected or anticipated. Although we believe our assumptions underlying our forward-looking statements are reasonable as of the date of this report, we cannot assure you that the forward-looking statements set out in this report will prove to be accurate. In some cases, you can identify forward-looking statements by words such as anticipate, believe, continue, could, estimate, expect, intend, may, plan, potential, predict, target, will, would, or the negative of these words or other comparable terminology. Some of the factors that could cause our actual results to differ materially from our expectations or beliefs are disclosed under the caption Risk Factors, as well as other sections of this report that include, without limitation: our capital resources, commercial market estimates, the potential safety, efficacy or other therapeutic benefits of our product candidates, the timing for initiation of, availability of data from, and completion of, our ongoing and planned clinical trials and the results of these clinical trials, the pathways for regulatory approval of our product candidates, our future research and development efforts, patent protection, effects of healthcare reform, reliance on third parties, and other risks set forth below. All forward-looking statements speak only as of the date on which they are made and we disclaim any intent to update forward-looking statements to reflect subsequent developments or actual results. Except as required by law, we assume no obligation to update any forward-looking statements publicly, or to revise any forward-looking statement to reflect events or developments occurring after the date of this report, even if new

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information becomes available in the future. Thus, you should not assume that our silence over time means that actual events are bearing out as previously expressed or implied in any such forward-looking statement.

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.

In this Annual Report on Form 10-K, unless the context requires otherwise, GBT, Company, we, our, and us me Global Blood Therapeutics, Inc.

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PART I

Item 1. *Business*

Overview

We are a clinical-stage biopharmaceutical company determined to discover, develop and deliver innovative treatments that provide hope to underserved patient communities. Our lead product candidate is voxelotor (previously known as GBT440), an oral, once-daily therapy that modulates hemoglobin s affinity for oxygen, which we believe inhibits hemoglobin polymerization in sickle cell disease, or SCD.

We are currently evaluating voxelotor in adult and adolescent patients with SCD in a Phase 3 clinical trial, which we call the HOPE Study. In June 2018, we completed a planned review of Part A of the HOPE Study. The primary endpoint (the proportion of patients with greater than 1 g/dL increase in hemoglobin versus baseline) was achieved, with a statistically significant increase in hemoglobin at both the 1500 mg and 900 mg doses of voxelotor after 12 weeks of treatment versus placebo. The data also demonstrated corresponding improvements in other markers of hemolysis as well as a favorable safety and tolerability profile for voxelotor. Based upon these data and results in this planned preliminary review of Part A, we began discussions with the U.S. Food and Drug Administration, or FDA about seeking an accelerated approval pathway for voxelotor for SCD. In December 2018, we announced that the FDA agreed with our proposal to use the accelerated regulatory approval pathway under the FDA s Subpart H regulations, or Subpart H, for voxelotor for the treatment of SCD, and that we plan to submit a new drug application, or NDA, under this pathway to the FDA. The FDA grants accelerated approval under Subpart H for new drugs that address serious or life-threatening illnesses and that provide meaningful therapeutic benefit. We recently completed a pre-NDA meeting for the voxelotor program. Additionally, in December 2018, we announced updated efficacy and safety results from Part A of the Phase 3 HOPE Study of voxelotor at both the 1500 mg and 900 mg doses after 24 weeks of treatment versus placebo. These results, from approximately 150 patients with SCD treated with voxelotor for 24 weeks at both doses versus placebo, showed a statistically significant increase in the primary endpoint and showed improvements in other hemolysis measures. Voxelotor also continued to show a favorable safety and tolerability profile at 24 weeks.

We are also evaluating the safety and pharmacokinetics of single and multiple doses of voxelotor in adolescent and pediatric patients with SCD in a Phase 2a clinical trial, which we call the HOPE-KIDS 1 Study.

In October 2015, the FDA granted Fast Track Designation for voxelotor for the treatment of SCD. In December 2015, the FDA granted Orphan Drug Designation for voxelotor for the treatment of SCD. In November 2016, voxelotor was granted Orphan Drug Designation in Europe for the treatment of SCD. In June 2017, the European Medicines Agency, or EMA, granted PRIME designation for voxelotor for the treatment of SCD. The PRIME program is a regulatory mechanism that provides for early and proactive EMA support to medicine developers to help patients benefit as early as possible from innovative new products that have demonstrated the potential to significantly address an unmet medical need. In January 2018, the FDA granted Breakthrough Therapy Designation to voxelotor for the treatment of SCD.

In August 2018, we entered into a license agreement with F. Hoffmann-La Roche Ltd. and Hoffmann-La Roche Inc. (together, Roche) pursuant to which Roche granted the company an exclusive and sublicensable worldwide license under certain patent rights and know-how to develop and commercialize inclacumab, a novel fully human monoclonal antibody against P-selectin, including any modified compounds targeting P-selectin and derived from inclacumab, for all indications and uses, except diagnostic use. Roche retained a non-exclusive, worldwide, perpetual, royalty-free license to inclacumab solely for any diagnostic use. We plan to develop inclacumab as a treatment for vaso-occlusive

crises in patients with SCD and we expect to be able to leverage the safety data from Roche s prior clinical studies, which were not in patients with SCD, as we proceed with our development of inclacumab.

SCD is marked by red blood cell, or RBC, destruction and occluded blood flow and hypoxia, leading to anemia, stroke, multi-organ failure, severe pain crises, and shortened patient life span. Voxelotor inhibits

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abnormal hemoglobin polymerization, the underlying mechanism that causes sickling of RBCs. In our clinical trials to date of voxelotor in SCD patients, we observed reduced markers of red blood cell destruction, improvements in anemia, improvements in markers of tissue oxygenation, and reduced numbers of sickled RBCs.

SCD is a genetic blood disorder caused by a single point mutation in the beta-chain of hemoglobin, which results in the formation of abnormal hemoglobin known as sickle hemoglobin, or HbS. Normally, oxygenated RBCs travel from the lung through blood vessels. Hemoglobin is the protein inside RBCs that carries oxygen and releases oxygen at the tissues. In SCD, when oxygen is released, HbS becomes sticky and aggregates into polymers, or long, rigid rods within RBC, much like a sword within a balloon. The RBCs assume a sickled shape and becomes inflexible, which can destroy RBCs, cause blockage in small blood vessels, block blood flow, and decrease oxygen delivery to tissues. As a result, beginning in early childhood, SCD patients suffer many clinical consequences, including unpredictable and recurrent episodes, or crises, of severe chronic and acute pain, anemia, stroke, spleen failure, pulmonary hypertension, acute chest syndrome, liver disease, kidney failure, other morbidities, and premature death. These consequences are directly related to reduced blood flow and insufficient oxygen delivery. According to a 2014 publication, in the United States, SCD shortens patient life expectancy by approximately 25 to 30 years even with available medical care.

Current treatment options for SCD are limited to one approved therapy for adults known as hydroxyurea, one recently approved treatment for patients age five years and older called L-glutamine (marketed as Endari™), blood transfusions and bone marrow transplantation. The utilization of these treatments is significantly limited. For example, utilization of hydroxyurea is limited due to suboptimal efficacy and significant toxicity. As a result, patients with SCD continue to suffer serious morbidity and premature mortality.

We believe there is a significant unmet medical need for a novel SCD therapy that:

- inhibits abnormal hemoglobin polymer formation, the underlying mechanism of RBC sickling;
- stops inappropriate RBC destruction and improves blood flow and oxygen delivery to tissues;
- reduces hemolytic anemia that leads to chronic organ damage and early mortality in patients with SCD;
- prevents or reduces the episodes or crises of severe pain associated with SCD;
- modifies the long-term course of the disease;
- is effective in all SCD genotypes, and in both children and adults;
- has a more favorable side effect profile than currently available therapies; and
- is available as a convenient, oral therapy.

Voxelotor s therapeutic approach was inspired by the natural activity of fetal hemoglobin, or HbF. HbF is present during fetal development and in early infancy until it is replaced with adult hemoglobin, and has an inherently increased oxygen affinity that allows a fetus to extract oxygen from the mother s blood. Typically, newborns with SCD do not experience RBC sickling until approximately six to nine months of age, after which HbF is usually no longer expressed. Additionally, it has been observed that rare individuals who have inherited both the HbS mutation as well as a gene deletion that allows them to continue to express 10% to 30% HbF in their RBCs into adulthood do not exhibit the clinical manifestations of SCD, despite expressing up to 90% HbS in their blood. HbF dilutes the concentration of deoxygenated HbS that can participate in hemoglobin polymerization, and thereby significantly reduces the formation of hemoglobin polymers.

Voxelotor is a novel, proprietary investigational drug that increases hemoglobin s affinity for oxygen by binding to the alpha-chain of hemoglobin. Voxelotor has been observed to keep a proportion of HbS in its oxygenated state so it

cannot participate in polymerization. Similar to HbF, by diluting total HbS with a proportion of voxelotor-bound hemoglobin, voxelotor prevents hemoglobin polymer formation. Based on its mechanism of action, we believe that voxelotor can reduce the physical and clinical manifestations of SCD.

In December 2014, we initiated our randomized, placebo-controlled, double-blind, single and multiple ascending dose Phase 1/2 clinical study of voxelotor in healthy subjects and patients with SCD. The study was conducted in three parts: single dose administration, followed by multiple dose administration, daily for 15 days in healthy subjects and 28 days in SCD subjects, and then followed by multiple dose administration, daily for up

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to six months in SCD subjects. In this clinical trial, we evaluated the safety, tolerability, pharmacokinetics, and pharmacodynamics of voxelotor, as well as exploratory markers of SCD activity, including anti-hemolytic effects and SCD-related clinical effects. Among the 41 SCD subjects who received multiple doses of voxelotor (at doses of either 1000mg, 900mg, 700mg or 500mg per day) for 28 days up to six months, 100% of study subjects demonstrated a hematologic response to voxelotor therapy, as evidenced by improvements in one or more markers of hemolysis and anemia (hemoglobin, unconjugated bilirubin and/or percentage reticulocyte counts). In addition, all study cohorts showed marked reductions in irreversibly sickled cells in the peripheral blood from baseline, and, all study subjects treated for 90 days to up to six months showed sustained improvement in bilirubin and/or percentage reticulocyte counts, continued reductions in sickled RBCs and a median 1.0 g/dL increase in hemoglobin. In this clinical study, voxelotor was well tolerated through six months of dosing; the most common treatment-related adverse events were mild to moderate headaches and gastrointestinal disorders, which occurred in similar rates in the placebo arms.

In August 2016, we initiated our open-label, single- and multiple-dose Phase 2a clinical study of voxelotor in adolescent and pediatric patients with SCD that we refer to as the HOPE-KIDS 1 Study. In July 2017, we expanded this open-label trial to include a single-dose cohort in children aged 6-11 and in June 2018, the study was amended to include children down to age 4. The HOPE-KIDS 1 Study is designed to evaluate the safety, tolerability, pharmacokinetics, or PK, and exploratory treatment effect of voxelotor in a pediatric population (age 4 to 17) with SCD. The study is being conducted in three parts: the single-dose Part A portion included two cohorts of patients who received a single oral dose of 600 mg of voxelotor. Part A is complete, with seven patients aged 12 to 17 years enrolled and six patients aged 6 to 11 years enrolled. Part B (enrollment is complete) explored the safety of multiple doses of voxelotor administered to patients age 12 to 17 for 24 weeks. The doses evaluated, 900 mg per day (n=25) and 1500 mg per day (n=15), were consistent with those administered in our completed Phase 3 clinical trial of voxelotor in adult and adolescent patients with SCD. Part C is currently evaluating the 1500 mg dose (or weight-based equivalent) of voxelotor in up to 50 patients ages 4 to 17 years for up to 48 weeks.

In Part A of the HOPE-KIDS 1 Study, among the 13 SCD patients who received a single oral dose of 600 mg of voxelotor, 100% of the study patients demonstrated that voxelotor was well tolerated, with no serious or severe adverse events related to study drug observed. In addition, the PK and half-life of voxelotor were similar in adolescents (age 12 to 17) and adults, with results supporting once-daily dosing and a high specificity for hemoglobin. In Part B, among the 21 SCD adolescent patients who received multiple doses of voxelotor at 900 mg per day for whom data were available at 24 weeks, 43 percent of patients demonstrated a hematologic response to voxelotor therapy, as evidenced by improvements in one or more markers of hemolysis and anemia (hemoglobin, unconjugated bilirubin and percentage reticulocyte counts) and 55 percent of patients showed a numerical decrease in transcranial doppler (TCD) flow at 24 weeks. TCD velocity is utilized by physicians as a measure of stroke risks in pediatric and adolescent SCD patients. Among the 11 SCD adolescent patients who received multiple doses of voxelotor at 1500 mg per day for whom data were available at 16 weeks, 55 percent of patients demonstrated a hematologic response to voxelotor therapy, as evidenced by improvements in one or more markers of hemolysis and anemia (hemoglobin, unconjugated bilirubin and percentage reticulocyte counts). In addition, 12 out of the 15 patients who were enrolled at 1500 mg in Part B had normal TCD velocity at baseline, and all patients remained normal when assessed at week 12. One patient with a conditional TCD velocity (defined as > = 170 cm/sec, but < 200 cm/sec) at baseline normalized at week 24 of treatment, corresponding to a decreased in a stroke risk category, with concordant improvements in hemoglobin and reticulocytes observed. In this clinical study, voxelotor was well tolerated; the most common treatment-related adverse events were mild to moderate headaches, nausea, rash and vomiting.

In the fourth quarter of 2016, we initiated a randomized, double-blind, placebo-controlled, multi-national Phase 3 clinical trial of voxelotor in SCD that we refer to as the HOPE Study. Under its original design, the HOPE Study was designed to enroll up to approximately 435 adult and adolescent SCD patients, age 12 years and older, who have had at least one episode of vaso-occlusive crisis, or VOCs, in the previous year. The HOPE Study was to be conducted in

two parts: Part A, comparing two dose levels of voxelotor (900 mg and 1500 mg) versus placebo, for 12-weeks in approximately 150 patients; followed by Part B, a 24-week study designed to

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include 250 patients randomized to placebo or a dose of voxelotor selected based on the results of Part A. The main objectives of Part A were to select the optimal dose, define the final secondary endpoints for Part B and qualify the Patient Reported Outcome, or PRO, instrument we developed as a potential key secondary endpoint, measuring SCD symptom exacerbation, in addition to overall SCD symptoms as compared to placebo. Part A also assessed the traditionally defined VOC as well as hospitalizations and red blood cell transfusions as secondary endpoints. The primary efficacy endpoint of the HOPE Study is the proportion of patients who achieve a >1 g/dL increase in hemoglobin at 24 weeks of treatment compared to baseline.

In June 2018, we announced positive top-line preliminary clinical results for Part A of the HOPE Study. Among the 154 patients who had data available at 12-weeks, 58 percent of patients taking voxelotor 1500 mg per day and 38 percent of patients taking voxelotor 900 mg per day achieved a greater than 1 g/dL increase in hemoglobin versus 9 percent of patients taking placebo. This data compares favorably to the hemoglobin increase assumption agreed to with the FDA in the HOPE Study protocol of a 35 percent response rate. Statistically significant and dose-dependent improvements in hemoglobin, reticulocytes and bilirubin occurred with both voxelotor doses, further demonstrating an improvement in hemolytic anemia. There were numerically fewer VOC episodes in both voxelotor doses than in the placebo group, which as anticipated did not reach statistical significance due to limited patient follow-up. The PRO data were difficult to interpret due to low baseline symptom scores and high inter-subject and intra-subject variability, and accordingly we are not utilizing the PRO as a key secondary endpoint. Voxelotor was generally safe and well tolerated with similar safety profiles between the two doses. There was no evidence of tissue hypoxia at either dose.

Based upon these Part A clinical results meeting the primary endpoint of a proportion of patients achieving a >1 g/dL of hemoglobin with voxelotor, reductions seen in other markers of hemolysis and the safety profile demonstrated, we announced in June 2018 that we believed voxelotor met the standard for an accelerated regulatory approval pathway under Subpart H and that we were in discussions with the FDA regarding the potential for such approval including the design of required post-marketing confirmatory studies for voxelotor for the treatment of SCD. The FDA grants accelerated approval under Subpart H for new drugs that address serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments. Pursuing accelerated approval under Subpart H does not ensure faster development timelines or ensure regulatory approval. In addition, any drug approved under Subpart H, including voxelotor if it were approved, is required to be further evaluated in at least one post-marketing confirmatory study to verify clinical benefit and receive full approval. In December 2018, we announced that we reached agreement with the FDA to submit an NDA for voxelotor under an accelerated approval pathway. The planned NDA filing will include approximately 270 patients (approximately 150 patients from Part A of the HOPE study and an additional approximate120 patients enrolled in the study beyond the Part A enrollment) that have reached at least 24 weeks of treatment. The FDA also agreed that we could utilize TCD flow as the primary endpoint in the confirmatory study for purposes of full approval. We recently completed a pre-NDA meeting for the voxelotor program.

Additionally, in December 2018, we announced positive updated efficacy and safety from Part A of the HOPE Study at 24-weeks. Among the 154 patients in Part A who received multiple doses of voxelotor at either 900 mg per day or 1500 mg per day or placebo for whom data were available at 24 weeks, 65 percent of patients taking 1500 mg per day of voxelotor and 33 percent of patients taking 900 mg per day of voxelotor achieved a greater than 1 g/dL increase in hemoglobin versus 10 percent of patients taking placebo. Overall, voxelotor demonstrated a hematologic response, as evidenced by improvements in one or more markers of hemolysis and anemia (hemoglobin, unconjugated bilirubin and percentage reticulocyte counts). Voxelotor was well tolerated with similar safety profiles between the two doses. There were fewer VOCs despite substantial increases in hemoglobin, as evidenced by numerically fewer VOC episodes and a lower VOC incidence rate (per person-year) in both voxelotor doses than in the placebo group. As before, there was no evidence of impairment of tissue oxygenation at either dose.

We believe there is a significant market opportunity in SCD. The U.S. Centers for Disease Control, or CDC, estimates the prevalence of SCD at approximately 100,000 individuals in the United States, where newborn screening is mandatory. It is estimated that the prevalence of SCD in Europe is approximately 60,000 individuals. The global incidence of SCD is estimated to be 250,000 to 300,000 births annually. One study

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estimates that in the United States, the average annual cost for the care of an adult patient with the most common genotype of SCD exceeds $200,000, and the cumulative lifetime costs exceed $8.0 million over an assumed 50-year lifespan, driven primarily by hospital admissions, physician fees, clinic and emergency department visits, and the costs of diagnostic procedures and outpatient consultations.

We own or jointly own and have exclusively licensed rights to our product candidates in the United States, Europe and other major markets. We are the sole owner of issued U.S. patents covering voxelotor, including its composition of matter, methods of use, and a polymorph of voxelotor. These issued patents covering voxelotor will expire between 2032 and 2035, absent any applicable patent term extensions. We own or co-own additional pending patent applications in the United States and multiple foreign countries relating to our lead product candidate voxelotor.

To execute on the opportunities presented by our research and development portfolio, we have assembled a team of employees, management and directors rich in scientific experience and capabilities in drug discovery, development and commercialization. Our management has a successful track record in developing and commercializing drug candidates. In aggregate, our management team has contributed to several drug approvals, including Avastin®, Herceptin®, Kaletra®, Kyprolis®, Ravicti® and Rituxan®. We intend to leverage this expertise and experience to rapidly advance the development of voxelotor for SCD and advance other product candidates. Beyond evaluating voxelotor in SCD, we are also engaged in other research and development activities, all of which are currently in earlier development stages. In addition, we regularly evaluate opportunities to in-license, acquire or invest in new business, technology or assets or engage in related discussions with other business entities.

Our Development Pipeline

The following table summarizes our development programs, potential indications, and their current stages of development:

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Overview of SCD

SCD is a grievous disease that can lead to hemolytic anemia, meaning the destruction of RBCs within blood vessels, and vaso-occlusion, which means blocked blood flow to tissues, as well as progressive multi-organ damage and early death. Beginning in childhood, patients suffer unpredictable and recurrent episodes or crises of severe pain due to blocked blood flow to organs, which often lead to physical and psychosocial disability. In addition, the constant destruction of RBCs with the release of their contents into the blood often leads to damaged or diseased blood vessels, which further exacerbate blood flow obstruction and multi-organ damage. Consequences of SCD can manifest in early childhood and may include stroke, spleen failure, pulmonary hypertension, acute chest syndrome, liver disease, kidney failure, leg ulcers, priapism, which is a medical emergency due to refractory penile erection, and premature death. According to a 2014 publication, in the United States, SCD shortens patient life expectancy by approximately 25 to 30 years even with available medical care.

SCD is a genetic blood disorder caused by a single gene mutation in the beta-chain of hemoglobin, which results in mutant hemoglobin known as HbS. Hemoglobin is the protein in RBCs that carries oxygen from the lungs to the body s tissues, releases oxygen at the tissues, and returns carbon dioxide from the tissues back to the lungs. Hemoglobin accomplishes this by binding and then releasing oxygen through allosterism, which means the hemoglobin molecule changes its shape to have a high affinity for oxygen in the lungs, where oxygen is abundant, and to have a low affinity for oxygen in the tissues, where oxygen must be released. Oxyhemoglobin, the high oxygen affinity form of hemoglobin, is formed in the lungs during respiration, when oxygen binds to the hemoglobin molecule. Deoxyhemoglobin, the low oxygen affinity form of hemoglobin, is formed when oxygen molecules are removed from the binding site as blood flows from the lungs to the tissues in the body. In patients with SCD, deoxygenated HbS, molecules polymerize to form long, rigid rods within an RBC, much like a sword within a balloon. As a consequence, the normally round and flexible RBC becomes rigid and elongate into a sickled shape. Sickled RBCs do not flow properly in the bloodstream; they clog small blood vessels and reduce blood flow to the organs. This results in inadequate oxygen delivery, or hypoxia, to all body tissues, which can lead to multi-organ failure and premature death.

The following graphic illustrates the process by which sickling occurs in SCD patients as a result of the polymerization of deoxygenated HbS in an RBC, leading to occluded blood flow, in contrast to a normal RBC:

SCD manifests in individuals who inherit at least one HbS gene from a parent and an additional mutation on the second beta globin gene from the other parent. There are several different genotypes of SCD, including the following major genotypes:

HbSS, or sickle cell anemia, where both genes are HbS;
HbSC, where one gene is HbS, and the other is HbC (inherited by a non-SCD impacted parent); and
HbS/ßthal, where one gene is HbS, and the other is Beta thalassemia.

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Market Opportunity in SCD

The CDC estimates the prevalence of SCD at approximately 100,000 individuals in the United States, where newborn screening is mandatory. The incidence of SCD is estimated at approximately 1 in 2,000 to 2,500 newborns in the United States. It is estimated that the prevalence of SCD in Europe is approximately 60,000 individuals. The global incidence of SCD is estimated to be 250,000 to 300,000 births annually. SCD is concentrated in populations of African, Middle Eastern and South Asian descent.

Of SCD patients in the United States, approximately 45% are under the age of 18, and approximately 60% to 65% have the HbSS genotype, which is often referred to as sickle cell anemia, with the remaining 35% to 40% having other genotypes. In all genotypes of SCD, the mechanism that leads to the consequences of the disease involves the polymerization of HbS in its deoxygenated state, which results in RBC sickling. We believe that because of this common underlying mechanism, voxelotor may show activity across all SCD genotypes. Our Phase 3 HOPE Study enrolled SCD patients with all genotypes of SCD.

SCD is associated with high treatment costs. One study estimates that in the United States, the average annual cost for the care of an adult patient with the most common genotype of SCD exceeds $200,000, and the cumulative lifetime costs exceed $8.0 million over an assumed 50-year lifespan, driven primarily by hospital admissions, physician fees, clinic and emergency department visits and the costs of diagnostic procedures and outpatient consultations. As a result, we believe that a safe, effective and convenient oral treatment for SCD would be well received by patients, physicians and payors.

Current Treatment Options and Their Limitations

SCD remains a significant unmet medical need. The first drug approved to treat SCD, known as hydroxyurea, which was initially approved as a chemotherapy drug, was approved by the FDA in 1998 for the treatment of sickle cell anemia in adults with 3 or more painful crises per year. Hydroxyurea is currently the only drug approved for SCD, and it is not approved for pediatric SCD patients in the United States. The use of hydroxyurea is significantly limited by its side effect profile, variable patient responses and concerns regarding long-term toxicity. Hydroxyurea s side effects include impairment of fertility, suppression of white blood cells, or neutropenia, and suppression of platelets, or thrombocytopenia, which place patients at risk for infection and bleeding. In July 2017, the FDA approved L-glutamine oral powder for patients age five and older with SCD to reduce severe complications associated with the disorder. In January 2018, Emmaus Life Sciences, Inc., the marketer for Endari™ (L-glutamine oral powder) announced that the product is now available to patients.

In addition to hydroxyurea treatment and L-glutamine, transfusions with normal blood are an option to help alleviate anemia, which is a common symptom of SCD, and reduce sickling of RBCs. Blood transfusions have a number of limitations, including the expense of treatment, lack of uniform accessibility and risks ranging from allergic reactions to serious complications such as blood-borne infection and iron overload, which can cause organ damage. The only potentially curative treatment currently available for SCD patients is bone marrow transplantation, which requires a suitable matching donor and carries significant risks, including an approximately 5% mortality rate. Despite the current standard of care, including hydroxyurea, blood transfusion and palliative therapy for acute pain attacks, patients with SCD continue to suffer serious morbidity and premature mortality.

In light of the devastating effects of SCD on patients and the high costs of care for these patients, there is a significant unmet need for a treatment that:

- inhibits abnormal hemoglobin polymer formation, the underlying mechanism of RBC sickling;

stops inappropriate RBC destruction and improves blood flow and oxygen delivery to tissues;
reduces hemolytic anemia that leads to chronic organ damage and early mortality in patients with SCD;
prevents or reduces the episodes or crises of severe pain associated with SCD;
modifies the long-term course of the disease;
is effective in all SCD genotypes, and in both children and adults;
has a more favorable side effect profile than currently available therapies; and
is available as a convenient, oral therapy.

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Overview of Hemoglobin Biology and Voxelotor s Mechanism of Action

As described above, hemoglobin transports oxygen from the lungs to the body s tissues, releases oxygen into the tissues, and returns carbon dioxide from the tissues back to the lungs by changing its shape to be high affinity for oxygen in the lungs, where oxygen is abundant, and low affinity for oxygen in the tissues, where oxygen must be released. An important tool for assessing how readily hemoglobin acquires and binds oxygen in the lungs and releases oxygen into the tissues is the oxygen equilibrium curve, or OEC. The OEC represents the proportion of oxyhemoglobin, measured as the percentage of oxygen saturation (O2 % saturation) on the vertical axis relative to the amount of oxygen dissolved in blood, indicated as the oxygen tension, or partial pressure of oxygen (pO2) measured in millimeters of mercury (mmHg), on the horizontal axis.

We have demonstrated in preclinical models that our novel hemoglobin modifiers, including voxelotor, bind to hemoglobin, resulting in increased oxygen affinity. The effect of voxelotor on the measured OEC (Oxygen Equilibrium Curve) is a shift of the curve to the left. In other words, at a given prevailing oxygen tension in the blood, we have observed a higher percentage of oxygen saturation, or a higher proportion of oxyhemoglobin in the blood, following the administration of voxelotor.

In various studies of SCD, scientists have demonstrated that hemoglobin in the oxygenated state is a potent inhibitor of HbS polymerization. Since HbS polymerization occurs in the deoxygenated state, we believe that increasing the proportion of oxyhemoglobin, or left-shifting the OEC, should delay the polymerization of HbS and prevent the sickling of RBCs, which may ameliorate many of the clinical manifestations of SCD. Importantly, we are able to measure the proportion of hemoglobin modification (%HbMOD), which is expressed as the percentage of hemoglobin molecules occupied or bound by voxelotor.

HbF, which is present during fetal development and persists for up to six to nine months in infants until it is replaced by adult hemoglobin, has an inherent high affinity for oxygen, which is critical for a developing fetus to capture oxygen from the mother s blood. Newborns with SCD do not experience RBC sickling until approximately six to nine months of age, after which HbF is no longer expressed. Additionally, it has been observed that rare individuals who have inherited the HbS mutation and a gene deletion that allows them to continue to express 10% to 30% HbF in their RBCs into adulthood do not exhibit the clinical manifestations of SCD, despite expressing up to 90% HbS, in their blood. HbF dilutes the concentration of deoxygenated HbS that can participate in polymerization, and thereby prevents hemoglobin polymer from forming.

Based on these observations, we believe that to delay polymerization of HbS, voxelotor would need to bind to only approximately 10% to 30% of the total hemoglobin in a patient s blood. One theoretical concern regarding increasing the affinity of hemoglobin for oxygen is that excessive oxygen affinity could prevent hemoglobin from releasing oxygen into the tissues, thus causing hypoxia. However, we have not observed any findings from our clinical programs that demonstrated any evidence of such tissue impairment. Based on HbF data, our animal toxicology studies, and our clinical studies, we believe our target modification of the total hemoglobin in a patient s blood would not adversely compromise oxygen delivery to the tissues. This is supported by exercise testing we have performed in SCD patients and healthy volunteers showing normal oxygen consumption and the absence of a dose level or exposure related increase in erythropoietin levels in patients enrolled in the HOPE Study.

Overview of Voxelotor Clinical Trials

Phase 1/2 Clinical Trial of Voxelotor

In December 2014, we initiated our first clinical trial of voxelotor, a randomized, placebo-controlled, double-blind, single and multiple ascending dose study in which we evaluated the safety, tolerability, pharmacokinetics and pharmacodynamics of voxelotor in healthy subjects and patients with SCD. We refer to this Phase 1/2 clinical study as the GBT440-001 study. This clinical study was conducted at Quintiles Drug Research Unit at Guy s Hospital in London, United Kingdom, and was conducted in three parts, as shown in Figure 1 below: Part A (single dose administration), Part B (multiple dose administration, daily for 15 days in healthy subjects and 28 days in SCD subjects), and Part C (multiple dose administration, daily for 90 days in

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SCD subjects). An extension study for patients in Part C to dose some patients for up to 6 months is referred to as GBT440-024. We evaluated voxelotor s ability to prevent the hemolysis or destruction of RBCs in SCD subjects primarily by measuring the blood levels of hemoglobin, bilirubin and reticulocyte counts. We also measured LDH as an additional marker of hemolysis; however it is generally more variable and nonspecific because it is released from tissues other than RBCs and does not measure extravascular hemolysis which is the primary hemolytic mechanism in SCD. In this clinical trial, we also evaluated the effect of voxelotor on morphologic sickling of RBCs. We believe that findings of decreased hemolysis and anti-sickling activity provide evidence of inhibition of sickle hemoglobin polymerization, which may translate into improved symptoms, reduction in clinical events (such as VOC) and reduced organ damage due to RBC sickling.

Figure 1 Study Design of our Phase 1/2 Clinical Trial of Voxelotor

Overall, a total of 370 subjects, including 283 healthy subjects (including subjects with renal or hepatic impairment) and 53 adult SCD subjects and 28 adolescent subjects with SCD (12 to 17 years of age), and 6 pediatric subjects with SCD (6 to 11 years of age) have been administered single or multiple doses of voxelotor across 15 GBT-sponsored clinical studies. Subjects received single or multiple doses of voxelotor (up to 15 days in healthy subjects, and up to 180 days in subjects with SCD). The studies included 2 Phase 1/2 studies in healthy subjects and subjects with SCD (GBT440-001 and its extension study GBT440-024), 1 Phase 2a study in pediatric participants with SCD (GBT440-007, also referred to as HOPE KIDS 1), and 12 clinical pharmacology studies. The most commonly reported adverse events, or AEs, regardless of treatment causality, across SCD subjects included mild or moderate headache, back pain, pain, diarrhea, pain in extremity and rash. All events of diarrhea were mild. Most of these events resolved without treatment and are easily monitored. Of these events, treatment-emergent adverse event were diarrhea, headache and rash. Some subjects with SCD experienced acute painful sickle cell crisis, which was thought to be related to underlying SCD, and not to voxelotor.

In our Phase 1/2 clinical study, we had no drug-related serious adverse events, or SAEs, reported. A total of 16 SAEs (12 from adult subjects and 4 from adolescent subjects), each of which were assessed to be not related to study drug, were reported in SCD subjects.

Among the 41 SCD patients who received multiple doses of voxelotor (at doses of either 500 mg, 700 mg, 900 mg, or 1000 mg per day) in our Phase 1/2 clinical study for 28 days up to six months, 100% of study subjects demonstrated a hematologic response to voxelotor therapy, as evidenced by significant improvement in one or more clinical markers of hemolysis and anemia (hemoglobin, unconjugated bilirubin and/or percentage reticulocyte counts). In addition, all study cohorts showed marked reductions in irreversibly sickled RBCs in the peripheral blood from baseline, and all study subjects treated for 90 days up to six months showed sustained improvement in bilirubin and/or percentage of reticulocyte counts, continued reductions in sickled RBCs and a

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median 1.0g/dL increase in hemoglobin. There was no evidence of tissue hypoxia; trends to erythropoietin reductions and the reduction in reticulocyte counts were consistent with an improvement in tissue oxygen delivery; oxygen delivery to tissues at rest and during exercise was normal.

The tables below show that SCD subjects in our Phase 1/2 study who were treated for 90 days to six months with voxelotor showed a durable and significant hemoglobin increase as compared to placebo. In addition, SCD subjects in this study showed sustained improvements in bilirubin level as well as counts of reticulocyte and irreversibly sickled cells, and a greater increase in hemoglobin than at day 28.

Durable Effect: Significant Hemoglobin Increase Maintained with Dosing for 3-6 Months

All Patients Dosed with Voxelotor Showed A Reduction in Hemolysis, Reticulocytes, and Sickled Cells

[a]Data available for n=4 [b]Data available for n=5 [c]Data available for n=0 [d]Data available for n=11 ns: not significant

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Figure 2 Peripheral Blood Smear of a Voxelotor-Treated Subject at Baseline (Day -1) and Day 90

Representative images from Voxelotor-treated subject

Day 1 **Day 90 (Voxelotor 700 mg)**

Phase 2a HOPE KIDS 1 Study

In August 2016, we initiated our open-label, single and multiple-dose Phase 2a clinical study of voxelotor in adolescent and pediatric patients with SCD which we refer to as the HOPE-KIDS 1 Study. As shown below in Figure 3, an ongoing open-label, single- and multiple-dose Phase 2a study is evaluating the safety, tolerability, pharmacokinetics and exploratory treatment effect of voxelotor in pediatric patients aged 4 to 17 years with SCD. Part A of the study evaluated a single 600 mg dose of voxelotor in 13 patients aged 6 to 17 years, while Part B was designed to explore voxelotor at doses of 900 mg and 1500 mg per day administered to 40 patients ages 12 to 17 for 24 weeks. Part C of the study is currently enrolling and will evaluate multiple voxelotor doses at 1500 mg dose (or weight-based equivalent) in up to 50 patients aged 4 to 17 years for up to 48 weeks.

Part A pharmacokinetics, or PK, data in adolescents (12 to 17 years) was reported at the 2017 European Hematology Association Congress and demonstrated that the PK and half-life of voxelotor were similar in adolescents and adults with results supporting once-daily dosing. Part A data for pediatric patients (6 to 11 years) was presented at the 2017 American Society of Hematology Annual Meeting, or ASH. Voxelotor PK exposures were higher in children compared with adolescents and adults, which informs dose selection for future pediatric studies in children under 12 years of age.

The primary objective of Part B was to assess the effect of voxelotor on anemia. Secondary objectives include effect on clinical measures of hemolysis, PK (PK parameters determined using population PK analysis). Additionally, we were able to assess the exploratory endpoint of transcranial doppler flow or TCD measures in this study as TCD is a measure of stroke risk in pediatric and adolescent SCD patients. TCD measurement was not a primary or secondary endpoint or eligibility criteria in the HOPE KIDS-1 Study. Part B data for adolescent patients who received multiple doses of voxelotor at 900 mg per day was previously reported at the 2018 European Hematology Association Congress and Part B interim analysis of data for adolescent patients who received multiple doses of voxelotor at 1500 mg per day was presented at the 2018 ASH. Part B demonstrated a hematologic response to voxelotor therapy, as evidenced by improvements in one or more markers of hemolysis and anemia (hemoglobin, unconjugated bilirubin and percentage reticulocyte counts).

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Figure 3 Study Design of our Phase 2a Clinical Trial of Voxelotor

HOPE KIDS 1 PART A (600 mg of voxelotor)

Results that were reported at the 2017 European Hematology Association Congress, or EHA, for the 12-17 year old cohort (n=7) demonstrated that:

- Voxelotor was well tolerated;
- No serious or severe adverse events related to study drug observed; and
- The PK and half-life of voxelotor were similar in adolescents (age 12 to 17) and adults, with results supporting once-daily dosing and a high specificity for hemoglobin.

Results that were presented at the 2017 American Society of Hematology Annual Meeting, or ASH for the 6-11 year old cohort (n=6) demonstrated that:

- Voxelotor was well tolerated, with no treatment-related adverse events reported;
- Voxelotor exposures in children were generally higher than those observed in adults and adolescents; and
- Using a model that combined data from adults, adolescents and children, a weight-based dosing approach in children could achieve similar exposure levels to the doses of voxelotor currently being investigated in the Phase 3 HOPE Study in SCD patients age 12 and older.

HOPE KIDS 1 PART B (900 mg and 1500 mg of voxelotor)

Our EHA presentation in June 2018 analyzed 25 patients who received voxelotor at a dose of 900 mg/day for up to 24 weeks in Part B. The median age of the patients was 14 years. 88% of patients were on hydroxyurea and 44% had no VOCs in the prior year. Data showed the following results achieved with voxelotor treatment:

- Increased hemoglobin levels and improved clinical measures of hemolysis at 24 weeks, were observed by changes from baseline in hemoglobin, percent of reticulocytes, and percent of unconjugated bilirubin (efficacy at week 24 is available for 21 of 25 subjects; one patient is excluded due to a concurrent event at week 24 and 3 patients did not reach week 24);
  - 43% of patients (9 of 21) achieved a hemoglobin response >=1 g/dL with a median hemoglobin change from baseline of 0.7 g/dL;

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55% of patients (11 of 20) had a numerical decrease in transcranial doppler (TCD) flow at 24 weeks; among hemoglobin responders (>=1 g/dL), 88% (7 of 8) had a numerical decrease in TCD at 24 weeks;
Voxelotor was well tolerated consistent with results in adults;
Drug-related adverse events related to voxelotor were grade 1 or 2, except one grade 3 urticaria that did not recur with continued dosing; and
The most common drug-related adverse events (occurring in two or more patients) were nausea, vomiting, headache and rash.

The Part B results presented at ASH in December 2018 were an interim analysis of data from patients treated with voxelotor at a dose of 1500 mg/day. The presentation included safety data for 15 patients and efficacy data for 11 patients (who had completed 16 weeks of treatment). The median age of the patients was 14 years. 100% of patients were on hydroxyurea and 33% of patients had no VOCs in the prior year. Key findings included the following for voxelotor at the 1500 mg:

The majority of adolescents achieved robust and sustained improvement in hemoglobin and reduced hemolysis consistent with results from HOPE in both adolescents and adults;
55% of patients (6 of 11) achieved a hemoglobin response >1 g/dL;
Other clinical measures of hemolysis also improved concordantly (see Figure 4);
Patients with normal TCD velocity at baseline remained within the normal range at week 12;
One patient with a conditional TCD velocity at baseline normalized at week 24, corresponding to a decrease in stroke risk category, with concordant improvements in hemoglobin and reticulocytes observed (see Figure 5);
1500 mg/day of voxelotor was well tolerated; and
The most common treatment-related adverse events (occurring in 2 or more patients) were mild to moderate headaches and nausea.

Figure 4 Improvement in Anemia and Hemolysis Confirmed

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Figure 5 Conditional TCD Patient Converted to Normal on Treatment

Phase 3 HOPE Study of Voxelotor

The HOPE Study is a randomized, double-blind, placebo-controlled, multi-national, Phase 3 clinical trial. The original design of the HOPE Study was to enroll up to approximately 435 adult and adolescent SCD patients age 12 and older who have had at least one episode of VOC in the previous year (see Figure 6). The HOPE Study was designed to be conducted in two parts: the initial Part A, which was to compare two dose levels of voxelotor (900 mg and 1500 mg) versus placebo, and include up to 150 patients; followed by Part B, which would have included 250 patients randomized to placebo or the dose of voxelotor selected based on the results of Part A. The main objectives of Part A were to select the optimal dose for Part B, define the final secondary endpoints for Part B and qualify the PRO instrument. Part A also assessed the traditionally defined VOC as well as hospitalizations and red blood cell transfusions as secondary endpoints. The primary efficacy endpoint of the HOPE Study is the proportion of patients who achieve a >1 g/dL increase in hemoglobin at 24 weeks of treatment compared to baseline.

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Figure 6 Phase 3 HOPE Study Design

In June 2018, we announced positive preliminary topline data for Part A of the HOPE Study in approximately 154 patients at week 12. The primary endpoint was achieved and statistically significant results for both doses of voxelotor studied (1500 mg and 900 mg) vs. placebo. The PRO data were difficult to interpret due to low baseline symptom scores and high inter-subject and intra-subject variability, and accordingly we are no longer utilizing the PRO as a key secondary endpoint. The 12-week clinical results demonstrated:

- 58% of patients achieved primary endpoint of Hb response >1 g/dL;
- Statistically significant and dose-dependent improvements in hemoglobin, reticulocytes and indirect bilirubin occurred with both voxelotor doses, further demonstrating an improvement in hemolytic anemia;
- Improvements in these clinical measures of anemia and hemolysis were similar in patients with or without background use of hydroxyurea. Approximately 64 percent of patients enrolled in Part A are on background use of hydroxyurea;
- Voxelotor was generally safe and well tolerated with similar safety profiles between the two doses;
- There were numerically fewer VOC episodes in both voxelotor groups than in the placebo group, which as anticipated did not reach statistical significance due to limited duration of treatment; and
- There was no evidence of tissue hypoxia at either dose.

Based on the above positive top-line data results, in June 2018 we announced that we believed voxelotor met the standard for potential accelerated approval under Subpart H and that we were in discussions with the FDA related to this pathway. In December 2018, we announced that the FDA agreed with our proposal to use an accelerated regulatory approval pathway under Subpart H for voxelotor for the treatment of SCD, and that we plan to submit an NDA under this pathway. The FDA grants accelerated approval under Subpart H for new drugs that address serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments. Pursuing accelerated approval under Subpart H does not ensure faster development timelines

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or ensure regulatory approval. In addition, any drug approved under Subpart H, including voxelotor if it were approved, is required to be further evaluated in at least one post-marketing confirmatory study to verify clinical benefit. Our planned NDA filing for the voxelotor program will include approximately 270 patients (150 patients from Part A of the HOPE study and approximately 120 additional patients enrolled in the study beyond the Part A enrollment) that have reached at least 24 weeks of treatment. The primary efficacy endpoint of the HOPE Study remains the same, the proportion of patients who achieve a >1 g/dL increase in hemoglobin at 24 weeks of treatment compared to baseline. The secondary efficacy endpoints in the HOPE Study include change from hemoglobin at week 24, change from baseline in hemolysis measures and annualized incidence rate of VOC at week 72. In December 2018, we also announced that the FDA agreed that we could utilize TCD flow as the primary endpoint in our planned confirmatory study for full approval. We recently completed a pre-NDA meeting for the voxelotor program.

In December 2018 at ASH, we presented an updated efficacy and safety analysis of the 154 patients in Part A of the HOPE Study at 24 weeks. Key findings included the following:

- 65% of patients taking voxelotor at the 1500 mg/day dose ($p<0.0001$) and 33 percent of patients taking voxelotor at the 900 mg/day dose ($p=0.0159$) achieved a greater than 1 g/dL increase in hemoglobin versus 10% of patients taking placebo. (Figure 7);
- Hemoglobin improved rapidly at the earliest timepoint measured (2 weeks) and was sustained through 24 weeks. (Figure 8);
- Voxelotor 1500 mg increased hemoglobin to a mean of 10 g/dL at 24 weeks from a baseline of 8.6 g/dL, consistent with a clinically meaningful improvement in anemia;
- The improvement in hemoglobin was similar in patients with or without background use of hydroxyurea. Approximately 64% percent of patients were receiving hydroxyurea at study entry and throughout the study. (Figure 9);
- Improvements in hemoglobin, reticulocytes and indirect bilirubin occurred with both voxelotor doses, further demonstrating an improvement in hemolysis consistent with inhibition of Hb polymerization. (Figures 10 and Figure 11);
- Voxelotor was generally safe and well tolerated with similar safety profiles between the two doses;
- There were fewer VOCs despite substantial increases in hemoglobin. Specifically, there were numerically fewer VOC episodes: 109 in the 1500 mg arm, 113 in the 900 mg arm and 131 in the placebo arm; and a lower VOC incidence rate (per person-year): 2.77 in the 1500 mg arm, 2.85 in the 900 mg arm and 3.41 in the placebo arm; and
- There was no evidence of impairment of tissue oxygenation at either dose.

Figure 7 Dramatic Improvements in Anemia

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Figure 8 Anemia Improvement was Rapid, Robust and Dose-Dependent

Figure 9 Anemia Improved With or Without Hydroxyurea

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Figure 10 Reticulocytes Decreased Consistent with Decreased Red Blood Cell Destruction (Hemolysis)

Figure 11 Indirect Bilirubin Decrease Consistent with Decreased Red Blood Cell Destruction

European Union Regulatory Path for Voxelotor

We have been engaged in discussions with European regulatory authorities to define the future development plan for voxelotor. The objectives of these regulatory interactions include discussion of study design for additional clinical trials, trial endpoints and the development of voxelotor in other patient populations, including pediatrics.

In November 2016, the European Commission, or EC, granted Orphan Drug Designation status in the European Union, or EU, for voxelotor for the treatment of SCD. In June 2017, the European Medicines Agency, or EMA, granted PRIME designation for voxelotor for the treatment of SCD. The PRIME program is a regulatory mechanism that provides for early and proactive EMA support to medicine developers to help patients benefit as early as possible from innovative new products that have demonstrated the potential to significantly address an unmet medical need.

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Manufacturing

We do not own or operate, and currently have no plans to establish, any manufacturing facilities. We currently depend on third-party contract manufacturing organizations, or CMOs, for all of our requirements of raw materials, drug substance and drug product for our nonclinical research and our ongoing clinical trials of our lead product candidate voxelotor. We have entered into commercial manufacturing agreements with some of our current CMOs. We intend to continue to rely on CMOs for later-stage development and commercialization of voxelotor, as well as the development and commercialization of any other product candidates, including inclacumab. Although we rely on CMOs, we have personnel and third-party consultants with extensive manufacturing experience to oversee the relationships with our contract manufacturers.

We believe the synthesis of the drug substance for voxelotor is reliable and reproducible from readily available starting materials, and the synthetic routes are amenable to large-scale production and do not require unusual equipment or handling in the manufacturing process. We have obtained an adequate supply of the drug substance for voxelotor from our CMOs to satisfy our immediate clinical and nonclinical demands. We have implemented improvements to our drug substance manufacturing process to further ensure production capacity adequate to meet future development and potential commercial demands.

We have completed development for a solid oral formulation of a tablet form of voxelotor as well as a pediatric dispersible tablet formulation of voxelotor.

Intellectual Property

We strive to protect the proprietary technology that we believe is important to our business, including seeking and maintaining patents and patent applications intended to cover our product candidates and compositions, their methods of use and processes for their manufacture, and any other aspects of inventions that are commercially important to the development of our business. We also rely on trade secrets to protect aspects of our business that are not amenable to, or that we do not consider appropriate for, patent protection.

We plan to continue to expand our intellectual property portfolio. We endeavor to promptly file domestic and international patent applications for new commercially valuable inventions, including applications directed to compositions and methods of treatment created or identified from our ongoing development of our product candidates. Our success will depend in part on our ability to obtain and maintain patent and other proprietary rights protecting our commercially important technology, inventions and know-how related to our business, defend and enforce our current and future issued patents, if any, preserve the confidentiality of our trade secrets and operate without infringing the valid and enforceable patents and proprietary rights of third parties. We also rely on know-how, continuing technological innovation and potential in-licensing opportunities to develop and maintain our intellectual property portfolio.

The patent positions of biopharmaceutical companies like us are generally uncertain and involve complex legal, scientific and factual questions. In addition, the coverage claimed in a patent application can be significantly reduced before the patent, if any, is issued, and patent scope can be reinterpreted by the courts after issuance. Moreover, many jurisdictions permit third parties to challenge issued patents in administrative proceedings, which may result in further narrowing or even cancellation of patent claims. We cannot predict whether the patent applications we are currently pursuing will issue as patents in any particular jurisdiction or whether the claims of any patents, if issued, will provide sufficient protection from competitors for our business.

Because patent applications in the United States and certain other jurisdictions are maintained in secrecy for 18 months or potentially even longer, and since publication of discoveries in the scientific or patent literature often lags behind actual discoveries, we cannot be certain of the priority of inventions covered by pending patent applications. Moreover, we may have to participate in interference proceedings or derivation proceedings declared by the United States Patent and Trademark Office, or USPTO, to determine the priority of inventions.

Patents

Our patent portfolio includes multiple issued U.S. patents, as well as multiple U.S. and foreign patent applications in various stages of prosecution or allowance. Our primary patents and patent applications relate to

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our general HbS intellectual property portfolio, which includes our lead product candidate voxelotor and its development program.

Our HbS intellectual property portfolio is comprised of multiple patent families of patents and patent applications relating to voxelotor and/or analogs that inhibit Hb polymerization. These patent families include patents and patent applications specifically related to our lead product candidate voxelotor covering certain compositions of matter, methods of use, method of manufacture, formulations, and polymorphs of voxelotor, as well as certain compositions of matter, methods of use, method of manufacture, formulations, and polymorphs. These patent applications are pending in a variety of jurisdictions, including the United States, jurisdictions under the Patent Cooperation Treaty and other countries.

With regard to voxelotor specifically, we are the sole owner of issued U.S. patents covering voxelotor, including its composition of matter, methods of use and a polymorph of voxelotor. These issued U.S. patents covering voxelotor will expire between 2032 and 2035, absent any applicable patent term extensions. Any patents that may issue from our pending patent applications relating to voxelotor in the United States or from corresponding foreign patent applications, if issued, are expected to expire between 2032 and 2037, absent any applicable patent term extensions. Some of these pending patent applications are jointly owned by us and Regents of the University of California, or the Regents, as described below.

Our other patents in our HbS intellectual property portfolio are comprised of additional issued U.S. patents covering voxelotor analogs. These patents, and any patents that may issue from our pending patent applications relating to voxelotor analogs in the United States or from corresponding foreign patent applications, if issued, are currently expected to expire between 2032 and 2034, absent any applicable patent term extensions. Some of these pending patent applications are jointly owned by us and the Regents, as described below.

In addition, we have exclusively licensed from the Regents worldwide patent rights covering voxelotor and certain voxelotor analogs, some of which patent rights we jointly own with the Regents. In exchange for our exclusive license, we have agreed to pay a royalty to the Regents of less than 1% on future net sales and to use commercially reasonable efforts to develop, manufacture, market and sell the products covered by the licensed patents. The risks associated with joint ownership of patent rights are more fully discussed under Risk Factors-Risks Related to Our Intellectual Property.

Beyond our HbS intellectual property portfolio, we own other issued U.S. patents, seek to obtain additional issued patents, and file patent applications relating to our other research and development programs over time.

Patent term

The base term of a U.S. patent is 20 years from the filing date of the earliest-filed non-provisional patent application from which the patent claims priority, assuming that all maintenance fees are paid. The term of a U.S. patent can be lengthened by patent term adjustment, which compensates the owner of the patent for administrative delays at the USPTO the extent of which is offset by delays by the patent owner before the USPTO in obtaining the patent. In some cases, the term of a U.S. patent is shortened by a terminal disclaimer that reduces its term to that of an earlier-expiring patent. The term of a U.S. patent may be eligible for patent term extension under the Drug Price Competition and Patent Term Restoration Act of 1984, referred to as the Hatch-Waxman Act, to account for at least some of the time the drug is under development and regulatory review after the patent is granted. With regard to a drug for which FDA approval is the first permitted marketing of the active ingredient, the Hatch-Waxman Act allows for extension of the term of one U.S. patent that includes at least one claim covering the composition of matter of an FDA-approved drug, an FDA-approved method of treatment using the drug and/or a method of manufacturing the FDA-approved drug. The

extended patent term cannot exceed the shorter of five years beyond the non-extended expiration of the patent or 14 years from the date of the FDA approval of the drug. Some foreign jurisdictions, including Europe and Japan, have analogous patent term extension provisions, which allow for extension of the term of a patent that covers a drug approved by the applicable foreign regulatory agency. In the future, if our lead product candidate voxelotor or any other product candidates receive FDA approval, we would expect to apply for patent term extension on patents, if issued, covering those products, their methods of use and/or methods of manufacture.

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Trade secrets

In addition to patents, we rely on trade secrets and know-how to develop and maintain our competitive position. We typically rely on trade secrets to protect aspects of our business that are not amenable to, or that we do not consider appropriate for, patent protection. We protect trade secrets and know-how by establishing confidentiality agreements and invention assignment agreements with our employees, consultants, scientific advisors and contractors. These agreements generally provide that all confidential information developed or made known during the course of an individual or entities relationship with us must be kept confidential during and after the relationship. These agreements also typically provide that all inventions resulting from work performed for us or relating to our business and conceived or completed during the period of employment or assignment, as applicable, shall be our exclusive property. In addition, we take other appropriate precautions, such as physical and technological security measures, to guard against misappropriation of our proprietary information by third parties.

Sales and Marketing

We intend to begin building a commercial infrastructure in the United States prior to New Drug Application submission to ensure that a commercial team is in place at the time of potential FDA approval. Approximately 100,000 Americans have been diagnosed with SCD and approximately 85% of those living with SCD reside in 17 states. Many SCD patients receive care from a hematologist or another sickle cell care provider. Thus, the US commercial market for SCD is highly concentrated both in terms of geography and prescribing audience. We expect to be able to efficiently support the commercial launch of voxelotor by building our own targeted commercial organization including internal sales personnel, key payer account management, marketing and distribution support. We expect to hire less than 75 sales representatives in the US to support voxelotor and we plan to also build a patient support program to support commercial launch.

We are considering building additional capabilities that may be necessary to effectively support the commercialization of voxelotor outside of the United States. These capabilities will likely focus on a limited number of core European markets, where SCD is prevalent. Where appropriate, we may also utilize strategic partners, distributors or contract sales forces to expand the commercial availability of voxelotor. We currently do not expect that we will require large pharmaceutical partners for the commercialization of our product candidates, although we may consider partnering in certain territories, New Molecular Entities, or NMEs, or indications for other strategic purposes. We intend to evaluate our commercialization strategy as we advance our preclinical programs in other rare disease indications.

Competition

The biopharmaceutical industry is highly competitive. There are many public and private biopharmaceutical companies, universities, governmental agencies and other research organizations actively engaged in the research and development of products that may be similar to our product candidates or address similar markets. In addition, the number of companies seeking to develop and commercialize products and therapies similar to our product candidates is likely to increase.

In the area of SCD, we expect to face competition from the two currently FDA approved treatments: hydroxyurea (marketed as DROXIA or Hydrea by Bristol-Myers Squibb Company as well as in generic form), approved for reducing the frequency of painful crises and need for blood transfusions in patients with sickle cell anemia for the treatment of adults with SCD and Endari™ (marketed by Emmaus), approved for the reduction of acute complications of SCD in patients age five years and older. Several companies are also developing product candidates for chronic treatment in SCD, and several other agents are in early clinical trials investigating new mechanisms of action for the chronic treatment of SCD. We also expect to face competition from one-time therapies for patients with severe SCD,

including hematopoietic stem cell transplantation, gene therapy and gene editing. For example, bluebird bio, Inc. is currently engaged in the clinical development of LentiGlobin BB305, which aims to treat SCD by inserting a functional human beta-globin gene into the patient s own hematopoietic stem cells, or HSCs, ex vivo and then transplanting the modified stem cell into the patient s bloodstream.

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Bluebird has indicated it plans to pursue an accelerated development path for its gene therapy product in SCD. While not directly competitive with preventative agents like voxelotor, several agents are also in development for the treatment of VOC in patients with SCD, including rivipansel, which is being developed by Pfizer Inc. Pfizer announced that the Phase 3 trial for rivipansel is expected to be completed in the second quarter of 2019. In addition, Novartis AG is engaged in the clinical development of crizanlizumab, an anti-P-selectin monoclonal antibody for the treatment of VOC in patients with SCD. In January 2019, Novartis announced that crizanlizumab has been granted FDA s breakthrough therapy designation, and that Novartis expects to file a new drug application for crizanlizumab in the first half of 2019.

Some of our potential competitors, 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 treatments and the commercialization of those treatments. Mergers and acquisitions in the biotechnology and pharmaceutical industries may result in even more resources being concentrated among a smaller number of our competitors. Our commercial opportunity could be reduced or eliminated if our competitors develop and commercialize products that are safer, more effective, are more convenient or are less expensive than any products that we may develop. Our competitors also may obtain FDA or other regulatory approval for their products 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.

Government Regulation

Government authorities in the United States at the federal, state and local level and in other countries extensively regulate, among other things, the research, development, testing, manufacture, quality control, approval, labeling, packaging, storage, record-keeping, promotion, advertising, distribution, post-approval monitoring and reporting, marketing and export and import of drug products. Pricing of such products is also subject to regulation in many countries. Generally, before a new drug can be marketed, considerable data demonstrating its quality, safety and efficacy must be obtained, organized into a format specific to each regulatory authority, submitted for review and approved by the regulatory authority.

U.S. drug development

In the United States, the FDA regulates drugs under the Federal Food, Drug, and Cosmetic Act, or FDCA, and its implementing regulations. Drugs are also subject to other federal, state and local statutes and regulations. 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. 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 to administrative or judicial sanctions. These sanctions could include, among other actions, the FDA s refusal to approve pending applications, withdrawal of an approval, a clinical hold, untitled or warning letters, product recalls or withdrawals from the market, product seizures, total or partial suspension of production or distribution injunctions, fines, refusals of government contracts, restitution, disgorgement, or civil or criminal penalties. Any agency or judicial enforcement action could have a material adverse effect on us.

Our product candidates must be approved by the FDA through the New Drug Application, or NDA, process before they may be legally marketed in the United States. The process generally involves the following:

completion of extensive nonclinical studies in accordance with applicable regulations, including the FDA s GLP regulations;

submission to the FDA of an Investigational New Drug, or IND, application, which must become effective before human clinical trials may begin;

approval by an independent institutional review board, or IRB, or ethics committee at each clinical trial site before each trial may be initiated;

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performance of adequate and well-controlled human clinical trials in accordance with applicable IND regulations, good clinical practices, or GCPs, and other clinical-trial related regulations to establish the safety and efficacy of the investigational drug for each proposed indication;

submission to the FDA of an NDA, for a new drug;

a determination by the FDA within 60 days of its receipt of an NDA whether to accept it for filing and review;

satisfactory completion of an FDA pre-approval inspection of the manufacturing facility or facilities where the drug is produced to assess compliance with current good manufacturing practices, or cGMPs, to assure that the facilities, methods and controls are adequate to preserve the drug s identity, strength, quality and purity;

potential FDA audit of the nonclinical and/or clinical trial sites that generated the data in support of the NDA; and

FDA review and approval of the NDA, including consideration of the views of any FDA advisory committee, prior to any commercial marketing or sale of the drug in the United States.

The nonclinical and clinical testing and approval process requires substantial time, effort and financial resources, and we cannot be certain that any approvals for any of our product candidates, including voxelotor, will be granted on a timely basis, or at all. The data required to support an NDA are generated in two distinct development stages: nonclinical and clinical. The nonclinical development stage generally involves synthesizing the active component, developing the formulation and determining the manufacturing process, as well as carrying out non-human toxicology, pharmacology and drug metabolism studies in the laboratory, which support subsequent clinical testing in humans. As the drug sponsor, we must submit the results of the nonclinical studies, together with manufacturing information, analytical data, any available clinical data or literature and a proposed clinical protocol, to the FDA as part of the IND. An IND is a request for authorization from the FDA to administer an investigational drug product to humans, and must become effective before human clinical trials may begin.

The clinical stage of development involves the administration of the drug candidate to healthy volunteers or patients under the supervision of qualified investigators, generally physicians not employed by or under the trial sponsor s control, in accordance with GCPs, which include the requirement that all research subjects provide their informed consent for their participation in any clinical trial. Clinical trials are conducted under protocols detailing, among other things, the objectives of the clinical trial, dosing procedures, subject selection and exclusion criteria, and the parameters to be used to monitor subject safety and assess efficacy. Each protocol, and any subsequent amendments to the protocol, must be submitted to the FDA as part of the IND. Further, each clinical trial must be reviewed and approved by an independent IRB for each institution at which the clinical trial will be conducted to ensure that the risks to individuals participating in the clinical trials are minimized and are reasonable in relation to anticipated benefits. The IRB also approves the informed consent form that must be provided to each clinical trial subject or his or her legal representative and must monitor the clinical trial until completed. There are also requirements governing the reporting of ongoing clinical trials and completed clinical trial results to public registries.

Clinical trials

Clinical trials are generally conducted in three sequential phases, known as Phase 1, Phase 2 and Phase 3 trials, which may overlap.

Phase 1 clinical trials generally involve a small number of healthy volunteers who are initially exposed to a single dose and then multiple doses of the product candidate. The primary purpose of these clinical trials is to assess the metabolism, pharmacologic action, side effect tolerability and safety of the product candidate.

Phase 2 clinical trials typically involve studies in disease-affected patients to determine the dose of the product candidate required to produce the desired benefits. At the same time, safety and further

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pharmacokinetic and pharmacodynamic information is collected, possible adverse effects and safety risks are identified and a preliminary evaluation of efficacy is conducted.

Phase 3 clinical trials generally involve large numbers of patients at multiple sites and are designed to provide the data necessary to demonstrate the effectiveness of the product candidate for its intended use, its safety in use, and to establish the overall benefit/risk relationship of the product candidate and provide an adequate basis for product approval. Phase 3 clinical trials may include comparisons with placebo and/or other comparator treatments. The duration of treatment is often extended to mimic the actual use of a product during marketing.

Post-approval trials, sometimes referred to as Phase 4 clinical trials, may be conducted after initial marketing approval, to gain additional experience from the treatment of patients in the intended therapeutic indication. In certain instances, FDA may mandate the performance of Phase 4 clinical trials as a condition of approval of an NDA.

As the drug sponsor, we must submit progress reports detailing the results of the clinical trials and other information at least annually to the FDA, as well as written IND safety reports to the FDA and the study investigators for serious and unexpected suspected adverse events, findings from other studies or animal or in vitro testing suggesting a significant risk to humans exposed to the drug and any clinically important increase in the rate of a serious suspected adverse reaction over that listed in the protocol or investigator brochure. The sponsor must submit an IND safety report within 15 calendar days after the sponsor determines that the information qualifies for reporting. The sponsor also must notify the FDA of any unexpected fatal or life-threatening suspected adverse reaction within seven calendar days after the sponsor s initial receipt of the information. Phase 1, Phase 2 and Phase 3 clinical trials may not be completed successfully within any specified period, if at all. The FDA or the sponsor may suspend or terminate a clinical trial 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 trial at its institution if the clinical trial is not being conducted in accordance with the IRB s requirements or if the drug has been associated with unexpected serious harm to patients. Additionally, some clinical trials are overseen by an independent group of qualified experts organized by the clinical trial sponsor, known as a data safety monitoring board or committee. This group provides authorization for whether or not a trial may move forward at designated check points based on access to certain data from the trial. Concurrent with clinical trials, companies usually complete additional animal studies and must also develop additional information about the chemistry and physical characteristics of the drug as well as finalize a process for manufacturing the product in commercial quantities in accordance with cGMP requirements. The manufacturing process must be capable of consistently producing quality batches of the drug candidate and, among other things, must include methods for testing the identity, strength, quality and purity of the final drug product. Additionally, appropriate packaging must be selected and tested and stability studies must be conducted to demonstrate that the drug candidate does not undergo unacceptable deterioration over its shelf life.

NDA and FDA review process

The results of nonclinical studies and clinical trials, together with other detailed information, including extensive manufacturing information and information on the composition of the drug and proposed labeling, are submitted to the FDA in the form of an NDA requesting approval to market the drug for one or more specified indications. The FDA reviews an NDA to determine, among other things, whether a drug is safe and effective for its intended use and whether the product is being manufactured in accordance with cGMP requirements to assure and preserve the product s identity, strength, quality and purity. FDA approval of an NDA must be obtained before a drug may be legally marketed in the United States.

Under the Prescription Drug User Fee Act, or PDUFA, as amended, each NDA is typically accompanied by a user fee (adjusted on an annual basis). According to the FDA s fee schedule, effective through September 30, 2019, the user fee for an NDA is $2,588,478. PDUFA also imposes an annual prescription drug product program fee for human drugs ($309,915). Fee waivers or reductions are available in certain

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circumstances, including a waiver of the application fee for the first application filed by a small business having fewer than 500 employees. Additionally, an application for a product that has been designated as a drug for a rare disease or condition (referred to as an orphan drug) under section 526 of the FDCA is not subject to an application fee unless the application includes an indication for other than a rare disease or condition. Voxelotor for the treatment of sickle cell disease has been granted orphan drug designation by the FDA and by the European Commission.

The FDA reviews all NDAs submitted before it accepts them for filing and may request additional information rather than accepting an NDA for filing. The FDA is supposed to make a decision on accepting an NDA for filing within 60 days of receipt of the submission. Once the NDA is accepted for filing, the FDA begins an in-depth review of the NDA. Under the goals and policies agreed to by the FDA under PDUFA, the FDA is supposed to complete its initial review of an NDA that it has accepted for review and respond to the applicant within stated periods (within 10 months for a standard NDA and six months for an NDA designated by the agency for priority review). However, the FDA does not always meet its PDUFA goal dates for standard and priority NDAs, and the review process is often significantly extended by FDA requests for additional information or clarification.

Before approving an NDA, the FDA will conduct a pre-approval inspection of the manufacturing facilities for the new product (including the facilities of contract manufacturers, if applicable) to determine whether they comply with cGMP requirements. The FDA will not approve the product unless it determines that the manufacturing processes and facilities are in compliance with cGMP requirements and adequate to assure consistent production of the product within required specifications. The FDA may also audit data from clinical trials to ensure compliance with GCP requirements. Additionally, the FDA may refer applications for novel drug products or drug products which 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. There are likely to be extensive discussions between the FDA and the applicant during the review process. The review and evaluation of an NDA by the FDA is very comprehensive and time consuming and may take longer than originally planned to complete.

In addition, under Subpart H of FDA s NDA regulations, which governs accelerated approval, the FDA may approve an NDA for a new drug product on the basis of adequate and well-controlled clinical trials establishing that the drug product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity. The FDA grants accelerated approval under Subpart H for new drugs that address serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments. Drugs approved under Subpart H are required to be further evaluated in at least one post-marketing study to verify clinical benefit. As a condition of accelerated approval, the FDA may impose marketing restrictions to limit distribution or use to assure safe use of the drug. Pursuing accelerated approval under Subpart H does not ensure faster development timelines or ensure regulatory approval.

After the FDA evaluates an NDA, it will issue an approval letter or a complete response letter. An approval letter authorizes commercial marketing of the drug with specific prescribing information for specific indications. A complete response letter indicates that the review cycle of the application is complete and the application will not be approved in its present form, and usually describes all of the specific deficiencies in the NDA identified by the FDA. The complete response letter may require additional clinical data and/or additional clinical trial(s), and/or other significant and time-consuming requirements related to clinical trials, nonclinical studies or manufacturing. If a complete response letter is issued, the applicant may either resubmit the NDA, addressing all of the deficiencies identified in the letter, withdraw the application, or request a hearing. Even if such data and information is submitted, the FDA may ultimately decide that the NDA does not satisfy the criteria for approval.

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United States Orphan drug designation

We were granted orphan drug designation for voxelotor for the treatment of SCD by the FDA in 2015. Under the Orphan Drug Act in the United States, the FDA may grant orphan designation to a drug 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 in limited circumstances). Orphan product designation must be requested before submitting an NDA. 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, but does confer other potential development and commercialization benefits as described below.

If we submit an NDA seeking approval for voxelotor for the treatment of sickle cell disease, this NDA submission should qualify for the orphan user fee exemption from the PDUFA application fee. In addition, we should qualify for additional incentives, including tax credits for qualifying clinical trials, and may also qualify for a substantial period of market exclusivity. 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 for the same indication for seven years from the date of such approval, except in limited circumstances, such as a showing of clinical superiority to the product with orphan exclusivity by means of greater effectiveness, greater safety, or by providing a major contribution to patient care. Competitors, however, may receive approval of different products for the indication for which the orphan product has exclusivity and may obtain approval for the same product for a different indication than that for which the orphan product has exclusivity. A competitor could also block the approval of one of our products for seven years by obtaining orphan product exclusivity for the same product (or a competitor product that contains our product candidate) for the same indication we are seeking (although we are not aware that any competitor is seeking to develop voxelotor for sickle cell disease alone or as part of a competitor s product). If a drug designated as an orphan product receives marketing approval for an indication broader than what is designated, it may not be entitled to orphan product exclusivity. Orphan drug status in the European Union, or EU, has similar, but not identical, requirements and benefits.

Expedited development and review programs

In addition to the US orphan drug designation, our product candidate voxelotor has received a Fast Track designation from the FDA for the potential treatment of sickle cell disease. The FDA s Fast Track program is intended to expedite or facilitate the process for reviewing new drugs that are intended to treat a serious or life threatening condition, where nonclinical or clinical data demonstrate the potential to address unmet medical needs for the condition. Fast Track designation applies to both the product and the specific indication for which it is being studied.

Any product submitted to the FDA for marketing, including under a Fast Track program, may be eligible for other types of FDA programs intended to expedite development and review, such as priority review and accelerated approval under Subpart H. Any product is eligible for priority review if it treats a serious or life-threatening condition and, if approved, would provide a significant improvement in safety and effectiveness compared to available therapies. The FDA will attempt to direct additional resources to the evaluation of an application for a new drug designated for priority review.

Additionally, our product candidate voxelotor has received a breakthrough therapy designation from the FDA for the potential treatment of sickle cell disease. The benefits of breakthrough therapy designation include the same benefits as a Fast Track designation, in addition to intensive guidance from FDA to ensure an efficient drug development program. Fast Track designation, priority review, accelerated approval and breakthrough designation do not change

the standards for approval but may expedite the development or approval process.

Pediatric information

Under the Pediatric Research Equity Act, as amended, an NDA or supplement to an NDA must contain data to assess the safety and efficacy of the drug for the claimed indications in all relevant pediatric

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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 pediatric data or full or partial waivers. A sponsor who is planning to submit a marketing application for a drug that includes a new active ingredient, new indication, new dosage form, new dosing regimen or new route of administration is required to submit an initial Pediatric Study Plan, or PSP, within sixty days of an end-of-Phase 2 meeting or, if there is no end-of-Phase 2 meeting as early as practicable before the initiation of the Phase 3 or Phase 2/3 study. The initial PSP must include an outline of the pediatric study or studies that the sponsor plans to conduct, including study objectives and design, age groups, relevant endpoints and statistical approach, or a justification for not including such detailed information, and any request for a deferral of pediatric assessments or a full or partial waiver of the requirement to provide data from pediatric studies along with supporting information. The FDA and the sponsor must reach agreement on the PSP. A sponsor can submit amendments to an agreed-upon initial PSP at any time if changes to the pediatric plan need to be considered based on data collected from nonclinical studies, early phase clinical trials, and/or other clinical development programs.

Post-marketing requirements

Following approval of a new product, a pharmaceutical company and the approved product are subject to continuing regulation by the FDA, including, monitoring and recordkeeping activities, reporting of adverse experiences and complying with complex promotion and advertising requirements, which include restrictions on promoting drugs for uses or for patient populations for which the drug was not approved (known as off-label use), and limitations on industry-sponsored scientific and educational activities and on interactions with healthcare providers. Although physicians may prescribe legally available drugs for off-label uses, manufacturers may not market or promote such off-label uses. Prescription drug promotional materials must be submitted to the FDA in conjunction with their first use of these materials, and may be required to be reviewed in advance in certain circumstances such as a new product launch. Further, if there are any modifications to the drug, including changes in indications, labeling, or manufacturing processes or facilities, the pharmaceutical company may be required to submit and obtain FDA approval of a new NDA or NDA supplement, which may require additional data or the conduct of additional nonclinical studies and clinical trials. 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 Risk Evaluation and Mitigation Strategy, or REMS, or the conduct of post-marketing studies to assess a newly discovered safety issue.

FDA regulations require that products be manufactured in specific approved facilities and in accordance with cGMP requirements. We rely, and expect to continue to rely, on third parties for the production of clinical and commercial quantities of our products in accordance with cGMP requirements. Our third party manufacturers must comply with cGMP requirements that require among other things, quality control and quality assurance, the maintenance of records and documentation, and the obligation to investigate and correct any deviations from cGMP. Drug manufacturers and other entities involved in the manufacture and distribution of approved drugs 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 cGMP requirements and other laws. Accordingly, manufacturers must continue to expend time, money, and effort in the area of production and quality control to maintain cGMP compliance. The discovery of violative conditions, including failure to conform to cGMP requirements, could result in enforcement actions, and the discovery of problems with a product after approval may result in restrictions on a product, manufacturer or holder of an approved NDA, including recall.

Other regulatory matters

Manufacturing, sales, promotion and other activities following product approval are also subject to regulation by numerous regulatory authorities in addition to the FDA, including, in the United States, the Centers for Medicare &

Medicaid Services, or CMS, other divisions of the Department of Health and Human Services, the United States Department of Justice, the Drug Enforcement Administration, the Consumer Product Safety

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Commission, the Federal Trade Commission, the Occupational Safety & Health Administration, the Environmental Protection Agency and state and local governments.

For example, in the United States, sales, marketing and scientific/educational programs must also comply with state and federal fraud and abuse laws. These laws include the federal Anti-Kickback Statute, which makes it illegal for any person, including a prescription drug manufacturer (or a party acting on its behalf) to knowingly and willfully solicit, receive, offer, or pay any remuneration that is intended to induce or reward referrals, including the purchase, recommendation, order, or prescription of a particular drug, for which payment may be made under a federal healthcare program, such as Medicare or Medicaid. Violations of this law are punishable by up to five years in prison, criminal fines, administrative civil money penalties and exclusion from participation in federal healthcare programs. In addition, the Patient Protection and Affordable Health Care Act, as amended by the Health Care and Education Reconciliation Act of 2010, or collectively the ACA, among other things, amends the intent requirement of the federal Anti-Kickback Statute and criminal healthcare fraud statutes created by the federal Health Insurance Portability and Accountability Act of 1996. A person or entity no longer needs to have actual knowledge of the statute or specific intent to violate it. Moreover, the ACA provides that the government may assert that a claim including items or services resulting from a violation of the federal Anti-kickback Statute constitutes a false or fraudulent claim for purposes of the False Claims Act.

Moreover, although as a drug manufacturer we would not submit claims directly to payors, drug manufacturers can be held liable under the federal False Claims Act, which prohibits anyone from knowingly presenting, or causing to be presented, for payment to federal programs (including Medicare and Medicaid) claims for items or services, including drugs, that are false or fraudulent, claims for items or services not provided as claimed, or claims for medically unnecessary items or services. The government may deem manufacturers to have caused the submission of false or fraudulent claims by, for example, providing inaccurate billing or coding information to customers or promoting a product off-label. In addition, our future activities relating to the reporting of wholesaler or estimated retail prices for our products, the reporting of prices used to calculate Medicaid rebate information and other information affecting federal, state, and third-party reimbursement for our products, and the sale and marketing of our products, are subject to scrutiny under this law. Penalties for a False Claims Act violation include three times the actual damages sustained by the government, plus mandatory civil penalties for each separate false claim, the potential for exclusion from participation in federal healthcare programs, and the potential implication of various federal criminal statutes.

Pricing and rebate programs must comply with the Medicaid rebate requirements of the U.S. Omnibus Budget Reconciliation Act of 1990 and more recent requirements in the ACA. If products are made available to authorized users of the Federal Supply Schedule of the General Services Administration, additional laws and requirements apply. The handling of any controlled substances must comply with the U.S. Controlled Substances Act and Controlled Substances Import and Export Act. Products must meet applicable child-resistant packaging requirements under the U.S. Poison Prevention Packaging Act. Manufacturing, sales, promotion and other activities are also potentially subject to federal and state consumer protection and unfair competition laws.

The distribution of pharmaceutical products is subject to additional requirements and regulations, including extensive record-keeping, licensing, storage and security requirements intended to prevent the unauthorized sale of pharmaceutical products.

The failure to comply with any of these laws or regulatory requirements subject firms to possible legal or regulatory action. Depending on the circumstances, failure to meet applicable regulatory requirements can result in criminal prosecution, fines or other penalties, injunctions, recall or seizure of products, total or partial suspension of production, denial or withdrawal of product approvals, or refusal to allow a firm to enter into supply contracts, including government contracts. Any action against us for violation of these laws, even if we successfully defend

against it, could cause us to incur significant legal expenses and divert our management s attention from the operation of our business. Prohibitions or restrictions on sales or withdrawal of future products marketed by us could materially affect our business in an adverse way.

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

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modifications to product labeling; (iii) the voluntary 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.

United States patent term restoration and marketing exclusivity

Depending upon the timing, duration and specifics of the FDA approval of any of our drug 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 an NDA, plus the time between the submission date of an NDA and the approval of that application, except that the review period is reduced by any time during which the applicant failed to exercise due diligence. Only one patent applicable to an approved drug is eligible for the patent term extension and the application for the extension must be submitted prior to the expiration of the patent. The United States Patent and Trademark Office, or USPTO, in consultation with the FDA, reviews and approves any application for patent term extension or restoration. In the future, we may apply for restoration of patent term for our voxelotor product candidate, depending on the expected length of the clinical trials and other factors involved in the filing of the relevant NDA.

Marketing exclusivity provisions under the FDCA provide a five-year period of non-patent marketing exclusivity within the United States to the first applicant to obtain approval of an NDA for a new chemical entity. A drug is a new chemical entity if the FDA has not previously approved any other new drug containing the same active moiety, which is the molecule or ion responsible for the action of the drug substance. So far as we are aware, voxelotor would qualify as a new chemical entity under these provisions. During the exclusivity period, the FDA may not accept for review an abbreviated new drug application, or ANDA, or a 505(b)(2) NDA submitted by another company for another drug based on the same active moiety, regardless of whether the drug is intended for the same indication as the original innovator drug or for another indication, where the applicant does not own or have a legal right of reference to all the data required for approval. However, an application may be submitted after four years if it contains a certification of patent invalidity or non-infringement to one of the patents listed with the FDA by the innovator who holds the NDA for the active agent.

The FDCA also provides three years of marketing exclusivity for an NDA, or supplement to an existing NDA for a drug product that contains an active moiety that has been previously approved if new clinical investigations, other than bioavailability studies, that were conducted or sponsored by the applicant are deemed by the FDA to be essential to the approval of the application, for example for new indications, dosages or strengths of an existing drug. This three-year exclusivity covers only the modification for which the drug received approval on the basis of the new clinical investigations and does not prohibit the FDA from approving ANDAs for drugs containing the active agent for the original indication.

Five-year and three-year exclusivity will not delay the submission or approval of a full NDA by a competitor. However, an applicant submitting a full NDA would be required to conduct or obtain a right of reference to all of the nonclinical studies and clinical trials necessary to demonstrate safety and efficacy. Orphan drug exclusivity, as described above, may offer a seven-year period of marketing exclusivity in the United States. Pediatric exclusivity is another type of regulatory market exclusivity in the United States which, if granted, adds six months to the end of existing exclusivity periods and patent terms, and may be granted based on the voluntary completion of a pediatric trial in accordance with an FDA-issued pre-approval written request for such a pediatric trial where information

relating to the use of the product candidate in a pediatric population may produce health benefits in that population.

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European Union drug development, Orphan Drug and PRIME designations

In the EU, our product candidates may also be subject to extensive regulatory requirements. As in the United States, medicinal products can only be marketed if a marketing authorization from the competent regulatory authorities has been obtained.

Similar to the United States, the various phases of nonclinical and clinical research in the EU are subject to significant regulatory controls. Although the EU Clinical Trials Directive 2001/20/EC has sought to harmonize the EU clinical trials regulatory framework, setting out common rules for the control and authorization of clinical trials in the EU, the EU Member States have transposed and applied the provisions of the Directive differently. This has led to significant variations in the member state regimes. Under the current regime, before a clinical trial can be initiated it must be approved in each of the EU countries where the trial is to be conducted by two distinct bodies: the National Competent Authority, or NCA, and one or more Ethics Committees, or ECs. Under the current regime all suspected unexpected serious adverse reactions to the investigated drug that occur during the clinical trial have to be reported to the NCA and ECs of the Member State where they occurred.

In April 2014, the EU adopted a new Clinical Trials Regulation (EU) No 536/2014, which is set to replace the current Clinical Trials Directive 2001/20/EC. It is expected that the new Clinical Trials Regulation (EU) No 536/2014 will apply in 2019 with a three-year transition period. It will overhaul the current system of approvals for clinical trials in the EU. Specifically, the new regulation, which will be directly applicable in all member states, aims at simplifying and streamlining the approval of clinical trials in the EU. For instance, the new Clinical Trials Regulation provides for a streamlined application procedure via a single entry point and strictly defined deadlines for the assessment of clinical trial applications.

In November 2016, the European Commission, acting on a positive recommendation from the Committee for Orphan Medicinal Products, or COMP, of the European Medicines Agency, or EMA, designated voxelotor as an orphan medicinal product for the treatment of sickle cell disease. Orphan drug status in the EU has similar, but not identical, requirements and benefits to US orphan drug status, including 10 years of marketing exclusivity from the approval of the marketing application, designated product-specific consultation by the EMA, and certain reductions or exemptions in regulatory fees.

In June 2017, the European Medicines Agency, or EMA, granted PRIME designation for voxelotor for the treatment of SCD. The PRIME program is a new regulatory mechanism that provides for early and proactive EMA support to medicine developers to help patients benefit as early as possible from innovative new products that have demonstrated the potential to significantly address an unmet medical need.

European Union drug review and approval

In the European Economic Area, or EEA, which is comprised of the 28 Member States of the EU plus Norway, Iceland and Liechtenstein, medicinal products can only be commercialized after obtaining a Marketing Authorization, or MA. There are two types of marketing authorizations:

The Community MA is issued by the European Commission through the Centralized Procedure, based on the opinion of the Committee for Medicinal Products for Human Use, or CHMP, of the EMA, and is valid throughout the entire territory of the EEA. The Centralized Procedure is mandatory for certain types of products, such as biotechnology medicinal products, orphan medicinal products, advanced-therapy medicines such as gene-therapy, somatic cell-therapy or tissue-engineered medicines, and medicinal products containing a new active substance indicated for the treatment of HIV, AIDS, cancer, neurodegenerative disorders, diabetes, auto-immune and other immune

dysfunctions, and viral diseases. This mandatory Centralized Procedure applies in the case of voxelotor for sickle cell disease, in light of the 2016 designation of voxelotor as an orphan medicinal product for the treatment of sickle cell disease.

The Centralized Procedure is optional for products containing a new active substance not yet authorized in the EEA, or for products that constitute a significant therapeutic, scientific or technical innovation or which are in the interest of public health in the EU.

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National MAs, which are issued by the competent authorities of the Member States of the EEA and only cover their respective territory, are available for products not falling within the mandatory scope of the Centralized Procedure. Where a product has already been authorized for marketing in a Member State of the EEA, this National MA can be recognized in another Member States through the Mutual Recognition Procedure. If the product has not received a National MA in any Member State at the time of application, it can be approved simultaneously in various Member States through the Decentralized Procedure. Under the Decentralized Procedure an identical dossier is submitted to the competent authorities of each of the Member States in which the MA is sought, one of which is selected by the applicant as the Reference Member State, or RMS. The competent authority of the RMS prepares a draft assessment report, a draft summary of the product characteristics, or SPC, and a draft of the labeling and package leaflet, which are sent to the other Member States (referred to as the Member States Concerned) for their approval. If the Member States Concerned raise no objections, based on a potential serious risk to public health, to the assessment, SPC, labeling, or packaging proposed by the RMS, the product is subsequently granted a national MA in all the Member States (i.e., in the RMS and the Member States Concerned).

Under the above-described procedures, before granting the MA, the EMA or the competent authorities of the Member States of the EEA make an assessment of the risk-benefit balance of the product on the basis of scientific criteria concerning its quality, safety and efficacy.

European Union new chemical entity exclusivity

In the EU, new chemical entities, sometimes referred to as new active substances, qualify for eight years of data exclusivity upon marketing authorization and an additional two years of market exclusivity. The data exclusivity, if granted, prevents regulatory authorities in the EU from referencing the innovator s data to assess a generic application for eight years, after which generic marketing authorization can be submitted, and the innovator s data may be referenced, but not approved for two years. The overall ten-year period will be extended to a maximum of 11 years if, during the first eight years of those ten years, the marketing authorization holder obtains an authorization for one or more new therapeutic indications which, during the scientific evaluation prior to their authorization, are determined to bring a significant clinical benefit in comparison with existing therapies.

European Union orphan designation and exclusivity

In the EU, the European Commission, after reviewing the opinion of the EMA s Committee for Orphan Medicinal Products grants orphan drug designation to promote the development of products that are intended for the diagnosis, prevention or treatment of life-threatening or chronically debilitating conditions affecting not more than 5 in 10,000 persons in the EU Community (or where it is unlikely that the development of the medicine would generate sufficient return to justify the investment) and for which no satisfactory method of diagnosis, prevention, or treatment has been authorized (or, if a method exists, the product would be a significant benefit to those affected).

In the EU, orphan drug designation entitles a party to financial incentives such as reduction of fees or fee waivers and ten years of market exclusivity is granted following medicinal product approval. This period may be reduced to six years if the orphan drug designation criteria are no longer met, including where it is shown that the product is sufficiently profitable not to justify maintenance of market exclusivity. Orphan drug designation must be requested before submitting an application for marketing approval. Orphan drug designation does not convey any advantage in, or shorten the duration of, the regulatory review and approval process. In November 2016 we were granted orphan drug designation in the EU for voxelotor for the potential treatment of SCD.

Rest of the world regulation

For other countries outside of the EU and the United States, such as countries in Eastern Europe, Latin America or Asia, the requirements governing the conduct of clinical trials, product licensing, pricing and reimbursement vary from country to country. Additionally, the clinical trials must be conducted in accordance with GCP requirements and the applicable regulatory requirements and the ethical principles that have their origin in the Declaration of Helsinki.

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If we fail to comply with applicable foreign regulatory requirements, we may be subject to, among other things, fines, suspension or withdrawal of regulatory approvals, product recalls, seizure of products, operating restrictions and criminal prosecution.

Reimbursement

Sales of our products will depend, in part, on the extent to which our products will be covered by third-party payors, such as government health programs, commercial insurance and managed healthcare organizations, as well as the level of reimbursement such third-party payors provide for our products. Patients and providers are unlikely to use our products unless coverage is provided and reimbursement is adequate to cover a significant portion of the cost of our products. In the United States, no uniform policy of coverage and reimbursement for drug products exists, and one payor s determination to provide coverage and adequate reimbursement for a product does not assure that other payors will make a similar determination. Accordingly, decisions regarding the extent of coverage and amount of reimbursement to be provided for any of our products will be made on a payor-by-payor basis. The coverage determination process is often time-consuming and costly and is likely to require us to provide scientific and clinical support for the use of our product candidates to each payor individually, with no assurance that coverage and adequate reimbursement will be obtained.

The United States government, state legislatures and foreign governments have shown significant interest in implementing cost containment programs to limit the growth of government-paid health care costs, including price-controls, restrictions on reimbursement and requirements for substitution of generic products for branded prescription drugs. For example, the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act of 2010, or collectively the ACA, contains provisions that may reduce the profitability of drug products through increased rebates for drugs reimbursed by Medicaid programs, extension of Medicaid rebates to Medicaid managed care plans, and mandatory discounts for certain Medicare Part D beneficiaries and annual fees based on pharmaceutical companies share of sales to federal health care programs. Adoption of general controls and measures, coupled with the tightening of restrictive policies in jurisdictions with existing controls and measures, could limit payments for pharmaceutical drugs.

The Medicaid Drug Rebate Program requires pharmaceutical manufacturers to enter into and have in effect a national rebate agreement with the Secretary of the Department of Health and Human Services as a condition for states to receive federal matching funds for the manufacturer s outpatient drugs furnished to Medicaid patients. Effective in 2010, the ACA made several changes to the Medicaid Drug Rebate Program, including increasing pharmaceutical manufacturers rebate liability by raising the minimum basic Medicaid rebate on most branded prescription drugs from 15.1% of average manufacturer price, or AMP, to 23.1% of AMP, and adding a new rebate calculation for line extensions (i.e., new formulations, such as extended release formulations) of solid oral dosage forms of branded products, creating a new methodology by which rebates are calculated for drugs that are inhaled, infused, instilled, implanted or injected, as well as potentially impacting their rebate liability by modifying the statutory definition of AMP. The ACA also expanded the universe of Medicaid utilization subject to drug rebates by requiring pharmaceutical manufacturers to pay rebates on Medicaid managed care utilization as of 2010 and by expanding the population potentially eligible for Medicaid drug benefits (phased-in by 2014). Pricing and rebate programs must also comply with the Medicaid rebate requirements of the U.S. Omnibus Budget Reconciliation Act of 1990.

The Medicare Prescription Drug, Improvement, and Modernization Act of 2003, or the MMA, established the Medicare Part D program to provide a voluntary prescription drug benefit to Medicare beneficiaries. Under Part D, Medicare beneficiaries may enroll in prescription drug plans offered by private entities that provide coverage of outpatient prescription drugs. Unlike Medicare Parts A and B, Part D coverage is not standardized. Part D prescription drug plan sponsors are not required to pay for all covered Part D drugs, and each drug plan can develop its own drug

formulary that identifies which drugs it will cover and at what tier or level. While all Medicare drug plans must give at least a standard level of coverage set by Medicare, Part D prescription drug plan sponsors are not required to pay for all covered Part D drugs, and each drug plan can develop its own drug formulary that identifies which drugs it will cover and at what tier or level. However, Part D prescription drug formularies must include drugs within each therapeutic category and class of covered Part D drugs, though not

necessarily all the drugs in each category or class. Any formulary used by a Part D prescription drug plan must be developed and reviewed by a pharmacy and therapeutic committee. Government payment for some of the costs of prescription drugs may increase demand for drugs for which we obtain marketing approval. Any negotiated prices for any of our products covered by a Part D prescription drug plan will likely be lower than the prices we might otherwise obtain. Moreover, while the MMA applies only to drug benefits for Medicare beneficiaries, private payors often follow Medicare coverage policy and payment limitations in setting their own payment rates. Any reduction in payment that results from the MMA may result in a similar reduction in payments from non-governmental payors.

For a drug product to receive federal reimbursement under the Medicaid or Medicare Part B programs or to be sold directly to U.S. government agencies, the manufacturer must extend discounts to entities eligible to participate in the 340B drug pricing program. The required 340B discount on a given product is calculated based on the AMP and Medicaid rebate amounts reported by the manufacturer. As of 2010, the ACA expanded the types of entities eligible to receive discounted 340B pricing, although under the current state of the law these newly eligible entities (with the exception of children s hospitals) will not be eligible to receive discounted 340B pricing on orphan drugs. As 340B drug pricing is determined based on AMP and Medicaid rebate data, the revisions to the Medicaid rebate formula and AMP definition described above could cause the required 340B discount to increase.

The American Recovery and Reinvestment Act of 2009 provides funding for the federal government to compare the effectiveness of different treatments for the same illness. The plan for the research was published in 2012 by the Department of Health and Human Services, the Agency for Healthcare Research and Quality and the National Institutes for Health, and periodic reports on the status of the research and related expenditures are made to Congress. Although the results of the comparative effectiveness studies are not intended to mandate coverage policies for public or private payors, it is not clear what effect, if any, the research will have on the sales of our drug candidates, if any such drug or the condition that they are intended to treat are the subject of such research. It is also possible that comparative effectiveness research demonstrating benefits in a competitor s drug could adversely affect the sales of our drug candidate. If third-party payors do not consider our drugs to be cost-effective compared to other available therapies, they may not cover our drugs after approval as a benefit under their plans or, if they do, the level of payment or utilization may not be sufficient to allow us to sell our drugs on a profitable basis.

In recent years, additional laws have resulted in direct or indirect reimbursement reductions for certain Medicare providers, including:

The Budget Control Act of 2011, among other things, created measures for spending reductions by Congress. A Joint Select Committee on Deficit Reduction, tasked with recommending a targeted deficit reduction of at least $1.2 trillion for the years 2013 through 2021, was unable to reach required goals, thereby triggering the legislation s automatic reduction to several government programs. These changes included aggregate reductions to Medicare payments to providers of up to 2% per fiscal year, which went into effect in April 2013 and will remain in effect through 2025 unless additional Congressional action is taken.

The American Taxpayer Relief Act of 2012, among other things, reduced Medicare payments to several providers, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years.

These laws, and future state and federal healthcare reform measures may be adopted in the future, any of which may result in additional reductions in Medicare and other healthcare funding and otherwise affect the prices we may obtain for any product candidates for which we may obtain regulatory approval or the frequency with which any such product candidate is prescribed or used.

As noted above, the marketability of any products for which we receive regulatory approval for commercial sale may suffer if the government and third-party payors fail to provide adequate coverage and reimbursement. We expect that an increasing emphasis on cost containment measures in the United States will continue to increase the pressure on pharmaceutical pricing. Coverage policies and third-party reimbursement

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rates may change at any time. Even if favorable coverage and reimbursement status is attained for one or more products for which we receive regulatory approval, less favorable coverage policies and reimbursement rates may be implemented in the future.

In many foreign countries, the proposed pricing for a drug must be approved before it may be lawfully marketed. The requirements governing drug pricing and reimbursement vary widely from country to country. For example, the EU provides options for its member states to restrict the range of medicinal products, for which their national health insurance systems provide reimbursement and to control the prices of medicinal products for human use. A member state may approve a specific price for the medicinal product or it may instead adopt a system of direct or indirect controls on the profitability of the company placing the medicinal product on the market. Historically, products launched in the EU do not follow price structures of the United States and generally prices tend to be significantly lower. There can be no assurance that any country that has price controls or reimbursement limitations for pharmaceutical products will allow favorable reimbursement and pricing arrangements for any of our products, if approved.

US Healthcare Reform

The ACA has had a significant impact on the healthcare industry. The ACA expanded coverage for the uninsured while at the same time containing overall healthcare costs. With regard to pharmaceutical products, the ACA, among other things, addressed a new methodology by which rebates owed by manufacturers under the Medicaid Drug Rebate Program are calculated for drugs that are inhaled, infused, instilled, implanted or injected, increased the minimum Medicaid rebates owed by manufacturers under the Medicaid Drug Rebate Program and extended the rebate program to individuals enrolled in Medicaid managed care organizations, established annual fees and taxes on manufacturers of certain branded prescription drugs, and a new Medicare Part D coverage gap discount program, in which manufacturers must agree to offer 50% point-of-sale discounts off negotiated prices of applicable brand drugs to eligible beneficiaries during their coverage gap period, as a condition for the manufacturer s outpatient drugs to be covered under Medicare Part D. The required discount was increased to 70% on January 1, 2019 pursuant to subsequent legislation.

Some of the provisions of the ACA have yet to be fully implemented, while certain provisions have been subject to judicial and Congressional challenges. The U.S. Supreme Court has upheld certain key aspects of the legislation, including a tax-based shared responsibility payment imposed on certain individuals who fail to maintain qualifying health coverage for all or part of a year, which is commonly the requirement that all individuals maintain health insurance coverage or pay a penalty, referred to as the individual mandate. However, the new presidential administration has indicated that enacting changes to the ACA is a legislative priority, and has discussed repealing and replacing or amending the ACA. While Congress has not passed repeal legislation to date, the 2017 Tax Reform Act includes a provision repealing the individual mandate, effective starting in 2019. In addition, in 2017 President Trump signed executive orders directing federal agencies with authorities and responsibilities under the ACA to waive, defer, grant exemptions from, or delay the implementation of any provision of the ACA that would impose a fiscal burden on states or a cost, fee, tax, penalty or regulatory burden on individuals, healthcare providers, health insurers, or manufacturers of pharmaceuticals or medical devices, and terminated the cost-sharing subsidies that reimburse insurers under the ACA. Since its enactment, there have been many judicial, President and Congressional challenges to numerous aspects of the ACA.

The full impact of the ACA, any law repealing, replacing, or modifying elements of it, and the political uncertainty surrounding its repeal, replacement, or modification on our business remains unclear. We expect that additional federal healthcare reform measures may be adopted in the future, any of which could limit the amounts that federal and state governments will pay for healthcare drugs and services, and in turn could significantly reduce the projected

value of certain development projects and reduce our profitability and may increase our regulatory burdens and operating costs.

For any of our product candidates, including voxelotor, which may obtain regulatory approval and are marketed in the United States, our arrangements with third-party payors, healthcare providers, and customers

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may expose us to broadly applicable fraud and abuse and other healthcare laws and regulations that may constrain the business or financial arrangements and relationships through which we market, sell and distribute any products for which we obtain marketing approval. In addition, we may be subject to health information privacy and security regulation by U.S. federal and state governments and foreign jurisdictions in which we conduct our business. In the United States, these laws include, without limitation, state and federal anti-kickback, false claims, physician transparency, and patient data privacy and security laws and regulations, including but not limited to the federal Anti-Kickback Statute, the federal False Claims laws, HIPAA, the Physician Payment Sunshine Act, and analogous state laws and regulations such as state anti-kickback and false claims laws and analogous non-U.S. fraud and abuse laws and regulations, may apply to sales or marketing arrangements and claims involving healthcare items or services reimbursed by non-governmental third-party payors, including private insurers.

Employees

As of December 31, 2018, we employed 171 full-time employees, including 117 in research and development and 54 in general and administrative, which includes our commercial team, in the United States. We have never had a work stoppage, and none of our employees is represented by a labor organization or under any collective-bargaining arrangements. We consider our employee relations to be good.

Research and Development

Research and development expenses recognized were $131.3 million for the year ended December 31, 2018, $87.8 million for the year ended December 31, 2017 and $62.2 million for the year ended December 31, 2016.

Financial Information about Segments

We operate in a single accounting segment dedicated to discovering, developing and commercializing novel therapeutics to treat grievous blood-based disorders. Refer to Note 1, Organization and Basis of Presentation in the Notes to Consolidated Financial Statements included elsewhere in this report.

Corporate Information

We were incorporated in Delaware in February 2011 and commenced operations in May 2012. Our principal executive offices are located at 171 Oyster Point Blvd., Suite 300, South San Francisco, California 94080. Our telephone number is (650) 741-7700 and our e-mail address is investor@gbt.com. Our Internet website address is www.gbt.com. No portion of our website is incorporated by reference into this Annual Report on Form 10-K.

You are advised to read this Annual Report on Form 10-K in conjunction with other reports and documents that we file from time to time with the Securities and Exchange Commission, or SEC. In particular, please read our Quarterly Reports on Form 10-Q and any Current Reports on Form 8-K that we may file from time to time. You may obtain copies of these reports directly from us or from the SEC. In addition, the SEC maintains information for electronic filers (including Global Blood Therapeutics, Inc.) at its website at www.sec.gov. We make our periodic and current reports available on our internet website, free of charge, as soon as reasonably practicable after such material is electronically filed with, or furnished to, the SEC.

Item 1A. ***Risk Factors***

This Annual Report on Form 10-K contains forward-looking information based on our current expectations. Because our business is subject to many risks and our actual results may differ materially from any forward-looking statements

made by or on behalf of us, this section includes a discussion of important factors that could affect our business, operating results, financial condition and the trading price of our common stock. You should carefully consider these risk factors, together with all of the other information included in this Annual Report on Form 10-K as well as our other publicly available filings with the SEC.

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Risks Related to Our Financial Position and Need for Additional Capital

We are a clinical development-stage biopharmaceutical company with a limited operating history. We have incurred significant losses since our inception and anticipate that we will continue to incur losses for the foreseeable future. We have only one product candidate in clinical development and have not generated any revenue since our inception, which, together with our limited operating history, may make it difficult for you to assess our future viability.

We are a clinical development-stage biopharmaceutical company with a limited operating history upon which you can evaluate our business and prospects. Biopharmaceutical product development is a highly speculative undertaking and involves a substantial degree of risk. To date, we have focused principally on developing our lead product candidate, voxelotor, which is our only product candidate in clinical development. In August 2018, we entered into an exclusive worldwide license agreement with F. Hoffman-LaRoche and Hoffman-La Roche Inc. (together, Roche) for the development and commercialization of inclacumab, a novel fully human monoclonal antibody against P-selectin, as a treatment for vaso-occlusive crises (VOC) in patients with SCD.

We are not profitable and have incurred losses in each year since our inception in February 2011 and the commencement of our principal operations in May 2012. Our net losses for the years ended December 31, 2018 and 2017 were $174.2 million and $117.0 million, respectively. As of December 31, 2018, we had an accumulated deficit of $472.2 million. We have not generated any revenue since our inception, and have financed our operations primarily through the sale of equity securities. We continue to incur significant research and development and other expenses related to our ongoing operations and expect to incur losses for the foreseeable future. We anticipate these losses will increase as we:

- continue to advance voxelotor in clinical development, including our completed Phase 3 HOPE Study and Phase 2a HOPE-KIDS 1 Study of voxelotor for the potential treatment of patients with SCD, and additional clinical trials ongoing or in the future in SCD patients;
- establish and maintain manufacturing and supply relationships with third parties that can provide adequate supplies (in amount and quality) of voxelotor to support further clinical development and, if approved, commercialization;
- seek and obtain regulatory and marketing approvals for voxelotor for SCD or any other indication we may pursue;
- build a sales and marketing organization or enter into selected collaborations to commercialize voxelotor for any indication, if approved;
- build a medical affairs organization to advance our engagement with healthcare providers and stakeholders;
- advance our other programs, including inclacumab, through nonclinical and clinical development and commence development activities for any additional product candidates we may identify and pursue; and
- expand our organization to support our research, development, medical, and commercialization activities and our operations as a public company.

We have never generated any revenues from product sales and may never be able to develop or commercialize a marketable drug product or achieve profitability. Even if we achieve profitability in the future, we may not be able to sustain profitability in subsequent periods. Our failure to maintain adequate cash reserves to advance our development programs or achieve approval to commercialize any products, or our failure to achieve sustained profitability would depress the value of our company and could impair our ability to raise capital, expand our business, diversify our

research and development pipeline, market voxelotor or any other product candidates we may identify and pursue (if approved), or continue our operations. Our prior losses, combined with expected future losses, have had and will continue to have an adverse effect on our stockholders equity and working capital.

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We will require substantial additional funding to achieve our business goals. If we are unable to obtain this funding when needed and on acceptable terms, we could be forced to delay, limit or terminate our product development efforts or other operations. Raising additional capital may subject us to unfavorable terms, cause dilution to our existing stockholders, restrict our operations or require us to relinquish rights to our product candidates and technologies.

We are currently advancing voxelotor through clinical development for SCD, including in a multi-national Phase 3 clinical trial in adult and adolescent patients with SCD called the HOPE Study. We are also evaluating the safety and pharmacokinetics of single and multiple doses of voxelotor in a Phase 2a clinical trial in adolescent and pediatric patients with SCD, which we expanded to include a new single-dose cohort in children aged 6-11. Voxelotor is currently our only product candidate in clinical development, although we are conducting nonclinical research activities in other programs. In December 2018, we announced that the U.S. Food and Drug Administration (FDA) agreed with our proposal to use an accelerated regulatory approval pathway for voxelotor for the treatment of SCD under the FDA s Subpart H regulations (Subpart H), and that we plan to submit an NDA under this pathway.

Developing biopharmaceutical products is expensive and time-consuming, and we expect our research and development expenses to increase substantially in connection with our ongoing activities, particularly as we advance voxelotor, inclacumab and other product candidates that we may identify and pursue in clinical trials. As of December 31, 2018 and 2017, we had working capital of $452.0 million and $298.0 million, respectively and capital resources consisting of cash and cash equivalents and short and long-term marketable securities totaling $591.8 million and $329.4 million, respectively. We expect that our existing capital resources consisting of cash and cash equivalents and marketable securities will be sufficient to fund our operations for at least the next twelve months. Because the outcome of any clinical development and regulatory approval process is highly uncertain, we cannot reasonably estimate the actual capital amounts necessary to successfully complete the development, regulatory approval process and commercialization of voxelotor or any other future product candidates.

Our operating plan may change as a result of many factors currently unknown to us, and we may need to seek additional funds sooner than planned, through public or private equity or debt financings or other sources, such as strategic collaborations or license and development agreements. Any additional fundraising efforts may divert our management from their day-to-day activities, which may adversely affect our ability to develop and commercialize voxelotor, inclacumab or any other product candidates that we may identify and pursue. Moreover, such financing may result in dilution to stockholders, imposition of debt covenants and repayment obligations, or other restrictions that may affect our business. In addition, we may seek additional capital due to favorable market conditions or strategic considerations even if we believe we have sufficient funds for our current or future operating plans.

Our future funding requirements will depend on many factors, including, but not limited to:

- the time and cost necessary to evaluate our completed Phase 3 HOPE Study and conduct and complete our ongoing Phase 2a HOPE-KIDS 1 Study of voxelotor for the potential treatment of SCD;
- the time and cost necessary to conduct and complete any additional clinical studies required to pursue regulatory approvals for voxelotor for SCD or any other indications, and the costs of post-marketing studies that could be required by regulatory authorities for any indications;
- the progress, data and results of our Phase 3 HOPE Study and Phase 2a HOPE-KIDS 1 Study, as well as potential other clinical trials of voxelotor for the potential treatment of SCD and our potential future clinical trials;

the progress, timing, scope and costs of our nonclinical studies, our clinical trials and other related activities, including our ability to enroll subjects in a timely manner for our potential future clinical trials of voxelotor for SCD or for inclacumab or any other product candidate that we may identify and develop;

the costs of obtaining clinical and commercial supplies of voxelotor, inclacumab and any other product candidates we may identify and develop;

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our ability to advance our development programs, including our program for the clinical investigation of voxelotor in SCD patients through nonclinical and clinical development, as well as inclacumab and any other potential product candidate programs we may identify and pursue, the timing and scope of these development activities, and the availability of accelerated approval for voxelotor and of any approval for any of our other product candidates;
our ability to successfully obtain any regulatory approvals from any regulatory authorities, and the scope of any such regulatory approvals, to market and sell voxelotor, inclacumab and any other product candidates we may identify and develop in any territory(ies);
our ability to successfully commercialize voxelotor, inclacumab and any other product candidates we may identify and develop in any territories;
the manufacturing, selling, and marketing costs associated with the potential commercialization of voxelotor, inclacumab and any other product candidates we may identify and develop, including the cost and timing of establishing our sales and marketing capabilities in any territory(ies);
the amount and timing of sales and other revenues from voxelotor, inclacumab and any other product candidates we may identify and develop, including the sales price and the availability of adequate third-party reimbursement;
the cash requirements of any future acquisitions or discovery of product candidates;
the time and cost necessary to respond to technological and market developments;
the extent to which we may acquire or in-license other product candidates and technologies, and the costs and timing associated with any such acquisitions or in-licenses;
our ability to attract, hire, and retain qualified personnel; and
the costs of maintaining, expanding, and protecting our intellectual property portfolio.

Additional funds may not be available when we need them, on terms that are acceptable to us, or at all. If adequate funds are not available to us on a timely basis, we may be required to delay, limit or terminate our development or commercialization activities for voxelotor, inclacumab or for any other product candidates we may identify and pursue, or be unable to expand our operations or otherwise capitalize on our business opportunities, as desired, which could materially and adversely affect our business, prospects, financial condition and results of operations.

Risks Related to Our Business and the Clinical Development, Regulatory Review and Approval of Our Product Candidates

If we are unable to obtain regulatory approval in one or more jurisdictions for voxelotor, inclacumab or any future product candidates that we may identify and develop, our business will be substantially harmed.

We cannot commercialize a product until the appropriate regulatory authorities have reviewed and approved the product candidate. Approval by the FDA and comparable foreign regulatory authorities is lengthy and unpredictable, and depends upon numerous factors. Approval policies, regulations, or the type and amount of clinical data necessary to gain approval may change during the course of a product candidate s clinical development and may vary among jurisdictions, which may cause delays in the approval or the decision not to approve an application. We have not obtained regulatory approval for any product candidate, including voxelotor, and it is possible that voxelotor, inclacumab and nor any other product candidates we may seek to develop in the future will ever obtain any regulatory approval.

Applications for voxelotor or any other product candidates we may develop could fail to receive regulatory approval for many reasons, including but not limited to:

we may not be able to demonstrate to the satisfaction of the FDA or comparable foreign regulatory authorities (including the European Medicines Agency, or EMA) that voxelotor or any other product candidates we may develop are safe and effective for any proposed indications;
the FDA or comparable foreign regulatory authorities may disagree with our plans or expectations regarding the pathways and endpoints for approval, including the availability of accelerated approval, or the design or implementation of our nonclinical studies or clinical trials;

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- the populations studied in our clinical programs may not be sufficiently broad or representative to assure safety or demonstrate efficacy in the full population for which we seek approval;
- the FDA or comparable foreign regulatory authorities may require additional nonclinical studies or clinical trials beyond those we anticipate;
- the FDA or comparable foreign regulatory authorities may disagree with our interpretation of data and results from our nonclinical studies or clinical trials;
- the data and results collected from nonclinical studies or clinical trials of voxelotor and any other product candidates that we may identify and pursue may not be sufficient to support the submission of a new drug application, or NDA, or any other submission for regulatory approval in any other jurisdiction;
- we may be unable to demonstrate to the FDA or comparable foreign regulatory authorities that a product candidate s risk-benefit ratio for its proposed indication is acceptable;
- the FDA or comparable foreign regulatory authorities may find deficiencies with or fail to approve the manufacturing processes, test procedures and specifications, or facilities of third-party manufacturers with which we contract and rely on for all clinical and commercial supplies of voxelotor and any other product candidates (if any); and
- the approval policies or regulations of the FDA or comparable foreign regulatory authorities may change in a manner that renders our development or manufacturing efforts insufficient for approval.

The lengthy regulatory review and approval process, as well as the inherent unpredictability of the results of nonclinical studies and clinical trials, and our reliance on third party manufacturers for any product candidates, may result in our failure to obtain regulatory approval to market voxelotor and other product candidates that we may pursue in the United States or elsewhere, which would significantly harm our business, prospects, financial condition and results of operations.

Access to expedited development and regulatory approval programs for voxelotor, including accelerated approval under Subpart H, may not actually lead to a faster development or regulatory review or approval process, may not lead to any approval, and may lead to a Subpart H approval that is later withdrawn.

We believe there may be an opportunity to accelerate the development and regulatory approval process for voxelotor through one or more of the FDA s expedited programs, such as fast track, breakthrough therapy, accelerated approval under Subpart H, or priority review, or through EMA s PRIME program, and we have pursued and intend to pursue such expedited programs for voxelotor. For example, we plan to submit an NDA for voxelotor for the treatment of SCD under the accelerated regulatory approval pathway under Subpart H. However, we cannot be assured that our NDA for voxelotor will be approved under Subpart H, or that voxelotor or any other product candidates that we may develop will qualify for or benefit from any such expedited programs in the United States, including under Subpart H, or any foreign regulatory jurisdictions.

In 2015, the FDA designated our investigation of voxelotor for the treatment of SCD as a Fast Track development program. Fast Track is intended to facilitate the development of drugs that treat serious conditions and demonstrate the potential to address an unmet medical need. While Fast Track designation may provide more frequent access and communication with the FDA, it does not ensure that regulatory review or approval for voxelotor will occur on an expedited basis, if at all.

In January 2018, the FDA granted breakthrough therapy designation to voxelotor for the treatment of SCD. A drug may be eligible for designation by FDA as a breakthrough therapy if the drug is intended, alone or in combination with one or more other drugs, to treat a serious or life-threatening condition and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints.

In December 2018, we announced that the FDA agreed with our proposal to use the accelerated regulatory approval pathway under Subpart H for voxelotor for the treatment of SCD, and that we plan to submit an NDA under this pathway. We also announced that the FDA agreed that transcranial doppler (TCD) flow velocity would be an acceptable primary endpoint in a post-approval confirmatory study to demonstrate stroke

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risk reduction for purposes of full approval. The FDA grants accelerated approval under Subpart H for new drugs that address serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments. Under Subpart H, the FDA may grant marketing approval for a new drug product on the basis of adequate and well-controlled clinical trials establishing that the drug product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity. Drugs approved under Subpart H are required to be further evaluated in at least one post-marketing study to verify clinical benefit. We have no assurance that our NDA for voxelotor will be approved under Subpart H, or that regulatory review or approval for voxelotor will occur on an expedited basis, if at all. In addition, we may not be able to complete at least one successful post-marketing confirmatory study required to maintain approval and achieve full approval, or data and results from our required post-marketing confirmatory program may not verify voxelotor s clinical benefit to maintain approval and achieve full approval.

Access to any expedited program through the FDA, including accelerated approval under Subpart H, or any other regulatory authority does not ensure faster development timelines or faster review or approval of any NDA compared to conventional FDA or foreign regulatory procedures, and it does not change many of the standards for approval or ensure that we will obtain regulatory approval for voxelotor or any other product candidates we may develop. Furthermore, access to any expedited program may be withdrawn by the FDA or a foreign regulatory authority if it believes that the program is no longer supported by data from our clinical development, and accelerated approval under Subpart H may be withdrawn if, among other reasons, required post-marketing confirmatory studies are not completed or if the FDA determines the results of post-marketing confirmatory studies do not verify clinical benefit.

In June 2017, the EMA granted PRIME designation for voxelotor for the treatment of SCD. The PRIME program is a regulatory mechanism that provides for early and proactive EMA support to medicine developers to help patients benefit as early as possible from innovative new products that have demonstrated the potential to significantly address an unmet medical need.

We are heavily dependent on the success of voxelotor in our development program for sickle cell disease, and all of our other programs are still in the earlier development stages. If we are unable to successfully complete clinical development, obtain regulatory approval for, and commercialize voxelotor for SCD, or experience delays in doing so, our business will be materially harmed.

To date, we have invested a majority of our efforts and financial resources in the nonclinical and clinical development of our lead and initial product candidate voxelotor, including conducting nonclinical studies and clinical trials and providing general and administrative support for these operations. We do not have any other clinical product candidates, and our only clinical development program for voxelotor is in SCD. Our future success is highly dependent on our ability to successfully develop, obtain and maintain regulatory approval for, and commercialize voxelotor for SCD, the only indication for which voxelotor is currently in clinical development. Before we can generate any revenues from sales of voxelotor, we must conduct substantial additional clinical development (including, among others, multiple ongoing clinical studies and toxicology studies, and possibly additional future nonclinical studies and clinical trials to demonstrate safety and efficacy of voxelotor for SCD or any other potential indication we may pursue). In addition, we will need to seek and obtain and maintain regulatory approval for SCD or any other potential indication, secure an adequate manufacturing supply to support larger clinical trials and commercial sales and build a commercial organization. Further, the success of voxelotor as a potential commercial product will also depend on patent and trade secret protection, acceptance of voxelotor by patients, the medical community and third-party payors, its ability to compete with other therapies, the status and availability of healthcare coverage and adequate reimbursement, and maintenance of an acceptable safety and efficacy profile following approval, among other factors. If we do not achieve all of these factors in a timely manner or at all, we could experience significant delays or an inability to successfully commercialize voxelotor, which would materially harm

our business.

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Voxelotor is currently our only product candidate to have advanced into clinical trials, and is currently only being tested in SCD. We are developing voxelotor as an oral, once-daily therapy for the potential treatment of SCD, and are currently evaluating voxelotor in SCD patients in our ongoing HOPE-KIDS 1 Study, which is a Phase 2a clinical trial in adolescent and pediatric SCD patients, and our completed multi-national HOPE Study, which is a Phase 3 clinical trial in adult and adolescent SCD patients.

All of our other programs are in earlier stages of research and development, and we have no other product candidates in clinical trials other than voxelotor. As a result, even after in-licensing the inclacumab program, we are very dependent on voxelotor for our business, prospects, financial condition and results of operations.

We are also very dependent on the data and results that we obtain over time from our most advanced clinical trial of voxelotor. In late 2016, we initiated the Phase 3 HOPE Study in SCD patients, aged 12 years and older, who have had at least one episode of vaso-occlusive crisis in the previous year. The primary endpoint of the HOPE Study relates to the proportion of patients who achieve an increase in hemoglobin levels (compared to baseline) as pre-specified in the study protocol. We have not previously conducted any clinical study of voxelotor in SCD patients using this primary endpoint, and we do not believe this measure has been used as a primary endpoint for any registration studies for any other SCD therapies. The HOPE Study also used a new patient reported outcomes, or PRO, instrument that we developed, and that has not been utilized before in any clinical studies, to generate data for a secondary endpoint in the HOPE Study.

In June 2018, we announced top-line data from Part A of the Phase 3 HOPE Study in approximately 154 patients, including that voxelotor achieved statistically significant results for both doses of voxelotor studied (1500 mg and 900 mg) after 12 weeks of treatment for the primary endpoint of a pre-specified increase in hemoglobin level versus placebo. We also announced that the PRO data in Part A of the HOPE Study were difficult to interpret due to low baseline symptom scores and high inter-subject and intra-subject variability, and as a result we do not plan to utilize the PRO as a secondary endpoint. In addition, we announced that there were numerically fewer vaso-occlusive crisis episodes for patients in each voxelotor arm as compared to placebo, although the result did not reach statistical significance. We also announced that we do not plan additional enrollment in the HOPE Study pending ongoing discussions with the FDA, but will continue dosing of patients currently enrolled in the study. In December 2018, we announced updated efficacy and safety results from Part A of the Phase 3 HOPE Study of voxelotor. Preliminary results from 154 patients with SCD treated with voxelotor for 24 weeks demonstrated rapid, robust and sustained improvements in hemoglobin levels and measures of hemolysis with a favorable safety and tolerability profile.

We continue to generate additional data from patients enrolled in the Phase 3 HOPE Study. There is a risk that the additional data generated could be different from, including less positive in terms of efficacy and/or safety, than the data generated and discussed with the FDA to date.

We do not know if the HOPE Study data and results will be sufficient to support accelerated approval for voxelotor by the FDA. If accelerated approval is not granted, then we would experience a significant delay in our voxelotor development program and in any potential approval, given our decision to pursue accelerated approval rather than continue HOPE Study enrollment and shift from Part A to Part B of the HOPE Study (as originally designed). As a result, failure to obtain accelerated approval for voxelotor under Subpart H will result in a significant delay in any potential approval of voxelotor. If we were required to pursue full approval for voxelotor (not under Subpart H), we might not achieve any such approval without further clinical studies of voxelotor, which would significantly delay or curtail any potential pathway to full approval.

As part of an NDA submission under Subpart H, if any, we must agree with the FDA on the design of, and commit to conduct, at least one post-marketing confirmatory study to verify the clinical benefit of voxelotor. In December 2018,

we announced that the FDA agreed that TCD flow velocity would be an acceptable primary endpoint in a post-marketing confirmatory study to demonstrate stroke risk reduction. Accelerated approval of voxelotor under Subpart H, if any, may be withdrawn (which would also mean full approval would not be achieved) if required post-marketing confirmatory studies are not completed or if the FDA determines the results of such studies do not verify clinical benefit. We do not have a special protocol assessment agreement in place with the FDA. In Europe, we are in the process of seeking input from various European regulatory authorities

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regarding a pathway to approval of voxelotor for the potential treatment of SCD patients based on the HOPE Study. We cannot be certain that voxelotor or any other product candidates that we seek to develop will be successful in nonclinical studies or clinical trials or receive and maintain any regulatory approvals. If we do not receive regulatory approval for, regulatory approval is withdrawn from, or we otherwise fail to successfully commercialize, voxelotor or any other product candidates, we are likely to need to spend significant additional time and resources to identify other product candidates, advance them through nonclinical and clinical development and apply for regulatory approvals, which would adversely affect our business, prospects, financial condition and results of operations.

The development of voxelotor as a potential disease-modifying anti-sickling agent in SCD patients represents a novel therapeutic approach, and there is a risk that the outcomes of our clinical trials will not be favorable or otherwise support any decision to seek or grant any regulatory approval.

We have concentrated our product research and development efforts on developing novel, mechanism-based therapeutics for the treatment of grievous blood-based disorders with significant unmet need, and our future success depends on the success of this therapeutic approach. The clinical trial requirements of the FDA and other comparable regulatory agencies and the criteria these regulators use to determine the safety and efficacy of any product candidate vary substantially according to the type, complexity, novelty and intended use and market of the potential product. To date, there are only two approved therapies for SCD, hydroxyurea and L-glutamine, and there are no approved therapies directed toward preventing the polymerization of hemoglobin molecules as a mechanism to reduce RBC sickling in SCD patients. As a result, the design and conduct of clinical trials for a therapeutic product candidate such as voxelotor that targets this mechanism in SCD patients are subject to unknown risks, and we may experience setbacks with our ongoing or planned clinical trials of voxelotor in SCD because of the limited clinical experience with its mechanism of action in these patients.

In particular, regulatory authorities in the United States and Europe have not issued definitive guidance as to how to measure and achieve efficacy in treatments for SCD. Based on our discussions with the FDA regarding the design for the HOPE Study, we have determined to measure change in hemoglobin levels as the primary endpoint in the Phase 3 HOPE Study. This primary endpoint has not been used previously in a registration study for any SCD treatment. As a result, regulators have not determined that such data would signify a clinically meaningful result in SCD patients or would support seeking or obtaining regulatory approval. In addition, we cannot be assured that this primary endpoint will be sufficient to support accelerated approval of voxelotor under Subpart H, which requires the FDA to agree that our hemoglobin-based primary endpoint is an intermediate clinical endpoint that is reasonably likely to predict clinical benefit.

We did not achieve statistically significant results with respect to either potential key secondary endpoint in Part A of the HOPE Study (relating to vaso-occlusive crisis episodes and to the PRO), and we may not achieve key endpoints in other clinical trials, such as any post-marketing confirmatory studies. In addition, we may not achieve the same results with respect to the primary endpoint in Part A of the HOPE Study in other ongoing of future clinical trials. Any inability to design clinical trials with protocols and endpoints acceptable to applicable regulatory authorities, and to obtain and maintain regulatory approvals for voxelotor and any other product candidates that we may pursue, would have an adverse impact on our business, prospects, financial condition and results of operations.

Results of earlier studies may not be predictive of future clinical trial results, and initial studies may not establish an adequate safety or efficacy profile for voxelotor, inclacumab and other product candidates that we may pursue to justify proceeding to advanced clinical trials or an application for regulatory approval.

The results of nonclinical studies and clinical trials of voxelotor, inclacumab and of any future product candidates that we may pursue may not be predictive of the results of later-stage clinical trials, and interim results of a clinical trial

may not necessarily predict final results. For example, we were previously pursuing the clinical development of voxelotor as a potential treatment for idiopathic pulmonary fibrosis, or IPF, and decided in October 2017 to halt development of voxelotor for IPF due to the totality of the data we obtained from two Phase 2a clinical trials and a Phase 1 study, which did not demonstrate sufficient overall clinical benefit to justify

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continuing the program. In addition, our nonclinical studies and clinical trials to date of voxelotor in SCD have involved mostly one genotype of SCD, known as HbSS, and the results of these studies may not be replicated in other genotypes of SCD in the HOPE Study or in subsequent clinical trials. The HOPE Study of voxelotor in SCD is not limited to only the HbSS genotype. Additionally, any positive results generated in our Phase 1/2 clinical trial of voxelotor in SCD in adults do not ensure that we will achieve similar results in our ongoing Phase 2a HOPE-KIDS 1 Study in adolescent and pediatric patients with SCD, which we expanded in July 2017 to include an additional single-dose cohort in children aged 6-11, or in any other potential studies of voxelotor. Our later stage clinical trials, including the HOPE Study, involve significantly broader patient populations than those in earlier clinical trials.

Product candidates in later stages of clinical trials, such as our HOPE Study, may fail to demonstrate the desired safety and efficacy despite having progressed through nonclinical studies and initial clinical trials. A number of companies in the biopharmaceutical industry have suffered significant setbacks in advanced clinical trials due to lack of efficacy or adverse safety profiles, notwithstanding promising results in earlier studies, and we cannot be certain that we will not face similar setbacks.

In addition, nonclinical and clinical data are often susceptible to various interpretations and analyses, and many companies that have believed their product candidates performed satisfactorily in nonclinical studies and clinical trials have nonetheless failed to obtain marketing approval, in part because of differing interpretations of data and results by regulatory authorities.

Our failure to demonstrate the required characteristics to support marketing approval for voxelotor, inclacumab or any other product candidate we may choose to develop in any ongoing or future clinical trials would substantially harm our business, prospects, financial condition and results of operations.

Before we are able to submit voxelotor for marketing approval, the FDA and comparable foreign regulatory authorities may impose additional requirements, the scope of which are not fully known at this time.

Before we can submit an NDA to the FDA for voxelotor for any potential indication, we must successfully complete our clinical trials. The FDA typically requires at least two pivotal, well-controlled Phase 3 clinical trials as a condition to the submission of an NDA and does not usually consider a single Phase 3 clinical trial to be adequate to support product approval. The FDA will typically only consider relying on one pivotal trial if, in addition, other well-controlled studies of the drug exist (for example, for other dosage forms or in other populations) or if the pivotal trial is a multi-center trial that provides highly reliable and statistically strong evidence of an important clinical benefit, such as effect on survival, organ function or PRO, and a confirmatory study would have been difficult to conduct on ethical grounds.

We plan to submit an NDA for voxelotor for the treatment of SCD under the accelerated approval pathway under Subpart H, and the FDA has agreed that TCD flow velocity would be an acceptable primary endpoint in a post-marketing confirmatory study to demonstrate stroke risk reduction. If accelerated approval under Subpart H is granted, we will be required to conduct post-marketing confirmatory studies sufficient to verify voxelotor s clinical benefit, and approval may be withdrawn (which would also mean full approval would not be achieved) if such studies are not completed or the FDA determines such studies are insufficient to verify clinical benefit. The FDA may also require a longer follow-up period for subjects treated with voxelotor prior to accepting an NDA submission. We do not have a special protocol assessment agreement in place with the FDA. In Europe, we are in the process of seeking input from various European regulatory authorities regarding a pathway to approval of voxelotor for the potential treatment of SCD patients based on the HOPE Study.

The FDA or the comparable foreign authorities may not consider the results of our ongoing, planned or potential future clinical trials, to be sufficient for approval of voxelotor for SCD patients, particularly to support potential accelerated approval under Subpart H. Any post-marketing confirmatory studies, and any additional clinical trials or data beyond that which we currently anticipate, that may be required by the FDA or comparable foreign regulatory authorities would result in increased costs and potential delays in the clinical development and marketing approval process, which may require us to expend more resources than are available to us. In addition, it is possible that the FDA and the comparable foreign authorities may have divergent opinions on the elements

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necessary for a successful NDA and marketing authorization application, or MAA, respectively, which may cause us to alter our development, regulatory and/or commercialization strategies.

We may encounter substantial delays in conducting or completing our clinical trials, which in turn will result in additional costs and may ultimately prevent successful or timely completion of the clinical development and commercialization of voxelotor, inclacumab or any other product candidates we may identify and pursue.

Before obtaining marketing approval from regulatory authorities for the sale of any our product candidates, we must conduct extensive clinical trials to demonstrate the safety and efficacy of the product candidates in humans. In addition, if accelerated approval under Subpart H is granted, we must conduct post-marketing confirmatory studies to verify clinical benefit. Clinical testing is expensive, time-consuming and uncertain as to outcome. Currently, we are conducting the ongoing Phase 2a HOPE-KIDS 1 Study and evaluating the completed Phase 3 HOPE Study of voxelotor. We cannot guarantee that these studies, and any other clinical trials, including any post-marketing confirmatory studies for voxelotor or any other product candidates we may pursue will be conducted as planned or completed on schedule, if at all. A failure of one or more clinical trials can occur at any stage of testing. Events that may prevent successful or timely completion of clinical development include:

- delays or failures in reaching a consensus with regulatory agencies on study design, including clinical endpoints sufficient to support an approval decision;
- delays or failures to receive approval for conduct of clinical studies in one or more geographies which could result in delays in enrollment and availability of data and results;
- delays or failures in reaching agreement on acceptable terms with a sufficient number of prospective contract research organizations, or CROs, and clinical trial sites, the terms of which can be subject to extensive negotiation and may vary significantly among different CROs and trial sites;
- delays in obtaining required Institutional Review Board, or IRB, or ethics committee approval for each clinical trial site;
- delays in recruiting a sufficient number of suitable patients to participate in our clinical trials;
- imposition of a clinical hold by any regulatory authority, including if imposed due to safety concerns after an inspection of our clinical trial operations or study sites;
- failure by our CROs, clinical sites, participating clinicians or patients, other third parties or us to adhere to clinical trial, regulatory or legal requirements;
- failure to perform in accordance with the FDA s good clinical practices, or GCPs, or applicable regulatory requirements in other countries;
- delays in the testing, validation, manufacturing and delivery of sufficient quantities of our product candidates or study related devices (such as the hand-held PRO instrument being used by patients in our HOPE Study) to the clinical sites and patients;
- delays in having patients enroll or complete participation in a study in accordance with applicable protocols or protocol amendments, or return for post-treatment follow-up;
- reduction in the number of participating clinical trial sites or patients, including by dropping out of a trial;
- failure to address in an adequate or timely manner any patient safety concerns that arise during the course of a trial;
- unanticipated costs or increases in costs of clinical trials of our product candidates;
- the occurrence of serious adverse events or other safety concerns associated with our product candidates; or
- changes in regulatory requirements and guidance that require amending or submitting new clinical protocols or obtaining additional IRB or other approvals to conduct or complete clinical studies of our product candidates.

We could also encounter delays if a clinical trial is suspended or terminated for any reason (which could occur as a result of termination by us, by the IRBs or ethics committees of the institutions in which such trials are being conducted, by an independent Safety Review Board for such trial, or by the FDA or other regulatory authorities). A clinical trial can be suspended or terminated for a wide variety of reasons, including failure to

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conduct the clinical trial in accordance with regulatory requirements or our clinical protocols, inspection of the clinical trial operations or trial site by us, or the FDA or other regulatory authorities resulting in the imposition of a clinical hold, unforeseen safety issues or adverse side effects, or failure to demonstrate a benefit from using a drug candidate. In addition, if we make manufacturing or formulation changes to our product candidates, we may need to conduct additional studies to bridge the development program from the data and results for the earlier product candidate to the modified product candidate.

Clinical trial delays could shorten any periods during which we may have the exclusive right to commercialize our product candidates or allow our competitors to bring products to market before we do, which could impair our ability to successfully commercialize our product candidates. In addition, any delays in completing our clinical trials will increase our costs, slow down our product candidate development and approval process or jeopardize our ability to maintain any accelerated approval (in the case of required post-marketing confirmatory studies, if any), and jeopardize our ability to commence product sales and generate revenues. Any of these occurrences may significantly harm our business, prospects, financial condition and results of operations.

Difficulty in enrolling patients or maintaining patient compliance with dosing or other requirements in our clinical trials could delay or prevent clinical trials of our product candidates, which in turn could delay or prevent our ability to obtain, or maintain, the regulatory approvals necessary to commercialize our product candidates.

Identifying and qualifying patients to participate in our ongoing and planned clinical trials of voxelotor, inclacumab, and any other product candidates that we may develop are critical to our success. Our clinical development efforts are initially focused on rare chronic blood diseases. For example, according to CDC estimates, the prevalence of SCD, for which voxelotor is being studied, is approximately 100,000 individuals in the United States. Accordingly, there are limited patient pools from which to draw for clinical trials in our target indications. We may not be able to identify, recruit, and enroll a sufficient number of subjects to complete our clinical trials of voxelotor because of the perceived risks and benefits of voxelotor, the availability of competing therapies and clinical trials, the proximity and availability of clinical trial sites for prospective subjects and the subject referral practices of physicians, among other factors.

Further, if subjects in our clinical trials fail to comply with our dosing regimens or other requirements in our clinical trials, we may not be able to generate clinical data acceptable to the FDA or comparable regulatory authorities in our trials. For example, in our HOPE Study enrolled participants used a PRO instrument to complete very frequent patient surveys generating data relevant to a secondary endpoint. Because the PRO data were difficult to interpret due to low baseline symptom scores and high inter-subject and intra-subject variability, we do not plan to utilize the PRO as secondary endpoint in Part B of the HOPE Study (under the original study design). If patients are unwilling or unable to participate in, complete or comply with the protocols for our studies for any reason, the timeline for recruiting subjects, conducting studies and obtaining regulatory approval of potential products may be delayed.

If we experience difficulties or delays in enrollment or are otherwise unable to successfully complete any clinical trial of voxelotor, or any other product candidates we may pursue, our costs are likely to increase, and our ability to obtain regulatory approval and generate product revenue from any of these product candidates will be impaired. Any of these occurrences would harm our business, prospects, financial condition and results of operations.

If serious adverse events or unacceptable side effects are identified during the development of our product candidates, we may need to delay, limit or terminate our clinical development activities.

Clinical trials by their nature utilize only a small sample of the potential patient population. For example, our Phase 3 HOPE Study in SCD patients represents only a very small fraction of all patients with SCD. Side effects of voxelotor,

inclacumab or any other product candidates that we may develop may be uncovered only in later stages of clinical trials, or only in trials involving different patient populations (such as pediatric patients),

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or only during post-approval studies or the safety reporting required for approved products. Many product candidates that initially showed promise in early stage testing have later been found to cause side effects that prevented their further development. Moreover, a nonclinical toxicology study with voxelotor in non-humans and clinical trials involving other hemoglobin modifiers (other than voxelotor) have shown a decrease in oxygen delivery to tissue when a significant percentage of hemoglobin is modified. Hemoglobin modifiers, by increasing HbS s affinity for oxygen, can cause a shift in oxygen levels, potentially resulting in tissue hypoxia. To date, clinical studies of voxelotor have not shown evidence of tissue hypoxia. However, if voxelotor or any other product candidates that we may develop are associated with tissue hypoxia or any other undesirable side effects or unexpected undesirable characteristics in clinical trials or nonclinical studies, we may need to abandon their development or limit their development to more narrow uses or subpopulations, which could adversely affect our business, prospects, financial condition and results of operations.

Although the FDA and the European Commission have each granted orphan drug designation for voxelotor for the potential treatment of SCD, we may not receive orphan drug designation for inclacumab or any other product candidates for which we may submit new applications for orphan drug designation, and any orphan drug designations that we have received or may receive in the future may not confer marketing exclusivity or other expected commercial benefits.

Our business strategy focuses on the development of product candidates for the treatment of rare, chronic blood disorders that may be eligible for FDA or European Union, or EU, orphan drug designation. Regulatory authorities in some jurisdictions, including the United States and the EU, may designate drugs for relatively small patient populations as orphan drugs. Under the Orphan Drug Act, the FDA may designate a drug as an orphan drug if it is intended to treat a rare disease or condition, which is generally defined as a patient population of fewer than 200,000 individuals annually in the United States. In the EU, the Committee for Orphan Medicinal Products of the EMA recommends orphan drug designation to promote the development of medical products that are intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting not more than five in 10,000 persons in the EU and for which no satisfactory method of diagnosis, prevention, or treatment is authorized (or in other very limited circumstances). In 2015 and 2016, respectively, the FDA and the European Commission (acting on a positive recommendation by the EMA) each granted orphan drug designation for voxelotor for the treatment of patients with SCD.

Generally, if a drug with an orphan drug designation subsequently receives the first marketing approval for the indication for which it has such designation, the drug is entitled to a period of marketing exclusivity, which precludes the FDA or the EMA from approving another marketing application for the same drug for the same indication for that time period. The applicable period is seven years in the United States and 10 years in the EU. The EU exclusivity period can be reduced to six years if a drug no longer meets the criteria for orphan drug designation or if the drug is sufficiently profitable so that market exclusivity is no longer justified. Orphan drug exclusivity may be lost if the FDA or EMA determines that the request for designation was materially defective or if the manufacturer is unable to assure sufficient quantity of the drug to meet the needs of patients with the rare disease or condition.

Although the FDA and the EMA have each granted orphan drug designation to voxelotor for the treatment of SCD, we may apply for orphan drug designation for voxelotor in other jurisdictions or for other indications, or for inclacumab or other product candidates we may develop and pursue in the future. Applicable regulatory authorities may not grant us these additional designations. In addition, the exclusivity granted under any orphan drug designations that we have received from the FDA and the EMA, or may receive from any other regulatory authorities (if any), may not effectively protect voxelotor or any other product candidate we pursue from competition because different drugs can be approved for the same condition. For example, in the United States, even after an orphan drug is approved, the FDA can subsequently approve another drug for the same condition if the FDA concludes that the later

drug is clinically superior, or the FDA can approve a competitor application for the same drug for a different indication than the orphan drug designation. Any inability to secure or maintain orphan drug designation or the exclusivity benefits of this designation would have an adverse impact on our ability to develop and commercialize our product candidates. In addition, even if any orphan drug

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designations we receive are maintained, we may be unable to realize significant commercial benefits from these regulatory exclusivities for voxelotor (if approved) or any other product candidate we pursue.

Even if we receive regulatory approval for our voxelotor, inclacumab or any other product candidate that we may develop and pursue, we will be subject to ongoing regulatory obligations and scrutiny and may be subject to significant restrictions relating to product labeling, distribution or other post-marketing requirements.

Even if a product candidate such as voxelotor is approved, regulatory authorities may still impose significant restrictions on its indicated uses, approved labeling, distribution or marketing or may impose ongoing requirements for potentially costly post-marketing studies. For example, we plan to submit an NDA seeking accelerated approval of voxelotor under Subpart H and if such accelerated approval is granted, we will be required to conduct post-marketing confirmatory studies to verify the clinical benefit of voxelotor. The FDA may restrict the approved labeling for voxelotor on any accelerated approval in a variety of ways, including with respect to the scope of the approved indication and may require statements of lack of demonstrated benefit (until demonstrated by required post-marketing confirmatory studies) or other restrictions or limitations in any approved product labeling under Subpart H. Furthermore, any new legislation addressing drug safety or other drug related issues could result in delays or increased costs to assure compliance. If voxelotor, inclacumab or any other product candidates that we may develop are approved, at a minimum they will each be subject to current standard ongoing regulatory requirements for labeling, packaging, storage, advertising, promotion, sampling, record-keeping and submission of safety and other post-market information, including both federal and state requirements in the United States. In addition, regulatory agencies may not approve the labeling claims that are necessary or desirable for the successful commercialization of voxelotor, inclacumab or any other product candidates. For example, the development of voxelotor for the prophylactic treatment of SCD in pediatric patients is an important part of our current business strategy, and if we are unable to obtain regulatory approval for this product candidate for the desired age ranges or other key labeling parameters, our business is likely to suffer.

In addition, manufacturers and manufacturers facilities are required to comply with extensive FDA requirements, including ensuring that quality control and manufacturing procedures conform to current good manufacturing practices, or cGMP s. For voxelotor, inclacumab and any other product candidates we may pursue, we are wholly reliant on third party contract manufacturers for clinical as well as any commercial supplies of product candidates and products. As such, we and our contract manufacturers are subject to continual review and periodic inspections to assess compliance with cGMP requirements and must continue to expend time, money, and effort in all areas of regulatory compliance, including manufacturing, production, and quality control. We will also be required to report certain adverse reactions and production problems, if any, to the FDA and comparable foreign regulatory authorities, and to comply with requirements concerning advertising and promotion for our products. In addition, we are subject to very rapid reporting obligations relating to any adverse events or serious adverse events relating to our product candidates and any approved products, if any. Our failure to report adverse events we become aware of within the prescribed timeframes could have serious negative consequences for our development programs, business and operations. In addition, any promotional communications or materials for prescription drugs are subject to a variety of complex legal and regulatory restrictions, including but not limited to consistency with the approved product s approved label. Failure to obey these standard marketing requirements for any approved product (if any) could have serious negative consequences for our commercialization activities (if any), business and operations.

If the FDA or any comparable foreign 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, or disagrees with a sponsor s activities relating to the promotion, marketing, or labeling of a product, these regulatory agencies may impose restrictions or sanctions on that product or us, including requiring withdrawal of the product from the market. In addition, in the United States, a wide range of commercialization and pre-launch

activities relating to a drug candidate are subject to potential for significant civil and/or criminal liability and sanctions under federal anti-kickback and fraud and abuse statutes and

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regulations. If we fail to comply with any of these complex applicable regulatory requirements, a regulatory agency or enforcement authority may:

- issue untitled or warning letters;
- impose civil or criminal penalties;
- impose injunctions;
- impose fines;
- impose additional specialized restrictions on the company s activities and practices;
- suspend regulatory approval;
- suspend ongoing clinical trials;
- seek voluntary product recalls and impose publicity requirements;
- refuse to approve pending applications or supplements to approved applications submitted by us;
- impose restrictions on our operations, including closing our contract manufacturers facilities; or
- seize or detain products.

As a company, we have no experience with obtaining approval for, launching or commercializing any product candidates or products, or with complying with most of these complex ongoing regulatory requirements. It will take significant effort and management attention to address compliance with these requirements in any jurisdiction for which we seek any product approval. Any government investigation of alleged violations of law could require us to expend significant time and resources in response, and could generate negative publicity even if significant liabilities do not result. Any failure to comply with these complex ongoing regulatory requirements may significantly and adversely affect our ability to obtain approval for, launch, commercialize and generate revenues from voxelotor, inclacumab or any future product candidates. If we are subject to regulatory sanctions or if regulatory approval for our product candidates is withdrawn or limited, our business, prospects, financial condition and results of operations would be significantly harmed.

Risks Related to Our Reliance on Third Parties

We rely, and will continue to rely, on third parties to conduct some of our nonclinical studies and all of our clinical trials and also to perform other tasks for us. If these third parties perform in an unsatisfactory manner, it may harm our business.

We have relied upon and plan to continue to rely upon third-party CROs, including our CROs for our clinical trials of voxelotor, to monitor and manage data for some of our ongoing nonclinical studies and for all of our clinical programs. We rely on these parties for execution of these nonclinical studies and clinical trials, and control only certain aspects of their activities. Nevertheless, we are responsible for ensuring that each of our studies and trials are conducted in accordance with the applicable protocol, legal, regulatory, and scientific standards and our reliance on the CROs does not relieve us of our regulatory responsibilities. We and our CROs and other vendors are required to comply with all applicable cGMPs, GCPs, and current good laboratory practices, or GLPs, which are regulations and guidelines enforced by the FDA, the Competent Authorities of the Member States of the European Economic Area, or EEA, and comparable foreign regulatory authorities. Regulatory authorities enforce these regulations through periodic inspections of study sponsors, principal investigators, study sites, manufacturing facilities, nonclinical testing facilities and other contractors. If we or any of our CROs or other vendors fail to comply with applicable regulations, the data generated in our nonclinical studies and clinical trials may be deemed unreliable and the applicable regulatory authorities may require us to repeat or to perform additional nonclinical and clinical studies before approving our marketing applications, which would delay the regulatory review and approval process, perhaps significantly.

In addition, the execution of nonclinical studies and clinical trials, the subsequent compilation and analysis of the data and results produced, and the supply of test product for our trials, requires coordination among various parties. In order for these functions to be carried out effectively and efficiently, it is imperative that these parties communicate and coordinate with one another. These third parties may terminate their agreements with us upon short notice for our uncured material breach, or under certain other circumstances. If any of our relationships with our third-party CROs or other key vendors (including manufacturing and testing

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facilities) terminates, we may not be able to enter into arrangements with alternative CROs or other key vendors on a timely basis or at all, or do so on commercially reasonable terms. In addition, our CROs and other key vendors are not our employees, and except for remedies available to us under our agreements with them, we cannot control whether they devote sufficient time and resources to our programs. Furthermore, these third party CROs or other key vendors may also have relationships with other entities, some of which may be our competitors. If CROs or other key vendors do not successfully carry out their contractual duties or obligations or meet expected deadlines, if they need to be replaced or if the quality or accuracy of the data and results they obtain or the test product they supply is compromised for any reason (including failure to adhere to our protocols, or regulatory requirements), our development activities may be extended, delayed, or terminated and we may not be able to seek or obtain regulatory approval for or successfully commercialize any of our product candidates. Switching or adding CROs or any other key vendors involves additional cost, time and management resources and focus. In addition, our CROs or other key vendors may also generate higher costs than anticipated.

Accordingly, our dependence on third-party CROs and other key vendors may subject us to challenges, delays and costs that have a material adverse impact on our business, prospects, financial condition and results of operations.

We rely entirely on third parties for the manufacturing of voxelotor, inclacumab and for any other product candidates we may pursue for nonclinical studies and clinical trials, and we expect to continue to do so for any product commercialization. Our business could be harmed if any of those third parties fail to provide us with sufficient quantities of drug product, or fail to do so at acceptable quality or quantity levels or prices.

We do not currently have, nor do we plan to acquire, the infrastructure or capability internally to manufacture drug supplies for our ongoing and planned clinical trials of voxelotor or any additional clinical trials that we may conduct for voxelotor, inclacumab or any other future product candidates, and we do not presently expect that we will establish or acquire the resources necessary to manufacture any of our product candidates on a commercial scale. We rely, and expect to continue to rely, wholly on third-party manufacturers to produce our product candidates for our clinical trials, including our HOPE Study, as well as for commercial manufacture or any required post-marketing studies if voxelotor (or any of our product candidates, if any) receives marketing approval. Although we generally do not begin a clinical trial unless we believe we have a sufficient supply of a product candidate to complete the trial, any significant delay or discontinuity in the supply of a product candidate, or the raw material components thereof, for an ongoing clinical trial due to the need to replace a third-party manufacturer could considerably delay the clinical development and potential regulatory approval of our product candidates, which could harm our business and results of operations. We expect to rely on multiple third parties for the manufacture of commercial supplies of voxelotor, inclacumab or any other product candidates, if approved.

We may be unable to establish or maintain any agreements with third-party manufacturers for voxelotor, inclacumab or any other product candidates, or to do so on acceptable terms. Even if we are able to establish or maintain agreements with third-party manufacturers for voxelotor, inclacumab or any other product candidates, reliance on third-party manufacturers entails additional risks, including:

- reliance on the third party for regulatory compliance and quality assurance;
- the possible breach or termination of the manufacturing agreement by the third party or by us, including at a time that is costly or inconvenient for us;
- the inability of the third party to satisfy our ordering requirements as to quality, quantity and/or price;
- the possible misappropriation of our proprietary information, including our trade secrets and know-how; and
- the unwillingness of the third party to extend or renew terms with us when desired.

Our reliance on third-party manufacturers in connection with inclacumab will entail additional potential risks. For example, we are transferring technology from Roche to a new third-party manufacturer for inclacumab. The technology transfer for inclacumab must be carefully planned and executed to ensure a successful transition to the new site and approval by the FDA of any investigational new drug application from the new site. This

technology transfer may not be successful. In addition, because of our lack of experience manufacturing a biologic product, we will have greater reliance on the expertise and experience of our third-party manufacturer for inclacumab.

Furthermore, all of our contract manufacturers are engaged with other companies to supply and/or manufacture materials or products for such companies, which exposes our manufacturers to regulatory and market risks for the production of such materials and products. As a result, failure to meet the regulatory requirements for the production of those materials and products may affect the regulatory assessment or clearance of our contract manufacturers facilities generally, and industry consolidation, pricing or other market factors may cause our contract manufacturers to scale back, terminate or refuse to renew desired arrangements for our materials. If the FDA or a comparable foreign regulatory agency finds deficiencies in or does not approve these facilities for the manufacture of our product candidates or if any agency later finds deficiencies or withdraws its approval in the future, we may need to find alternative manufacturing facilities. Any of these factors could negatively impact our ability to develop, obtain regulatory approval for or market our product candidates, if approved.

Voxelotor, inclacumab and any future product candidates that we may identify and pursue may compete with other product candidates and marketed drugs for access to manufacturing facilities. Any performance failure on the part of our existing or future manufacturers could delay clinical development or marketing approval. Although we currently have adequate supplies to conduct our ongoing clinical trials, if we are unable to enter into relationships with additional contract manufacturers, or our current or future contract manufacturers cannot perform as agreed, we may experience delays and incur additional costs in our clinical development and potential commercialization activities. Our current and anticipated future dependence upon others for the manufacturing of our product candidates and any marketed drugs may adversely affect our future profit margins and our ability to commercialize any product candidates that receive marketing approval on a timely and competitive basis.

If the contract manufacturing facilities on which we rely do not continue to meet regulatory requirements or are unable to meet our supply demands, our business will be harmed.

All entities involved in the preparation of therapeutics for clinical trials or commercial sale, including our existing contract manufacturers for voxelotor, are subject to extensive regulation. Components of a finished therapeutic product approved for commercial sale or used in late-stage clinical trials must be manufactured in accordance with cGMPs, or similar regulatory requirements outside the United States. These regulations govern manufacturing processes and procedures, including recordkeeping, 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 contaminants or to inadvertent changes in the properties or stability of our product candidates. Our failure, or the failure of our third-party manufacturers, to comply with applicable regulations could result in sanctions being imposed on us, including clinical holds, fines, injunctions, civil penalties, delays, suspension or withdrawal of approvals, license revocation, suspension of production, seizures or voluntary recalls of product candidates or marketed drugs, operating restrictions and criminal prosecutions, any of which could significantly and adversely affect clinical or commercial supplies of voxelotor, inclacumab or any of our future product candidates.

Among other requirements, we or our contract manufacturers must supply all necessary documentation in support of an NDA or MAA seeking approval of a product candidate on a timely basis and must adhere to GLP and cGMP regulations enforced by the FDA and other regulatory agencies through their facilities inspection programs. The facilities and quality systems of some or all of our third-party contractors must pass a pre-approval inspection for compliance with the applicable regulations as a condition of regulatory approval for voxelotor. In addition, the regulatory authorities may, at any time, audit or inspect a manufacturing facility involved with the preparation of voxelotor, inclacumab or any of our future product candidates or the associated quality systems. Although we oversee

the contract manufacturers, we cannot control the manufacturing process of, and are completely dependent on, our contract manufacturing partners for compliance with these complex regulatory requirements. If these manufacturers, facilities, records or systems do not pass pre-approval

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inspections and reviews, regulatory approval of voxelotor, inclacumab or any of our other future product candidates may never be granted or may be substantially delayed.

In addition, at any time following approval of a product for sale, the regulatory authorities also may 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 could 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.

Additionally, if supply from one approved manufacturer is interrupted, an alternative manufacturer would need to be qualified through a supplement to an NDA, MAA variation or equivalent foreign regulatory filing, which could result in further delay, uncertainty and costs. Regulatory agencies may also require additional clinical 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 programs, results and activities (including commercial timelines).

These factors could cause us to incur higher costs and could cause the delay or termination of clinical trials, regulatory submissions, required approvals, or commercialization of our 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 trials may be delayed or we could lose potential revenue.

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

Because we rely on third parties to manufacture voxelotor and to conduct other aspects of our clinical development activities, as well as for inclacumab and any other product candidates we may pursue, 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, other forms of agreement with any collaborators, CROs, manufacturers 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. 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 and confidential information may become known by our competitors, may inadvertently be 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 confidential information, or other unauthorized use or disclosure would impair our competitive position and may have a material adverse effect on our business.

Our agreements typically restrict the ability of certain collaborators, CROs, manufacturers, other key vendors and consultants to publish data, although many of our contracts provide for the right to publish data in specified circumstances. A significant breach of these publication provisions could impair our competitive position. In addition, we conduct joint research and development programs that may require us to share trade secrets and other confidential information. Despite our efforts to protect our trade secrets and confidential information, our competitors may discover them, either through breach of agreements relating to these programs, independent development or publication of information where we do not have proprietary or otherwise protected rights at the time of publication. A competitor s discovery of our trade secrets or confidential information would impair our competitive position and have an adverse impact on our business.

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Risks Related to Our Intellectual Property

If we or our licensors are unable to obtain and maintain sufficient intellectual property protection for our product candidates, or if the scope of the intellectual property protection obtained is not sufficiently broad, our competitors could develop and commercialize product candidates similar or identical to ours, and our ability to successfully commercialize voxelotor, inclacumab and other product candidates that we may pursue may be impaired. Changes in patent policy and rules could impair our ability to protect our products and increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our issued patents.

As is the case with other biopharmaceutical companies, our success depends in large part on our ability to obtain and maintain protection of the intellectual property, particularly patents, that we may exclusively license or own solely and jointly with others in the United States and other countries with respect to our product candidates and technology, including voxelotor and inclacumab. We seek to protect our proprietary position by filing patent applications in the United States and abroad related to our product candidates.

Obtaining and enforcing biopharmaceutical patents is costly, time consuming, uncertain and complex, and we or our licensors may not be able to file and prosecute all necessary or desirable patent applications, or maintain, enforce and license any patents that may issue from such patent applications, at a reasonable cost or in a timely manner. It is also possible that we will fail to identify patentable aspects of our research and development output before it is too late to obtain patent protection. We may not have the right to control the preparation, filing and prosecution of patent applications, or to maintain the rights to patents licensed to third parties. Therefore, these patents and applications may not be prosecuted and enforced in a manner consistent with the best interests of our business. If our current or future licensors, licensees or collaboration partners fail to establish, maintain or protect such patents and other intellectual property rights, such rights may be reduced or eliminated. If our licensors, licensees or collaboration partners are not fully cooperative or disagree with us as to the prosecution, maintenance or enforcement of any patent rights, such patent rights could be compromised.

The patent position of biotechnology and pharmaceutical companies generally is highly uncertain, involves complex legal, technological and factual questions and has in recent years been the subject of much litigation. In addition, the laws of foreign countries may not protect our rights to the same extent as the laws of the United States, or vice versa. Further, we may not be aware of all third-party intellectual property rights potentially relating to our product candidates. Publications of discoveries in the scientific literature often lag behind the actual discoveries, and patent applications in the United States and other jurisdictions are typically not published until 18 months after filing or, in some cases, not at all. Therefore, we cannot know with certainty whether we were the first to make the inventions claimed in our patents or pending patent applications, or that we were the first to file for patent protection of such inventions. As a result, the issuance, scope, validity, enforceability and commercial value of our patent rights are and will remain highly uncertain. The patent examination process may require us or our licensors, licensees or collaboration partners to narrow the scope of the claims of our or our licensors , licensees or collaboration partners pending and future patent applications, which may limit the scope of patent protection that may be obtained. Our pending and future patent applications may not result in patents being issued that protect voxelotor, inclacumab or any future product candidates, in whole or in part, or which effectively prevent others from commercializing competitive product candidates. Even if our patent applications issue as patents, they may not issue in a form that will provide us with any meaningful protection, prevent competitors from competing with us or otherwise provide us with any competitive advantage. Our competitors may be able to circumvent our patents by developing similar or alternative product candidates in a non-infringing manner, or by successfully seeking to narrow or invalidate our patents or render them unenforceable. Our and our licensors , licensees or collaboration partners patent applications cannot be enforced against third parties practicing the technology claimed in such applications unless and until a patent issues from such applications, and then only to the extent the issued claims cover the technology.

We cannot assure you that all of the potentially relevant prior art relating to our patents and patent applications has been found. If such prior art exists, it can invalidate a patent or prevent a patent from issuing from a pending patent application. Moreover, we may be subject to a third-party preissuance submission of prior

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art to the United States Patent and Trademark Office (the USPTO), or become involved in opposition, derivation, reexamination, *inter partes* review, post-grant review or interference proceedings challenging our patent rights or the patent rights of others. An adverse determination in any such submission, proceeding or litigation could reduce the scope of, or invalidate, our patent rights, allow third parties to commercialize our product candidates and compete directly with us, without payment to us, or result in our inability to manufacture or commercialize drugs without infringing third-party patent rights. In addition, if the breadth or strength of protection provided by our patents and patent applications is threatened, it could dissuade companies from collaborating with us to license, develop or commercialize voxelotor, inclacumab or any future product candidates.

In addition, the issuance of a patent is not conclusive as to its inventorship, scope, validity or enforceability, and our patents may be challenged in the courts or patent offices in the United States and abroad. Such challenges may result in loss of exclusivity or freedom to operate or in patent claims being narrowed, invalidated or held unenforceable, in whole or in part, which could limit our ability to stop others from using or commercializing similar or identical product candidates, or limit the duration of the patent protection of our product candidates. Given the amount of time required for the development, testing and regulatory review of new product candidates, patents protecting such candidates might expire before or shortly after such candidates are commercialized. As a result, our patent portfolio may not provide us with sufficient rights to exclude others from commercializing drugs similar or identical to ours.

The United States has enacted and is currently implementing wide-ranging patent reform legislation. The United States Supreme Court has ruled on several patent cases in recent years, either narrowing the scope of patent protection available in certain circumstances or weakening 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 future actions by the U.S. Congress, the federal courts, and the USPTO, the laws and regulations governing patents could change in unpredictable ways that would diminish the value of our patents and patent applications or narrow the scope of our patent protection, or weaken our ability to obtain new patents or to enforce our existing patents and patents that we might obtain in the future.

Assuming the other requirements for patentability are met, in the United States prior to March 15, 2013, the first to make the claimed invention is entitled to the patent, while outside the United States, the first to file a patent application is entitled to the patent. After March 15, 2013, under the Leahy-Smith America Invents Act (the AIA), enacted in 2011, the United States has moved to a first to file system similar to other countries systems. The AIA also includes a number of significant changes that affect the way patent applications are prosecuted, and may also affect patent litigation. The effects of these changes are currently unclear as the USPTO must still implement various regulations, the courts have yet to address certain of these provisions and the applicability of the AIA and new regulations remain to be issued. Accordingly, it is not clear what, if any, impact the AIA will have on the operation of our business. However, the AIA and its implementation could increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of patents that may issue from such patent applications, all of which could have a material adverse effect on our business and financial condition. Any further changes in either the patent laws or interpretation of the patent laws in the United States and other countries may diminish the value of our patents and patent applications or narrow the scope of our potential patent protection.

We may become subject to claims alleging infringement of third parties patents or proprietary rights and/or claims seeking to invalidate our patents, which would be costly, time consuming and, if successfully asserted against us, delay or prevent the development and commercialization of voxelotor, inclacumab or any future product candidates that we may develop.

We cannot assure that voxelotor, inclacumab or any future product candidates that we may develop will not infringe existing or future third-party patents. Because patent applications can take many years to issue and may be confidential for 18 months or more after filing, there may be applications now pending of which we are unaware and which may later result in issued patents that we may infringe by commercializing voxelotor or any

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future product candidates that we may develop. We may additionally be unaware of one or more issued patents that would be infringed by the manufacture, sale or use of voxelotor, inclacumab or any of our other product candidates.

We may in the future become party to, or be threatened with, adversarial proceedings or litigation against us regarding third party intellectual property rights with respect to voxelotor, inclacumab or our future product candidates, that would cause us to incur substantial expenses and, if successful against us, could cause us to pay substantial damages, including treble damages and attorneys fees if we are found to be willfully infringing a third party s patents. We may also be required to indemnify parties with whom we have contractual relationships against such claims. If a patent infringement suit were brought against us, we could be forced to stop or delay research, development, manufacturing or sales of the product or product candidate that is the subject of the suit. As a result of patent infringement claims, or in order to avoid potential claims, we may choose to seek, or be required to seek, a license from the third party to continue developing, manufacturing and marketing our product candidates and would most likely be required to pay license fees or royalties or both, that could be significant. These licenses may not be available on acceptable terms, or at all. Even if we were able to obtain a license, the rights may be nonexclusive, which would give our competitors access to the same intellectual property licensed to us. Ultimately, we could be prevented from commercializing a product, or forced to redesign it, or to cease some aspect of our business operations if, as a result of actual or threatened patent infringement claims, we are unable to enter into licenses on acceptable terms. Even if we are successful in defending against such claims, such litigation can be expensive, uncertain, and time consuming to litigate, and would divert management s attention from our core business. Any of these events could harm our business significantly.

In addition to infringement claims against us, if third parties prepare and file patent applications in the United States that also claim technology similar or identical to ours, we may have to participate in interference or derivation proceedings in the USPTO, to determine which party is entitled to a patent on the disputed invention. We may also become involved in similar opposition proceedings in the European Patent Office or similar offices in other jurisdictions regarding our intellectual property rights with respect to our product candidates and technology.

We may become involved in lawsuits to protect or enforce our patents or other intellectual property, which could be expensive, time consuming and unsuccessful.

Competitors or other parties may infringe our patents or other intellectual property. Although we are not currently involved in any litigation, if we were to initiate legal proceedings against a third party to enforce a patent covering one of our product candidates, the defendant could counterclaim that the patent covering our product candidate is invalid and/or unenforceable. In addition, there is an abbreviated regulatory pathway, under the Biologics Price Competition and Innovation Act of 2009, for the regulatory approval of biosimilar or interchangeable biologic products, which could create a litigation pathway for a third party to challenge patents covering inclacumab. In patent litigation in the United States, defendant counterclaims alleging invalidity and/or unenforceability are commonplace, and there are multiple potential grounds for a validity challenge or an unenforceability assertion. The outcome following legal assertions of invalidity and unenforceability is often highly unpredictable.

Interference or derivation proceedings provoked by third parties or brought by us or declared by the USPTO may be necessary to determine the priority of inventions with respect to our patents or patent applications. 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.

In addition, our defense of litigation, interference or derivation proceedings may fail and, even if successful, may result in substantial costs and distract our management and other employees. In addition, the uncertainties associated

with litigation could have a material adverse effect on our business and operations including our ability to raise the funds necessary to continue our clinical trials, continue our research programs, license necessary technology from third parties, or enter into development partnerships that would help us bring our product candidates to market.

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

We may be subject to claims that former employees, collaborators or other third parties have an interest in our patents or other intellectual property as an inventor or co-inventor. For example, inventorship disputes may arise from conflicting obligations of third parties involved in developing our product candidates or as a result of questions regarding co-ownership of potential joint inventions. Litigation may be necessary to defend against these and other claims challenging inventorship or ownership or we may enter into agreements to clarify the scope of our rights in such intellectual property. 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 and operations including our ability to raise the funds necessary to continue our clinical trials, continue our research programs, license necessary technology from third parties, or enter into development partnerships that would help us bring our product candidates to market. 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 jointly own patents and patent applications with third parties. Our ability to exploit or enforce these patent rights, or to prevent the third party from granting licenses to others with respect to these patent rights, may be limited in some circumstances.

We jointly own certain patents and patent applications with third parties. In the absence of an agreement with each co-owner of jointly owned patent rights, we will be subject to default rules pertaining to joint ownership. Some countries require the consent of all joint owners to exploit, license or assign jointly owned patents, and if we are unable to obtain that consent from the joint owners, we may be unable to exploit the invention or to license or assign our rights under these patents and patent applications in those countries. For example, we have exclusively licensed from the Regents of the University of California (the Regents), worldwide patent rights covering voxelotor and certain voxelotor analogs, some of which patent rights we jointly own with the Regents. Additionally, in the United States, each co-owner may be required to be joined as a party to any claim or action we may wish to bring to enforce these patent rights, which may limit our ability to pursue third party infringement claims.

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 employees former employers 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.

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If we are unable to protect the confidentiality of our trade secrets or other confidential information, the value of our technology could be materially adversely affected and our business would be harmed.

We seek to protect our confidential proprietary information, in part, by confidentiality agreements and invention assignment agreements with our employees, consultants, scientific advisors, contractors and collaborators. These agreements are designed to protect our proprietary information. However, we cannot be certain that such agreements have been entered into with all relevant parties, and we cannot be certain 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. For example, any of these parties may breach the agreements and disclose our proprietary information, including our trade secrets, and we may not be able to obtain adequate remedies for such breaches. We also seek to preserve the integrity and confidentiality of our confidential proprietary information by maintaining physical security of our premises and physical and electronic security of our information technology systems, but it is possible that these security measures could be breached. Enforcing a claim that a third party obtained illegally and is using trade secrets or confidential know-how is expensive, time consuming and unpredictable. The enforceability of confidentiality agreements may vary from jurisdiction to jurisdiction. If any of our confidential proprietary information were to be lawfully obtained or independently developed by a competitor, we would have no right to prevent such competitor from using that technology or information to compete with us, which could harm our competitive position. 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.

Failure to obtain or maintain trade secrets or confidential know-how trade protection could adversely affect our competitive position. Moreover, our competitors may independently develop substantially equivalent proprietary information and may even apply for patent protection in respect of the same. If successful in obtaining such patent protection, our competitors could limit our use of our trade secrets or confidential know-how.

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 USPTO and various governmental patent agencies outside of the United States in several stages over the lifetime of the patents and/or applications. We employ outside firms and rely on them to pay many of these fees. The USPTO and various non-U.S. governmental patent agencies require compliance with a number of complex 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, 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, with a material adverse effect on our business.

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

Filing, prosecuting and defending patents on our 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 worldwide, 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 may also export infringing products to territories where we have patent protection but patent enforcement is not strong. 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.

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Many companies have encountered significant problems in protecting and defending intellectual property rights throughout the world. 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, whether or not successful, 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.

Changes in patent laws or patent jurisprudence could diminish the value of patents in general, thereby impairing our ability to protect our products.

As is the case with other biopharmaceutical companies, our success is heavily dependent on intellectual property, particularly patents. Obtaining and enforcing patents in the biopharmaceutical industry involve both technological complexity and legal complexity. Therefore, obtaining and enforcing biopharmaceutical patents is costly, time-consuming and inherently uncertain. In addition, the AIA has been recently enacted in the United States, resulting in significant changes to the U.S. patent system.

An important change introduced by the AIA is that, as of March 16, 2013, the United States transitioned to a first-to-file system for deciding which party should be granted a patent when two or more patent applications are filed by different parties claiming the same invention. A third party that files a patent application in the USPTO after that date but before us could therefore be awarded a patent covering an invention of ours even if we had made the invention before it was made by the third party. This will require us to be cognizant going forward of the time from invention to filing of a patent application, but circumstances could prevent us from promptly filing patent applications on our inventions.

Among some of the other changes introduced by the AIA are changes that limit where a patentee may file a patent infringement suit and provide opportunities for third parties to challenge any issued patent in the USPTO. This applies to all of our U.S. patents, even those issued before March 16, 2013. Because of a lower evidentiary standard in USPTO proceedings compared to the evidentiary standard in United States federal courts necessary to invalidate a patent claim, a third party could potentially provide evidence in a USPTO proceeding sufficient for the USPTO to hold a claim invalid even though the same evidence would be insufficient to invalidate the claim if first presented in a district court action. Accordingly, a third party may attempt to use the USPTO procedures to invalidate our patent claims that would not have been invalidated if first challenged by the third party as a defendant in a district court action. The AIA and its implementation could increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our issued patents.

The USPTO recently has developed regulations and procedures to govern administration of the AIA, and many of the substantive changes to patent law associated with the AIA, and, in particular, the first to file provisions, only became effective on March 16, 2013. Accordingly, the courts have yet to address many of these provisions and it is not clear what, if any, impact the AIA will have on the operation of our business. The AIA and its implementation could increase the uncertainties and costs surrounding the prosecution of our or our licensors or collaboration partners patent applications and the enforcement or defense of our or our licensors or collaboration partners issued patents, all of which could have an adverse effect on our business and financial condition.

Additionally, the U.S. Supreme Court has ruled on several patent cases in recent years narrowing the scope of patent protection available in certain circumstances or weakening 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 has

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also contributed to uncertainty with respect to the value of patents, once obtained. Depending on decisions by the U.S. Congress, the federal courts, and the USPTO, the laws and regulations governing patents could change in unpredictable ways that could weaken our ability to obtain new patents or to enforce our existing patents and patents that we might obtain in the future. Similarly, the complexity and uncertainty of European patent laws has also increased in recent years. In addition, the European patent system is relatively stringent in the type of amendments that are allowed during prosecution. These changes could limit our ability to obtain new patents in the future that may be important for our business.

Risks Related to Commercialization

Even if voxelotor, inclacumab or any other product candidate that we may develop receives marketing approval, commercial success will depend upon the degree of market acceptance by physicians, patients, third-party payors and others in the medical community and marketplace.

If voxelotor, inclacumab or any other product candidates that we may pursue receives marketing approval, including any approval by the FDA under Subpart H, the product may nonetheless fail to gain sufficient market acceptance by physicians, patients, third-party payors and others in the medical community and marketplace. If any approved product does not achieve an adequate level of acceptance, we may not generate significant revenue from drug sales and we may not become profitable. Before granting reimbursement approval, healthcare payors may require us to demonstrate that our product candidates, in addition to treating the target indication, also provide incremental health benefits to patients. For example, there have been numerous instances of government and private payors placing restrictions on coverage for products approved by the FDA under Subpart H, so even if voxelotor were to receive accelerated approval from the FDA, healthcare payors may place restrictions on coverage for voxelotor. Our efforts to educate the medical community and third-party payors about the benefits of our product candidates may require significant resources and may never be successful. The degree of market acceptance of our product candidates, if approved for commercial sale, will depend on a wide range of factors, including:

- the demonstratedefficacy and potential advantages of our drugs compared to alternative treatments;
- our ability to offer our drugs for sale at competitive prices;
- the convenience and ease of administration of our drugs compared to alternative current and future treatments;
- the willingness of the target patient population to try new therapies and of physicians to prescribe these therapies;
- the availability of drugs and their ability to meet market demand, including a reliable supply for long-term chronic treatment;
- the strength of marketing and distribution support;
- the availability of third-party coverage and adequate reimbursement;
- the clinical indications and approved labeling, including any labeling restrictions in the event a product candidate is approved under Subpart H, for which the drug is approved;
- the prevalence and severity of any side effects and overall safety profile of the drug; and
- any restrictions on the use of the drug, including together with other medications.

If we are unable to establish sales and marketing capabilities or enter into agreements with third parties to market and sell our product candidates, we may be unsuccessful in commercializing our product candidates if approved by regulatory authorities.

Although some of our employees have experience with commercializing products while employed at other companies, as a company we have no experience selling and marketing our product candidates, as a management team we have

not commercialized any product candidates, and we currently have no sales organization. To successfully commercialize any products that may result from our development programs, we will need to develop commercial capabilities, either on our own or with others. If our product candidates receive regulatory approval, we intend to establish a sales and marketing organization with technical expertise and supporting distribution capabilities to commercialize our product candidates in major markets, which will be

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expensive, difficult, risky and time consuming. Any failure or delay in the development of our internal sales, marketing, and distribution capabilities would adversely impact the commercialization of our products, if any are approved.

Further, given our lack of prior experience in marketing and selling biopharmaceutical products, our initial estimate of the size of the required sales force may be materially more or less than the size of the sales force actually required to effectively commercialize our product candidates. As such, we may be required to hire substantially more sales representatives to adequately support the commercialization of our product candidates or we may incur excess costs as a result of hiring more sales representatives than necessary. With respect to certain geographical markets, we may enter into collaborations with other entities to utilize their local marketing and distribution capabilities, but we may be unable to enter into such agreements on favorable terms, if at all. If our future collaborators do not commit sufficient resources to commercialize our future products, if any, and we are unable to develop the necessary marketing capabilities on our own, we will be unable to generate sufficient product revenue to sustain our business. We may be competing with companies that currently have extensive and well-funded marketing and sales operations. Without an internal team or the support of a third party to perform marketing and sales functions, we would be unable to compete successfully against more established companies.

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

Our target patient populations are small, and accordingly the pricing, coverage and reimbursement of our product candidates, if approved, must be adequate to support our commercial infrastructure. Our per-patient prices must be sufficient to recover our development and manufacturing costs and potentially achieve profitability. Accordingly, the availability of government funded or private insurance coverage for our product candidates for any approved indications, and the extent of reimbursement by governmental and private payors, will be essential for most patients to be able to afford expensive treatments, such as we expect ours to be assuming approval. Sales of our product candidates will depend substantially, both domestically and abroad, on the extent to which the costs of our product candidates will be paid by third party payors, like private health insurers, including health maintenance, managed care, pharmacy benefit and similar healthcare management organizations, and government health administration programs, like Medicare and Medicaid. If reimbursement is not available, or is available only to limited levels, we may not be able to successfully commercialize our product candidates. Even if coverage is provided, the approved reimbursement amount may not be high enough to allow us to establish or maintain pricing sufficient to realize a sufficient return on our investment.

There is significant uncertainty related to the insurance coverage and reimbursement of newly approved drug products, and even more uncertainty related to the insurance coverage for products that receive accelerated approval by the FDA under Subpart H (including in the period before required post-marketing confirmatory studies to verify clinical benefit). The process for determining whether a third-party payor will provide coverage for a product may be separate from the process for setting the reimbursement rate that the payor will pay for the product. Third-party payors may limit coverage to specific products on an approved list, or formulary, which might not include all of the FDA-approved products for a particular indication. Moreover, a third-party payor s decision to provide coverage for a product does not imply that an adequate reimbursement rate will be approved. For example, the payor s reimbursement payment rate may not be adequate or may require co-payments that patients find unacceptably high. Additionally, coverage and reimbursement for products can differ significantly from payor to payor.

In the United States, significant decisions about reimbursement for new medicines are made by the Centers for Medicare & Medicaid Services, or CMS, an agency within the U.S. Department of Health and Human Services, as

CMS decides whether and to what extent a new medicine will be covered and reimbursed under Medicare and enters into contracts with drug manufacturers for discounted drug prices for Medicaid under the Medicaid Drug Rebate Program. The practices and requirements relating to the payment of rebates by drug manufacturers for Medicaid purchases are determined by each state, and in some cases, if a company does not enter into a rebate agreement, its Medicaid sales will be subjected to a prior authorization procedure that

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requires state agency approval to qualify a doctor s prescription for reimbursement. Limitations could also come from entities such as local Medicare carriers, fiscal intermediaries, or Medicare Administrative Contractors. Further, Medicare Part D, which provides a pharmacy benefit to certain Medicare patients, does not require participating prescription drug plans to cover all drugs within a class of products. Our business could be materially adversely affected if private or governmental payors, including Medicare Part D prescription drug plans, were to limit access to, or deny or limit reimbursement of, our product candidates.

Outside the United States, international operations are generally subject to extensive governmental price controls and other market regulations, and we believe the increasing emphasis on cost-containment initiatives in Europe, Canada, and other countries has and will continue to put pressure on the pricing and usage of our product candidates. In many countries, the prices of medical products are subject to varying price control mechanisms as part of national health systems, and changes to these regulations over time contribute to uncertainty regarding the ability to obtain pricing and usage approvals for our product candidates outside of the United States. In general, the prices of medicines under such systems are substantially lower than in the United States. Other countries allow companies to fix their own prices for medicines, but monitor and control company profits. Additional foreign price controls or other changes in pricing regulation could restrict the amount that we are able to charge for our product candidates. Accordingly, in markets outside the United States, the reimbursement for our products may be reduced compared with the United States and may be insufficient to generate commercially reasonable revenues and profits.

In many non-U.S. jurisdictions, the proposed pricing for a drug must be approved before it may be lawfully marketed. In many countries, the pricing review period begins after marketing or product licensing approval is granted and reimbursement may in some cases be unavailable. As a result, we might obtain marketing approval for a product in a particular country, but then be subject to price regulations that delay commercial launch of the product, possibly for lengthy time periods, which may negatively impact the revenues we are able to generate from the sale of the product in that country. The requirements governing drug pricing vary widely from country to country and products may be subject to continuing governmental control following approval. For example, the European Union provides options for its member states to restrict the range of medicinal products for which their national health insurance systems provide reimbursement and to control the prices of medicinal products for human use, including by approving a specific price for the medicinal product or adopting a system of direct or indirect controls on the profitability of the company placing the medicinal product on the market. There can be no assurance that any country that has price controls or reimbursement limitations for pharmaceutical products will allow favorable reimbursement and pricing arrangements for any of our products or product candidates.

Moreover, increasing efforts by governmental and third-party payors, in the United States and abroad, to cap or reduce healthcare costs may cause such organizations to limit both coverage and levels of reimbursement for new products approved and, as a result, they may not cover or provide adequate payment for our product candidates. We expect to experience pricing pressures in connection with the sale of any of our product candidates, due to the trend toward managed healthcare, the increasing influence of health maintenance organizations and additional legislative and political changes. The downward pressure on healthcare costs in general, particularly prescription drugs and surgical procedures and other treatments, has become very intense. For example, third-party payors are increasingly requiring higher levels of evidence of the benefits and clinical outcomes of new technologies, benchmarking against other therapies, seeking performance-based discounts, and challenging the prices charged. We cannot be sure that coverage will be available for any product we commercialize and, if available, that the reimbursement rates will be adequate. As a result, increasingly high barriers are being erected to the entry of new products. In addition, drug prices are under significant scrutiny in the markets in which our products may be sold, and drug pricing and other healthcare costs continue to be subject to intense political and social pressures which we anticipate will continue and escalate on a global basis. As a result, our business and reputation may be harmed, our stock price may be adversely impacted and experience periods of volatility, we may have difficulty raising funds and our results of operations may be adversely

impacted.

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In light of the large population of patients with SCD who reside in foreign countries, our ability to generate meaningful revenues in those jurisdictions may be limited due to the strict price controls and reimbursement limitations imposed by governments outside of the United States.

In some countries, particularly in the European Union, the pricing of prescription pharmaceuticals is subject to governmental control. In these countries, pricing negotiations with governmental authorities can take considerable time after the receipt of marketing approval for a drug. To obtain coverage and reimbursement or pricing approval in some countries, we may be required to conduct a clinical trial that compares the cost-effectiveness of our product candidate to other available therapies, or to meet other criteria for pricing approval.

Reimbursement systems in international markets vary significantly by country and by region. In some foreign markets, prescription pharmaceutical pricing remains subject to continuing governmental control even after initial approval is granted. For example, reimbursement in the European Union must be negotiated on a country-by-country basis and in many countries, the product cannot be commercially launched until reimbursement is approved. The negotiation process in some countries can be very lengthy. To obtain reimbursement or pricing approval in some countries, we may be required to conduct a clinical trial that compares the cost-effectiveness of our products to other available therapies.

In addition, pricing regulations outside of the United States vary widely from country to country. For example, the European Union provides options for its member states to restrict the range of medicinal products for which their national health insurance systems provide reimbursement and to control the prices of medicinal products for human use. There can be no assurance that any country that has price controls or reimbursement limitations for pharmaceutical products will allow favorable reimbursement and pricing arrangements for any of our products or product candidates. If reimbursement of our product candidates is unavailable or limited in scope or amount, or if pricing is set at unsatisfactory levels, our business and operations could be harmed, possibly materially, based on the large population of patients with SCD who reside in foreign countries.

Our future profitability will depend, in part, on our ability to commercialize our product candidates in markets within and outside of the United States and Europe. If we commercialize our product candidates in foreign markets, we would be subject to additional risks and uncertainties, including:

- the burden of complying with complex and changing foreign regulatory, tax, accounting, compliance and legal requirements;
- different medical practices and customs in foreign countries affecting acceptance in the marketplace;
- import or export licensing requirements;
- longer accounts receivable collection times;
- longer lead times for shipping;

language barriers for technical training;

reduced protection of intellectual property rights in some foreign countries, and related prevalence of bioequivalent or generic alternatives to therapeutics;

foreign currency exchange rate fluctuations;

patients ability to obtain reimbursement for our products in foreign markets; and

the interpretation of contractual provisions governed by foreign laws in the event of a contract dispute.

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Our business operations and current and future relationships with investigators, health care professionals, consultants, third-party payors and customers will be subject, directly or indirectly, to federal and state healthcare fraud and abuse laws, false claims laws, health information privacy and security laws, and other healthcare laws and regulations. If we are unable to comply, or have not fully complied, with such laws, we could face substantial penalties.

Although we do not currently have any products on the market, our current and future operations may be directly, or indirectly through our prescribers, customers and third-party payors, subject to various U.S. federal and state healthcare laws and regulations. These laws may impact, among other things, our current business operations, including our clinical research activities, and proposed sales, marketing and education programs and constrain our business and financial arrangements and relationships with healthcare providers, physicians and other parties through which we market, sell and distribute our products for which we obtain marketing approval. We may also be subject to additional healthcare, statutory and regulatory requirements and enforcement by foreign regulatory authorities in jurisdictions in which we conduct our business. The laws that may affect our ability to operate include the federal Anti-Kickback Statute, the federal False Claims laws, HIPAA, the Physician Payment Sunshine Act, and analogous state laws and regulations such as state anti-kickback and false claims laws and analogous non-U.S. fraud and abuse laws and regulations, may apply to sales or marketing arrangements and claims involving healthcare items or services reimbursed by non-governmental third-party payors, including the following:

- the U.S. federal Anti-Kickback Statute makes it illegal for any person, including a prescription drug manufacturer (or a party on its behalf) to knowingly and willfully solicit, offer, receive or pay any remuneration (including any kickback, bribe, or certain rebates), directly or indirectly, overtly or covertly, in cash or in kind, that is intended to induce or reward either the referral of an individual for, or the purchase, lease, order or recommendation of, any good, facility, item or service, for which payment may be made, in whole or in part, under U.S. federal healthcare programs such as Medicare and Medicaid. Violations of this law can result in criminal penalties and fines, administrative civil money penalties and exclusion from participation in federal healthcare programs. 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, and some federal courts have adopted very broad readings of the potential for violations of the statute;
- the U.S. federal false claims and civil monetary penalties laws, including the civil False Claims Act, which, among other things, impose criminal and civil penalties, including through civil whistleblower or qui tam actions, against individuals or entities (including manufacturers) knowingly presenting, or causing to be presented false or fraudulent claims for payment by a federal healthcare program or making a false statement or record material to payment of a false claim or avoiding, decreasing or concealing an obligation to pay money to the federal government. Penalties for a False Claims Act violation include three times the actual damages sustained by the government, plus mandatory civil penalties, the potential for exclusion from participation in federal healthcare programs and the potential implication of various federal criminal statutes. The government may deem manufacturers to have caused the submission of false or fraudulent claims by, for example, providing inaccurate billing or coding information to customers or promoting a product off-label. Claims which include items or services resulting from a violation of the federal Anti-Kickback Statute are false or fraudulent claims for purposes of the False Claims Act, and activities relating to the reporting of wholesaler or estimated retail prices, the reporting of prices used to calculate Medicaid rebate information and other information affecting federal, state and third-party product reimbursement are subject to scrutiny under this law. The civil False Claims Act has been used to assert liability on the basis of, among other things, kickbacks and other improper referrals, improperly reported government pricing metrics

such as Best Price or Average Manufacturer Price causing underpayment of rebates, improper use of Medicare provider or supplier numbers when detailing a provider of services, improper promotion (e.g. of off-label

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uses not expressly approved by the FDA in a product s label), and allegations as to misrepresentations with respect to the services rendered. Intent to deceive is not required to establish liability under the civil False Claims Act. Over time, False Claims Act lawsuits against biopharmaceutical companies have increased significantly in volume and breadth, leading to multiple substantial civil and criminal settlements regarding sales practices and promoting off label uses. Further, the government may further prosecute conduct constituting a false claim under the criminal False Claims Act;

the U.S. federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, which imposes criminal and civil liability for, among other things, knowingly and willfully executing, or attempting to execute, a scheme to defraud any healthcare benefit program, including private payors, knowingly and willfully embezzling or stealing from a healthcare benefit program, willfully obstructing a criminal investigation of a healthcare offense, or knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false statement, in connection with the delivery of, or payment for, healthcare benefits, items or services; similar to the U.S. 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;

HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act of 2009 and their respective implementing regulations, which imposes, among other things, specified requirements on covered entities and their business associates relating to the privacy, security and transmission of individually identifiable health information, including mandatory contractual terms and required implementation of technical safeguards of such information. HITECH also created new tiers of civil monetary penalties, amended HIPAA to make civil and criminal penalties applicable to business associates, and gave state attorneys general new authority to file civil actions for damage or injunctions in federal courts to enforce the federal HIPAA laws and seek attorneys fees and costs associated with pursuing federal civil actions;

the U.S. Federal Food, Drug and Cosmetic Act, which prohibits, among other things, the adulteration or misbranding of drugs, biologics and medical devices;

the U.S. federal legislation commonly referred to as Physician Payments Sunshine Act, enacted as part of the ACA, as amended by the Education Reconciliation Act of 2010 and its implementing regulations, which requires certain manufacturers of drugs, devices, biologics and medical supplies that are reimbursable under Medicare, Medicaid, or the Children s Health Insurance Program to report annually to the CMS information related to certain payments and other transfers of value to physicians (defined to include doctors, dentists, optometrists, podiatrists and chiropractors) and teaching hospitals, as well as ownership and investment interests held by the physicians described above and their immediate family members;

payment or reimbursement of prescription therapeutics by Medicaid or Medicare requires manufacturers to submit pricing information to CMS. The Medicaid Drug Rebate statute requires manufacturers to calculate and report price points, which are used to determine Medicaid rebate payments shared between the states and the federal government and Medicaid payment rates for certain therapeutics. For therapeutics paid under Medicare Part B, manufacturers must also calculate and report their Average Sales Price, which is used to determine the Medicare Part B payment rate. Many products are subject to an additional inflation penalty which can substantially increase rebate payments. In addition, the Veterans Health Care Act, or VHCA, requires manufacturers of drugs and biologics to calculate and report a different price to the Veterans Administration, or VA, which is used to determine the maximum price that can be charged to certain federal agencies, and includes an inflation penalty. All of these detailed and complex price

reporting requirements create risk of

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submitting false information to the government, and potential for liability including under the False Claims Act;

the VHCA also requires manufacturers of covered therapeutics participating in the Medicaid program to enter into Federal Supply Schedule contracts with the VA through which their covered therapeutics must be sold to certain federal agencies at the price reported to the VA. This necessitates compliance with applicable federal procurement laws and regulations, including submission of commercial sales and pricing information, and subjects manufacturers to contractual remedies as well as administrative, civil, and criminal sanctions. In addition, the VHCA requires manufacturers participating in Medicaid to agree to provide different mandatory discounts to certain Public Health Service grantees and other safety net hospitals and clinics under the 340B program based on the manufacturer s reported Medicaid pricing information. The 340B program has its own regulatory authority to impose sanctions for non-compliance;

analogous state laws and regulations, including: state anti-kickback and false claims laws, which may be broader in scope and apply regardless of payor; state laws that require pharmaceutical companies to comply with the pharmaceutical industry s voluntary compliance guidelines and the relevant compliance guidance promulgated by the U.S. federal government, or otherwise restrict payments that may be made to healthcare providers and other potential referral sources; state laws and regulations that require drug manufacturers to file reports relating to pricing and marketing information, which requires tracking gifts and other remuneration and items of value provided to healthcare professionals and entities; and state laws governing the privacy and security of health information in certain circumstances, many of which differ from each other in significant ways and often are not preempted by HIPAA, thus complicating compliance efforts;

the Foreign Corrupt Practices Act, or FCPA, prohibits any U.S. individual or business from paying, offering, or authorizing payment or offering of anything of value, directly or indirectly, to any foreign official, political party, or candidate for the purpose of influencing any act or decision of the foreign entity in order to assist the individual or business in obtaining or retaining business. The FCPA also obligates companies whose securities are listed in the United States to comply with accounting provisions requiring the company to maintain books and records that accurately and fairly reflect all transactions of the corporation, including international subsidiaries, and to devise and maintain an adequate system of internal accounting controls for international operations. Activities that violate the FCPA, even if they occur wholly outside the United States, can result in criminal and civil fines, imprisonment, disgorgement, oversight, and debarment from government contracts; and

European and other foreign law equivalents of each of the laws, including reporting requirements detailing interactions with and payments to healthcare providers.

Ensuring that our business arrangements with third parties comply with applicable healthcare laws and regulations is complex and could be costly. It is possible that governmental authorities will conclude that our business practices do not comply with current or future statutes, regulations or case law involving applicable fraud and abuse, price reporting or other healthcare laws and regulations. If our operations were found to be in violation of any of these requirements that may apply to us, we may be subject to significant civil, criminal, and administrative penalties, damages, fines, disgorgement, individual imprisonment, debarment from governmental contracting and refusal of orders under existing contracts, and exclusion from government funded healthcare programs, such as Medicare and Medicaid, any of which could substantially disrupt our business and operations. If the physicians or other providers or entities with whom we expect to do business are found not to be in compliance with applicable requirements, they

may be subject to criminal, civil or administrative sanctions, including exclusions from government funded healthcare programs.

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Although an effective compliance program can mitigate the risk of investigation and prosecution for violations of these requirements, the risks cannot be entirely eliminated. Moreover, achieving and sustaining compliance with applicable federal and state privacy, security, and fraud requirements may prove costly. Any action against us for violation of these requirements, even if we successfully defend against it, could cause us to incur significant legal expenses and divert our management s attention from our business and operation, and could negatively impact the price of our common stock.

The scope and enforcement of each of these laws is uncertain and subject to rapid change in the current environment of healthcare reform and other factors, including the lack of applicable precedent and regulations. Federal and state enforcement bodies regularly pursue a large number of investigations, prosecutions, convictions and settlements in the healthcare industry. Ensuring that our internal operations and future business arrangements with third parties comply with applicable healthcare laws and regulations will involve substantial costs. It is possible that governmental authorities will conclude that our business practices may not comply with current or future statutes, regulations, agency guidance or case law involving applicable fraud and abuse or other healthcare laws and regulations. If our operations are found to be in violation of any of the laws described above or any other governmental laws and regulations that may apply to us, we may be subject to significant penalties, including civil, criminal and administrative penalties, damages, fines, exclusion of products or individuals from U.S. government funded healthcare programs, such as Medicare and Medicaid, or similar programs in other countries or jurisdictions, disgorgement, individual imprisonment, additional reporting requirements and oversight if we become subject to a corporate integrity agreement or similar agreement to resolve allegations of non-compliance with these laws, contractual damages, reputational harm, diminished profits, and the curtailment or restructuring of our operations. Further, defending against any such actions can be costly, time-consuming and may require significant financial and personnel resources. Therefore, even if we are successful in defending against any such actions that may be brought against us, our business may be impaired. If any of the physicians or other providers or entities with whom we expect to do business is found to not be in compliance with applicable laws, they may be subject to criminal, civil or administrative sanctions, including exclusions from government funded healthcare programs and imprisonment. If any of the above occur, it could adversely affect our ability to operate our business and our results of operations.

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

In the United States, there have been and continue to be a number of legislative and regulatory changes and proposed changes regarding the healthcare system that could prevent or delay marketing approval of our drug candidates, restrict or regulate post-approval activities and affect our ability to profitably sell any drug candidates for which we obtain marketing approval. For example, in 2010, the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act, or the Affordable Care Act (the ACA), was passed, which substantially changes the way health care is financed by both governmental and private insurers, and significantly impacts the U.S. pharmaceutical industry. The provisions of the ACA of importance to the pharmaceutical and biotechnology industry are, among others, the following:

- an annual, nondeductible fee on any entity that manufactures or imports certain branded prescription drugs and biologic agents, which is apportioned among these entities according to their market share in certain government healthcare programs;
- an increase in the statutory minimum rebates a manufacturer must pay under the Medicaid Drug Rebate Program to 23.1% and 13% of the average manufacturer price for branded and generic drugs, respectively;
- a new Medicare Part D coverage gap discount program, in which manufacturers must agree to offer 50% point-of-sale discounts to negotiated prices of applicable brand drugs to eligible

beneficiaries during their coverage gap period, as a condition for the manufacturer s outpatient drugs to be covered under Medicare Part D;

extension of manufacturers Medicaid rebate liability to covered drugs dispensed to individuals who are enrolled in Medicaid managed care organizations, unless the drug is subject to discounts under the 340B drug discount program;

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- 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;
- expansion of eligibility criteria for Medicaid programs by, among other things, allowing states to offer Medicaid coverage to additional individuals and by adding new mandatory eligibility categories for certain individuals with income at or below 133% of the federal poverty level, thereby potentially increasing manufacturers Medicaid rebate liability;
- expansion of healthcare fraud and abuse laws, including the False Claims Act and the Anti-Kickback Statute, new government investigative powers, and enhanced penalties for noncompliance;
- expansion of the entities eligible for discounts under the Public Health Service pharmaceutical pricing program;
- new requirements under the federal Physician Payments Sunshine Act for drug manufacturers to report information related to payments and other transfers of value made to physicians and teaching hospitals as well as ownership or investment interests held by physicians and their immediate family members;
- a new Patient-Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research;
- establishment of a Center for Medicare and Medicaid Innovation at CMS to test innovative payment and service delivery models to lower Medicare and Medicaid spending, potentially including prescription drug spending; and
- aggregate reductions to Medicare Part B payments to providers of up to 2% per fiscal year, which became effective on April 1, 2013 and will remain in effect through 2027 unless additional congressional action is taken.

Since its enactment, there have been many judicial, President, and Congressional challenges to numerous aspects of the ACA. In 2012, the U.S. Supreme Court heard challenges to the constitutionality of the individual mandate and the viability of certain provisions of the Healthcare Reform Act. The Supreme Court s decision upheld most of the Healthcare Reform Act and determined that requiring individuals to maintain minimum essential health insurance coverage or pay a penalty to the Internal Revenue Service was within Congress s constitutional taxing authority. The full impact of the ACA, any law repealing and/or replacing elements of it, and the political uncertainty surrounding any repeal or replacement legislation on our business remains unclear.

Additionally, at the federal level, statutes and regulations routinely impact a variety of parameters relating to federal programs and Medicaid. For example, CMS s final rule regarding the Medicaid drug rebate program, issued in 2016, revised the manner in which the average manufacturer price is to be calculated by manufacturers participating in the program. At the state level, legislatures are increasingly passing legislation and implementing regulations designed to control pharmaceutical 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. The full impact of these federal and state laws and regulations, as well as other new laws and reform measures that may be proposed and adopted in the future, remains uncertain, but may result in additional reductions in Medicaid and other health care funding, or higher production costs which could have a material adverse effect on our customers and, accordingly, our financial operations.

There have been several recent U.S. congressional inquiries and proposed and adopted federal and state legislation designed to, among other things, bring more transparency to drug pricing, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for drugs and biologics. In addition, Congress and the Trump administration have each indicated that it will continue to seek new legislative and/or administrative measures to control drug costs. While any proposed measures will require authorization through additional legislation to become effective, Congress and the current U.S. presidential

administration have each indicated that it will continue to seek new legislative and/or administrative measures to control drug costs.

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At the state level, legislatures are increasingly 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 and marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing. In addition, regional health care authorities are increasingly using bidding procedures to determine what pharmaceutical products and which suppliers will be included in their prescription drug and other health care programs. These measures could reduce the ultimate demand for our products, once approved, or put pressure on our product pricing.

Moreover, there have been a number of other legislative and regulatory changes in recent years aimed at the biopharmaceutical industry. For instance, the Drug Quality and Security Act imposes obligations on manufacturers of biopharmaceutical products related to product tracking and tracing. Among the requirements of this legislation, manufacturers are required to provide certain information regarding the product to individuals and entities to which product ownership is transferred, will be required to label products with a product identifier, and are required keep certain records regarding the product. The transfer of information to subsequent product owners by manufacturers will eventually be required to be done electronically. Manufacturers are also required to verify that purchasers of the manufacturers products are appropriately licensed. Further, manufacturers have product investigation, quarantine, disposition, and FDA and trading partner notification responsibilities related to counterfeit, diverted, stolen, and intentionally adulterated products that would result in serious adverse health consequences or death to humans, as well as products that are the subject of fraudulent transactions or which are otherwise unfit for distribution such that they would be reasonably likely to result in serious health consequences or death.

We expect federal and state healthcare reform measures that may be adopted in the future, may result in more rigorous coverage criteria, increased regulatory burdens and operating costs, decreased net revenue from our pharmaceutical products and additional downward pressure on the price that we receive if voxelotor is approved for use. Any reduction in reimbursement from Medicare or other government programs may result in a similar reduction in payments from private payors. 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. These legislative and executive efforts have significantly increased uncertainty regarding the availability of healthcare programs, insurance coverage and reimbursement as a general matter as well as for our product candidates, and we cannot predict how these events will impact our business or operations. Accordingly, at this time it is difficult to determine the full impact of these efforts on our business. In the United States many patients with SCD participate in the Medicaid program, and the impact of uncertainty or changes relating to the ACA or healthcare programs, insurance coverage or reimbursement generally could be particularly significant for our SCD program if voxelotor is approved for use.

We face intense competition and rapid technological change and the possibility that our competitors may develop therapies that are similar, more advanced, or more effective than ours, which may adversely affect our financial condition and our ability to successfully commercialize our product candidates.

The biotechnology and pharmaceutical industries are intensely competitive and subject to rapid and significant technological change. We are currently aware of various existing therapies and development candidates that may compete with voxelotor and inclacumab for the potential treatment of SCD. For example, Novartis is developing crizanlizumab, which is a potential competitor of inclacumab. Both crizanlizumab and inclacumab are human monoclonal antibodies against P-selectin for the treatment of VOC in patients with SCD. Novartis has announced that it anticipates filing a biologics license application for crizanlizumab in the first half of 2019, which would result in a direct competitor entering the market significantly earlier than inclacumab. We have competitors both in the United States and internationally, including major multinational pharmaceutical companies, specialty pharmaceutical companies, and biotechnology companies. Many of our competitors have substantially greater financial, technical, and

other resources, such as larger research and development, marketing and manufacturing organizations. Additional mergers and acquisitions in the biotechnology and pharmaceutical industries may result in even more resources being concentrated in our competitors. As a result, these companies may obtain regulatory approval more rapidly than we are able to and may be more effective in selling and

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marketing their products as well. Smaller or early-stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large, established companies. 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 or less costly than any product candidate that we may develop, or achieve earlier patent protection, regulatory approval, product commercialization and market penetration than we do. Additionally, technologies developed by our competitors may render our potential product candidates uneconomical or obsolete, and we may not be successful in marketing our product candidates against competitors.

If the market opportunities for our product candidates are smaller than we believe they are, our revenue may be adversely affected, and our business may suffer. Our ability to successfully identify patients and acquire a significant market share will be necessary for us to achieve profitability and growth.

Our initial research and product development efforts are focused on the potential of voxelotor to treat SCD. Our projections of both the number of people who have SCD, as well as the subset of people with SCD who have the potential to benefit from treatment with voxelotor, are based on our beliefs and estimates. These estimates have been derived from a variety of sources, including the scientific literature, and may prove to be incorrect. Further, new studies may change the estimated incidence or prevalence of SCD. The number of patients may turn out to be lower than expected. The effort to identify patients with diseases we seek to treat is in early stages, and we cannot accurately predict the number of patients for whom treatment might be possible. Additionally, the potentially addressable patient population for our product candidates may be limited or may not be amenable to treatment with our product candidates, and new patients may become increasingly difficult to identify or gain access to, which would adversely affect our results of operations and our business. Restrictions on labeling of any approved product, including any restrictions that may be imposed in connection with any approval under Subpart H, may also limit the size of the potential market for our product candidates. Further, even if we obtain significant market share for our product candidates, because the potential target populations are small, we may never achieve profitability despite obtaining such significant market share.

Risks Related to Our Business and Industry

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

We are highly dependent on the management, research and development, clinical, financial and business development expertise of our executive officers, as well as the other members of our scientific and clinical teams. Although we have employment offer letters with each of our executive officers, each of them may terminate their employment with us at any time. We do not maintain key person insurance for any of our executives or employees.

Recruiting and retaining qualified scientific, medical and clinical and technical operations personnel and, if we progress the development of our drug pipeline toward scaling up for commercialization, sales and marketing personnel, will also be critical to our success. The loss of the services of our executive officers or other key employees could impede the achievement of our research, development and commercialization objectives and seriously harm our ability to successfully implement our business strategy. Furthermore, replacing executive officers and key employees may be difficult and may take an extended period of time because of the limited number of individuals in our industry with the breadth of skills and experience required to successfully develop, gain regulatory approval for and commercialize our product candidates. Competition to hire qualified personnel in our industry and geographic market is intense, and we may be unable to hire, train, retain or motivate these key personnel on acceptable terms given the competition among numerous pharmaceutical and biotechnology companies for similar personnel. Furthermore, to the

extent we hire personnel from competitors, we may be subject to allegations that they have been improperly solicited or that they have divulged proprietary or other confidential information, or that their former employers own their research output. We also experience competition for the hiring of scientific and clinical personnel from universities and research institutions. In

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addition, we rely on consultants and advisors, including scientific and clinical advisors, to assist us in formulating our research and development and commercialization strategy. Our consultants and advisors may be employed by employers other than us and may have commitments under consulting or advisory contracts with other entities that may limit their availability to us. If we are unable to continue to attract and retain high quality personnel, our ability to pursue our growth strategy will be limited.

We expect to expand our product development capabilities and potentially implement sales, marketing and distribution capabilities, and as a result, we may encounter difficulties in managing our growth, which could disrupt our operations.

As our development progresses, we expect to experience significant growth in the number of our employees and the scope of our operations, particularly in the areas of research, drug development, regulatory affairs and, if any of our product candidates are filed for or receives marketing approval, sales, marketing and distribution. To manage our anticipated future growth, we must continue to implement and improve our managerial, operational and financial systems, expand our facilities and continue to recruit and train additional qualified personnel. Due to our limited financial resources, we may not be able to effectively manage the expansion of our operations or recruit and train additional qualified personnel. The expansion of our operations may lead to significant costs and may divert our management and business development resources. Any inability to manage growth could delay the execution of our business plans or disrupt our operations.

If we are not successful in discovering, developing, acquiring or commercializing additional product candidates, our ability to expand our business and achieve our strategic objectives would be impaired.

Although a substantial amount of our effort will focus on the continued clinical testing, potential approval and commercialization of voxelotor, a key element of our strategy is to pursue, develop and commercialize a portfolio of products utilizing proprietary discovery and development technology. We are seeking to do so through our internal research programs and may also selectively pursue commercially synergistic in-licensing or acquisition of additional assets, such as inclacumab. With the exception of voxelotor, all of our other potential product candidates remain in the earlier development stages. Research programs to identify product candidates require substantial technical, financial and human resources, whether or not any product candidates are ultimately identified. Our research programs may initially show promise in identifying potential product candidates, yet fail to yield product candidates for clinical development for many reasons, including the following:

- the research methodology used may not be successful in identifying potential product candidates;
- competitors may develop alternatives that render our product candidates obsolete or less attractive;
- product candidates we develop may nevertheless be covered by third parties patents or other exclusive rights;
- the market for a product candidate may change during our program so that such a product may become unreasonable to continue to develop;
- a product candidate may on further study be shown to have harmful side effects, lack of potential efficacy or other characteristics that indicate it is unlikely to meet applicable regulatory criteria or remain reasonable to continue to develop;
- a product candidate may not be capable of being produced in commercial quantities at an acceptable cost, or at all; and
- a product candidate may not be accepted as safe and effective by patients, the medical community or third-party payors, if applicable.

If we fail to develop and successfully commercialize inclacumab or any other product candidates, our business and future prospects may be harmed and our business will be more vulnerable to any problems that we encounter in developing and commercializing voxelotor.

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

- impairment of our business reputation;
- withdrawal of clinical trial participants;
- costs due to related litigation;
- distraction of management s attention from our primary business;
- substantial monetary awards to patients or other claimants;
- increased warnings on product labels or additional restrictions imposed by regulatory authorities;
- the recall of our product candidates;
- the inability to commercialize our product candidates; and
- decreased demand for our product candidates, if approved for commercial sale.

We carry product liability insurance in amounts that we believe are sufficient in light of our current clinical programs, but we may not be able to maintain insurance coverage at a reasonable cost or in sufficient amounts to protect us against losses due to liability. If and when we obtain marketing approval for product candidates, we intend to expand our insurance coverage to include the sale of commercial products, but we may be unable to obtain product liability insurance on commercially reasonable terms or in adequate amounts. 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.

During the course of treatment, patients may suffer adverse events, including death, for reasons that may or may not be related to our product candidates. Such events can be time-consuming to address, could subject us to costly litigation, require us to pay substantial amounts of money to injured patients, can delay, negatively impact or end our opportunity to receive or maintain regulatory approval to market our product candidates, if approved, can require us to suspend or abandon our commercialization efforts of any approved product candidates, or can impair our ability to raise funds to pursue our development or commercialization efforts. Investigations of these events may interrupt our sales efforts, delay our regulatory approval process in other countries, or impact and limit the type of regulatory approvals our product candidates receive or 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.

If we fail to comply with environmental, health and safety laws and regulations, we could become subject to fines or penalties or incur costs that could harm our business.

We are subject to numerous environmental, health and safety laws and regulations, including those governing laboratory procedures and the handling, use, storage, treatment and disposal of hazardous materials and wastes. Our

operations involve the use of hazardous and flammable materials, including chemicals and biological materials. Our operations also produce hazardous waste products. We generally contract with third parties for the disposal of these materials and wastes. We cannot eliminate the risk of contamination or injury from these materials. In the event of contamination or injury resulting from our use of hazardous materials, we could be held liable for any resulting damages, and any liability could exceed our resources. We also could incur

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significant costs associated with civil or criminal fines and penalties for failure to comply with such laws and regulations.

Although we maintain workers compensation insurance to cover us for costs and expenses we may incur due to injuries to our employees resulting from the use of hazardous materials, this insurance may not provide adequate coverage against potential liabilities. We do not maintain insurance for environmental liability or toxic tort claims that may be asserted against us in connection with our storage or disposal of biological, hazardous or radioactive materials.

In addition, we may incur substantial costs in order to comply with current or future environmental, health and safety laws and regulations. These current or future laws and regulations may impair our research, development or production efforts. Our failure to comply with these laws and regulations also may result in substantial fines, penalties or other sanctions.

We may choose to use our financial and human resources to pursue a particular research program or product candidate and fail to capitalize on other programs or product candidates that may ultimately be more profitable or for which there is a greater likelihood of success.

Because we have limited resources, we may forego or delay the pursuit of opportunities with programs or product candidates or for indications that later prove to have greater commercial potential than those we do pursue. Our resource allocation decisions may cause us to fail to capitalize on viable commercial products or profitable market opportunities. Our spending on current and future research and development programs for product candidates, including voxelotor or inclacumab, may not yield any commercially viable products. If we do not accurately evaluate the commercial potential or target market for a particular product candidate, we may relinquish valuable rights to that product candidate through strategic collaboration, licensing or other partnering arrangements in cases in which it would have been more advantageous for us to retain sole development and commercialization rights to such product candidate, or we may allocate internal resources to a product candidate in a therapeutic area in which it would have been more advantageous to enter into a partnering arrangement.

Any collaboration arrangements that we might enter into in the future may not be successful, which could adversely affect our operations and financial condition.

We may seek collaboration arrangements with pharmaceutical or biotechnology companies for the development or commercialization of voxelotor, inclacumab and potential future product candidates. We may enter into these arrangements on a selective basis depending on the merits of retaining commercialization rights for ourselves as compared to entering into selective collaboration arrangements with leading pharmaceutical or biotechnology companies for our product candidates, both in the United States and internationally. To the extent that we decide to enter into collaboration agreements, we will face significant competition in seeking appropriate collaborators. Whether we reach a definitive agreement for any collaboration will depend, among other things, upon our assessment of the collaborator s resources and expertise, the terms and conditions of the proposed collaboration and the proposed collaborator s evaluation of a number of factors. Those factors may include the design or results of clinical trials, the likelihood of approval by the FDA or comparable foreign regulatory authorities, the potential market for a product candidate, the costs and complexities of manufacturing and delivering a product candidate to patients, the potential of competing products, any uncertainty with respect to our ownership of technology, which can occur if there is a challenge to our ownership without regard to the merits of the challenge and industry and market conditions generally. Moreover, collaboration arrangements are complex and time consuming to negotiate, document and implement, and we have not previously established our ability to undertake these activities successfully. We may not be successful in our efforts to establish and implement collaborations or other alternative arrangements should we so chose to enter into such arrangements. The terms of any collaborations or other arrangements that we may establish may not be

favorable to us.

Any future collaborations that we enter into may not be successful. The success of our collaboration arrangements will depend heavily on the efforts and activities of us and our collaborators. Collaborators generally have significant discretion in determining the efforts and resources that they will apply to these

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collaborations. Disagreements between parties to a collaboration arrangement regarding clinical development and commercialization matters can lead to delays in the development process or commercializing the applicable product candidate and, in some cases, costly and time-consuming disputes or termination of the collaboration arrangement. These disagreements can be difficult to resolve successfully, and any such termination or expiration would adversely affect us financially and could harm our business reputation. Many collaborations in the pharmaceutical and biotechnology industries do not result in successful outcomes, for a wide variety of reasons.

Our anticipated international operations may expose us to business, regulatory, political, operational, financial, pricing and reimbursement and economic risks associated with doing business outside of the United States.

Our business strategy currently incorporates potential international expansion as we evaluate data from our multi-national Phase 3 HOPE Study of voxelotor for the potential treatment of SCD inside and outside the United States, and plan to seek to obtain regulatory approval to and commercialize voxelotor in patient populations inside and outside the United States. If voxelotor is approved, we may hire sales representatives and conduct physician and patient association outreach activities outside of the United States. Doing business internationally involves a number of risks, including but not limited to:

- restrictions and obligations imposed by privacy regulations, such as provisions under the General Data Protection Regulation 2016/679, known as GDPR, applicable to the collection and use of personal health data in the European Union;
- multiple, conflicting, and changing laws and regulations such as tax laws, export and import restrictions, employment laws, regulatory requirements, and any requirements to obtain other governmental approvals, permits, and licenses;
- failure by us to obtain and maintain regulatory approvals for the sale or use of our products in various countries;
- additional potentially relevant third-party patent rights;
- complexities and difficulties in obtaining protection for and enforcing our intellectual property;
- difficulties in staffing and managing foreign operations;
- complexities associated with managing multiple payor reimbursement regimes, government payors, or patient self-pay systems;
- limits in our ability to penetrate international markets;
- financial risks, such as longer payment cycles, difficulty collecting accounts receivable, the impact of local and regional financial crises on demand and payment for our products, and exposure to foreign currency exchange rate fluctuations;
- natural disasters, political and economic instability, including wars, terrorism, and political unrest, outbreak of disease, boycotts, curtailment of trade, and other business restrictions;
- certain expenses including, among others, expenses for travel, translation, and insurance; and
- regulatory and compliance risks that relate to maintaining accurate information and control over sales and activities that may fall within the purview of the U.S. Foreign Corrupt Practices Act, its books and records provisions, or its anti-bribery provisions.

Any such factors may impose additional responsibilities, obligations or liability in relation to our planned activities outside the United States, and we may be required to put in place additional mechanisms and make additional expenditures to ensure compliance with existing and new requirements, which could significantly harm our future international expansion and operations and, consequently, our results of operations.

We are subject to certain U.S. and foreign anti-corruption, anti-money laundering, export control, sanctions, and other trade laws and regulations (collectively, Trade Laws). We can face serious consequences for violations.

Among other matters, Trade Laws prohibit companies and their employees, agents, clinical research organizations, legal counsel, accountants, consultants, contractors, and other partners from authorizing, promising, offering, providing, soliciting, or receiving directly or indirectly, corrupt or improper payments or

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anything else of value to or from recipients in the public or private sector. Violations of Trade Laws can result in substantial criminal fines and civil penalties, imprisonment, the loss of trade privileges, debarment, tax reassessments, breach of contract and fraud litigation, reputational harm, and other consequences. We have direct or indirect interactions with officials and employees of government agencies or government-affiliated hospitals, universities, and other organizations. We also expect our non-U.S. activities to increase in time. We engage third parties for clinical trials and/or to obtain necessary permits, licenses, patent registrations, and other regulatory approvals. We can be held liable for the corrupt or other illegal activities of our personnel, agents, or partners, even if we do not explicitly authorize or have prior knowledge of such activities.

Unfavorable global economic conditions could adversely affect our business, financial condition or results of operations.

Our ability to invest in and expand our business and meet our financial obligations, to attract and retain third-party contractors and collaboration partners and to raise additional capital depends on our operating and financial performance, which, in turn, is subject to numerous factors, including the prevailing economic and political conditions and financial, business and other factors beyond our control, such as the rate of unemployment, the number of uninsured persons in the United States, the results of presidential elections, other political influences and inflationary pressures. For example, an overall decrease in or loss of insurance coverage among individuals in the United States as a result of unemployment, underemployment or the potential repeal of certain provisions of the ACA, may decrease the demand for healthcare services and pharmaceuticals. If fewer patients are seeking medical care because they do not have insurance coverage, we may experience difficulties in any eventual commercialization of our product candidates and our business, results of operations, financial condition and cash flows could be adversely affected.

In addition, certain events have caused, and may cause or contribute to global financial crises, which have triggered and may in the future lead to extreme volatility and disruptions in the capital and credit markets. For example, in June 2016, the United Kingdom (the U.K). , held a referendum in which voters supported the exit of the U. K. from the EU (commonly referred to as Brexit), which could cause disruptions to and create uncertainty surrounding our business, including affecting our existing relationships with third parties that conduct some of our nonclinical studies and clinical trials and our ability to enter into new relationships with vendors and other third-party contractors, which could have an adverse effect on our business, financial results and operations. The referendum is non-binding, but if passed into law, negotiations would commence to determine the future terms of the U.K. s relationship with the EU, including the terms of trade between the U.K. and the EU. Brexit has already and could continue to adversely affect European and/or worldwide economic and market conditions and could continue to contribute to instability in the global financial markets. The measures could also adversely affect our ability to raise additional capital, potentially disrupt the markets in which we currently conduct and plan to conduct operations and the tax jurisdictions in which we operate and adversely change tax benefits or liabilities in these or other jurisdictions. In addition, changes in, and legal uncertainty with regard to, national and international laws and regulations may present difficulties for our clinical and regulatory strategy.

A severe or prolonged economic downturn could result in a variety of risks to our business, including reduced ability to raise additional capital when needed on acceptable terms, if at all. A weak or declining economy could also strain our relationships with our contractors and potential collaboration partners. Any of the foregoing could harm our business and we cannot anticipate all of the ways in which the current economic climate and financial market conditions could adversely impact our business.

Misconduct or other improper activities of our employees, agents, contractors or collaborators could adversely affect our reputation and our business, prospects, operating results and financial conditions.

We cannot ensure that our compliance controls, policies, and procedures will in every instance protect us from acts committed by our employees, agents, contractors or collaborators that would violate the law or regulations of the jurisdictions in which we operate, including FDA, healthcare, employment, foreign corrupt

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practices, environmental, competition, and patient privacy regulations. Misconduct by our employees, agents, contractors, or collaborators could include intentional or unintentional failures to:

- comply with EMA or FDA regulations or similar regulations of comparable foreign regulatory authorities;
- provide accurate information to the FDA or EMA or comparable foreign regulatory authorities;
- comply with cGMP regulations and manufacturing standards that we have established and comply with applicable healthcare fraud and abuse regulations in the jurisdictions in which we operate;
- report financial information or data accurately; or
- disclose unauthorized activities to us.

In particular, sales, marketing and business arrangements in the healthcare industry are subject to extensive laws and regulations intended to prevent fraud, misconduct, kickbacks, self-dealing and other abusive practices. These laws and regulations may restrict or prohibit a wide range of pricing, discounting, marketing and promotion, sales commission, customer incentive programs and other business arrangements. Misconduct could also involve the improper use of, including trading on, information obtained in the course of clinical trials, which could result in regulatory sanctions and serious harm to our reputation.

Additionally, our business activities may be subject to the Foreign Corrupt Practices Act, or FCPA, and similar anti-bribery or anti-corruption laws, regulations or rules of other countries in which we operate. The FCPA generally prohibits offering, promising, giving, or authorizing others to give anything of value, either directly or indirectly, to a non-U.S. government official in order to influence official action, or otherwise obtain or retain business. The FCPA also requires public companies to make and keep books and records that accurately and fairly reflect the transactions of the corporation and to devise and maintain an adequate system of internal accounting controls. Our business is heavily regulated and therefore involves significant interaction with public officials, including officials of non-U.S. governments. Additionally, in many other countries, the health care providers who prescribe pharmaceuticals are employed by their government, and the purchasers of pharmaceuticals are government entities; therefore, our dealings with these prescribers and purchasers are subject to regulation under the FCPA.

There is no certainty that all of our employees, agents, contractors, or collaborators, or those of our affiliates, will comply with all applicable laws and regulations, particularly given the high level of complexity of these requirements. We have adopted a code of conduct, but it is not always possible to identify and deter employee misconduct, and the precautions we take to detect and prevent this activity may be ineffective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to comply with these requirements. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business.

We or the third parties upon whom we depend may be adversely affected by earthquakes or other natural disasters and our business continuity and disaster recovery plans may not adequately protect us from a serious disaster.

Earthquakes or other natural disasters could severely disrupt our operations, and have a material adverse effect on our business, results of operations, financial condition and prospects. If a natural disaster, power outage or other event occurred that prevented us from using all or a significant portion of our headquarters, that damaged critical infrastructure, such as the manufacturing facilities of our third-party contract manufacturers, or that otherwise disrupted operations, it may be difficult or, in certain cases, impossible for us to continue our business for a substantial period of time. The disaster recovery and business continuity plans we have in place currently are limited and are unlikely to prove adequate in the event of a serious disaster or similar event. We may incur substantial expenses as a

result of the limited nature of our disaster recovery and business continuity plans, which, particularly when taken together with our lack of earthquake insurance, could have a material adverse effect on our business.

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Our internal computer systems, or those of our third party vendors, may fail or suffer security breaches, which could result in a material disruption of our drug development programs.

Despite the implementation of security measures, our internal computer systems and those of our third party vendors are vulnerable to damage from computer viruses, unauthorized access, natural disasters, terrorism, war and telecommunication and electrical failures. If such an event were to occur and cause interruptions in our operations, it could result in a material disruption of our drug development programs. For example, the loss of data from completed or ongoing clinical trials or nonclinical studies for any of our product candidates could result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce the data. To the extent that any disruption or security breach were to result in a loss of or damage to our data or applications, or inappropriate disclosure of confidential or proprietary information, we could incur liability and the further development of our product candidates could be delayed.

Risks Related to Our Equity Securities

We incur significant costs, and expend significant time and effort, to comply with the rules applicable to us as a public company, including Section 404 of the Sarbanes Oxley Act of 2002. If we fail to comply with these rules, including maintaining proper and effective systems of disclosure controls and internal controls over financial reporting, the accuracy and timeliness of our financial reporting may be adversely affected, and we could be subject to sanctions or other penalties that would harm our business.

As a public company, we are subject to the reporting requirements of the Securities Exchange Act of 1934, as amended (the Exchange Act), Section 404, or Section 404, of the Sarbanes-Oxley Act of 2002, or Sarbanes Oxley, and the rules and regulations of The NASDAQ Global Select Stock Market, or NASDAQ. The Exchange Act requires us to file accurate and timely quarterly, annual and current reports with the SEC. Section 404 generally requires our management and independent registered public accounting firm to report on the effectiveness of our internal control over financial reporting and requires us to include an opinion from our independent registered public accounting firm on the effectiveness of our internal control over financial reporting. We are also subject to significant corporate governance and executive compensation-related provisions of the Dodd-Frank Wall Street Reform and Consumer Protection Act, or Dodd-Frank, including the say on pay rules adopted by the SEC under Dodd-Frank. We incur significant legal, accounting and other expenses, and expend significant time and effort by management and other personnel, to comply with the rules applicable to us as a public company.

We carried out an evaluation, under the supervision and with the participation of our management, including our Chief Executive Officer and our Chief Financial Officer, of the effectiveness of our internal control over financial reporting for the purpose of providing the reports required by Section 404. Based on our assessment and using the Committee of Sponsoring Organizations of the Treadway Commission (COSO) criteria, our management, Chief Executive Officer and Chief Financial Officer, have concluded that, as of December 31, 2018, our internal control over financial reporting was effective. As required under Section 404 of Sarbanes-Oxley, our independent registered public accounting firm has tested the design and operating effectiveness of our controls over financial reporting and been required to provide an attestation report with respect to our internal control over financial reporting. During the course of our or their subsequent review and testing, however, material weaknesses or significant deficiencies may be identified and we may be unable to remediate them before we must provide the required reports. If material weaknesses or significant deficiencies in our internal control over financial reporting are identified in the future, we may not detect or remediate errors on a timely basis and our consolidated financial statements may be materially misstated. We or our independent registered public accounting firm may not be able to conclude on an ongoing basis that we have effective internal control over financial reporting, which could harm our operating results, cause investors to lose confidence in our reported financial information and cause the trading price of our stock to fall. In

addition, any failure to report our financial results on an accurate and timely basis could result in sanctions, lawsuits, delisting of our shares from NASDAQ or other adverse consequences that would materially harm our business.

Moreover, stockholder activism, the current political environment, and increased levels of government scrutiny and regulatory reform may lead to substantial new regulations and disclosure obligations for public

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companies, which may lead to additional compliance costs and impact the manner in which we operate our business in ways we cannot currently anticipate. Our management and other personnel will need to devote a substantial amount of time to any new compliance initiatives. In addition, any new rules and regulations will increase our legal and financial compliance costs and will make some activities more time consuming and costly. For example, we expect these rules and regulations to make it more difficult and more expensive for us to obtain director and officer liability insurance and we may be required to incur substantial costs to maintain our current levels of such coverage. New laws and regulations as well as changes to existing laws and regulations affecting public companies, including the provisions of Sarbanes-Oxley and rules adopted by the SEC and by NASDAQ, would likely result in increased costs to us as we respond to their requirements.

The market price of our common stock has been and may continue to be highly volatile.

The market price of our common stock has experienced volatility since our initial public offering in August 2015 and is likely to continue to be volatile. Our stock price could be subject to wide fluctuations in response to a variety of factors, including the following:

- adverse results or delays in, or the halting of, our nonclinical studies or clinical trials, including in our only clinical program, which is for voxelotor for the treatment of SCD;
- reports of adverse events in our clinical program for voxelotor for SCD, or other indications that we may pursue, or clinical trials of any other product candidates that we may develop;
- any delay in filing an NDA for voxelotor or an investigational new drug application, or IND, or NDA for inclacumab or for any other product candidates that we may develop and any adverse development or perceived adverse development with respect to the FDA s review of that IND or NDA;
- failure to develop successfully and commercialize voxelotor, inclacumab or any other product candidates that we may develop;
- adverse regulatory decisions affecting voxelotor, inclacumab or any other product candidates we may develop, including any delay in or denial of potential approval in accordance with our plans and expectations;
- inability to obtain additional funding;
- failure to prosecute, maintain or enforce our intellectual property rights;
- disputes or other developments relating to proprietary rights, including patents, litigation matters and our ability to obtain patent protection for our technologies;
- changes in laws or regulations applicable to future products;
- inability to obtain adequate product supply for our product candidates or the inability to do so at acceptable prices;
- introduction of new products, services or technologies by our competitors;
- failure to enter into or perform under strategic collaborations;
- failure to meet or exceed any financial projections that we or the investment community may provide;
- 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 or our competitors;
- 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;
- trading volume of our common stock; and

the other risks described in this Risk Factors section.

In addition, companies trading in the stock market in general, and NASDAQ 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 industry factors may negatively affect the market price of our common stock, regardless of our actual operating performance. For example, negative publicity

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regarding drug pricing and price increases by pharmaceutical companies has negatively impacted, and may continue to negatively impact, the markets for biotechnology and pharmaceutical stocks. In the past, following periods of volatility in the market, securities class-action litigation has often been instituted against companies. Such litigation, if instituted against us, could result in substantial costs and diversion of management s attention and resources, which could materially and adversely affect our business, financial condition, results of operations and growth prospects.

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 quarterly and annual operating results may fluctuate significantly in the future, which makes it difficult for us to predict our future operating results. Our operating results may fluctuate due to a variety of factors, many of which are outside of our control and may be difficult to predict, including the following:

- the timing and cost of, and level of investment in, research and development activities relating to our product candidates, which may change from time to time;
- the timing and success or failure of clinical trials for our product candidates or competing product candidates, or any other change in the competitive landscape of our industry, including consolidation among our competitors or partners;
- our ability to obtain regulatory approval for our product candidates, and the timing and scope of any such approvals we may receive;
- our ability to commercialize any of our product candidates, if approved, and the timing and costs of our commercialization activities;
- the cost of manufacturing our product candidates, which may vary depending on the quantity of production and the terms of our agreements with manufacturers;
- our ability to attract, hire and retain qualified personnel;
- expenditures that we will or may incur to acquire or develop additional product candidates and technologies;
- the level of demand for our product candidates, should they receive approval, which may vary significantly;
- future accounting pronouncements or changes in our accounting policies;
- the risk/benefit profile, cost and reimbursement policies with respect to our products candidates, if approved, and existing and potential future drugs that compete with our product candidates;
- whether any of our product candidates are subject to any compliance-related challenges or sanctions, or any intellectual-property related challenges; and
- the changing and volatile U.S., European and global economic environments.

The cumulative effects of these factors could 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. 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 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 financial guidance we may provide.

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

We will need additional capital in the future to continue our planned operations. To the extent we raise additional capital by issuing equity securities, our stockholders may experience substantial dilution. We may sell common stock, convertible securities or other equity securities in one or more transactions at prices and in a

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manner we determine from time to time. If we sell common stock, convertible securities or other equity securities in more than one transaction, 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.

We are also authorized to grant stock options and other equity-based awards to our employees, directors and consultants pursuant to our 2015 Stock Option and Incentive Plan (the 2015 Plan). The number of shares available for future grant under the 2015 Plan will automatically increase 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. In addition, in January 2017 our board of directors approved our 2017 Inducement Equity Plan, or 2017 Inducement Plan. The 2017 Inducement Plan enables us and our subsidiaries to grant non-qualified stock options and other equity-based awards to induce employees who are not currently employed by us or our subsidiaries to accept employment with us or our subsidiaries. As of December 31, 2018, the number of shares reserved for grant under the 2017 Inducement Plan was 458,350 shares, subject to adjustment for reorganization, recapitalization, stock dividend, stock split, or similar changes in our capital stock. In addition, we have reserved shares of common stock for issuance pursuant to our 2015 Employee Stock Purchase Plan, or 2015 ESPP, which number of shares will automatically increase each year on January 1, from January 1, 2016 to January 1, 2025, by the lesser of (i) 3,000,000 shares of common stock, (ii) 1% of all shares of our capital stock outstanding as of December 31 of the prior calendar year, or (iii) such lesser number of shares as determined by the administrator of our 2015 ESPP. Currently, we plan to register the increased number of shares available for issuance under the 2015 Plan and the 2015 ESPP each year. If our board of directors elects to increase the number of shares available for future grant under the 2015 Plan, the 2017 Inducement Plan or the 2015 ESPP, our stockholders may experience additional dilution, and our stock price may fall.

A significant portion of our total outstanding shares may be sold into the market in the near future, which could cause the market price of our common stock to drop significantly.

Sales of a substantial number of shares of our common stock in the public market could occur at any time. A significant portion of our outstanding shares of common stock are held by a small number of stockholders, including our directors, officers and significant stockholders. Sales by our stockholders of a substantial number of shares, or the expectation that such sales may occur, could significantly reduce the market price of our common stock.

We have also registered all shares of our common stock subject to options or other equity awards issued or reserved for future issuance under our equity incentive plans. As a result, these shares will be available for sale in the public market subject to vesting arrangements and exercise of options, and restrictions under applicable securities laws. In addition, our directors, executive officers and certain affiliates have established or may in the future establish programmed selling plans under Rule 10b5-1 of the Exchange Act, for the purpose of effecting sales of our common stock. If any of these events cause a large number of our shares to be sold in the public market, the sales could reduce the trading price of our common stock and impede our ability to raise future capital.

Additionally, certain holders of our common stock, or their transferees, have rights to require us to file one or more registration statements covering their shares or to include their shares in registration statements that we may file for ourselves or other stockholders. If we were to register the resale of these shares, they could be freely sold in the public market. If these additional shares are sold, or if it is perceived that they will be sold, in the public market, the trading price of our common stock could decline.

Our principal stockholders and management own a significant percentage of our stock and will be able to exert significant control over matters subject to stockholder approval.

Our executive officers, directors, five percent stockholders and their affiliates beneficially owned approximately 55.6% of our outstanding common stock as of February 22, 2019, based on the latest publicly available information.

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These stockholders have the ability to influence us through their ownership positions. These stockholders may be able to determine all matters requiring stockholder approval. For example, these stockholders, acting together, may be able to control elections of directors, amendments of our organizational documents, or approval of any merger, sale of assets, or other major corporate transaction. This may prevent or discourage unsolicited acquisition proposals or offers for our common stock that you may believe are in your best interest as one of our stockholders.

We have broad discretion in the use of our capital resources consisting of cash and cash equivalents and short and long-term marketable securities, and may invest or spend our capital resources in ways with which you do not agree or in ways that ultimately may not increase the value of your investment.

We have broad discretion over the use of our capital resources consisting of cash and cash equivalents and short and long-term marketable securities. You may not agree with our decisions, and our use of our capital resources may not yield any returns to our stockholders. We expect to use our existing capital resources to continue the clinical development of voxelotor for the treatment of SCD, including in evaluating our completed Phase 3 HOPE Study and in our ongoing Phase 2a HOPE-KIDS 1 Study and planned clinical pharmacology studies, our other research and development activities including other clinical and nonclinical studies, including for inclacumab, and for working capital and general corporate purposes. Our failure to apply our capital resources effectively could compromise our ability to pursue our growth strategy and we might not be able to yield a significant return, if any, on our investment of these resources. Our stockholders will not have the opportunity to influence our decisions on how to use our capital resources.

Provisions in our restated certificate of incorporation and amended and restated bylaws, 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 restated certificate of incorporation, amended and restated bylaws 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 restated certificate of incorporation and amended and restated bylaws 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 bylaws; 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 bylaws.

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 restated certificate of incorporation or amended and restated bylaws or Delaware law that has the effect of delaying or deterring a change in control could limit the opportunity for our

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

We have incurred substantial losses during our history and do not expect to become profitable in the near future and we may never achieve profitability. To the extent that we continue to generate taxable losses, unused losses will carry forward to offset future taxable income, if any, until such unused losses expire. Under Sections 382 and 383 of the Internal Revenue Code of 1986, as amended, if a corporation undergoes an ownership change, generally defined as a greater than 50% change (by value) in its equity ownership over a three-year period, the corporation s ability to use its pre-change net operating loss carryforwards, or NOLs, and other pre-change tax attributes (such as research tax credits) to offset its post-change income or taxes may be limited. We experienced an ownership change as a result of our IPO and an ownership change as a result of our follow-on offerings, however we do not believe that these ownership changes will significantly limit our ability to use these pre-change NOL carryforwards. We may experience subsequent shifts in our stock ownership, including as a result of our future follow-on offering, some of which are outside of our control. As a result, if we earn net taxable income, our ability to use our pre-change NOL carryforwards to offset U.S. federal taxable income may become 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. In addition, pursuant to the Tax Cuts and Jobs Act of 2017 we may not use net operating loss carry-forwards arising in taxable years beginning after December 31, 2017 to reduce our taxable income in any year by more than 80% and we may not carry back any net operating losses arising in taxable years ending after December 31, 2017 to prior years. These new rules apply regardless of the occurrence of an ownership change .

We do not currently intend to pay dividends on our common stock, and, consequently, our stockholders ability to achieve a return on their investment will depend on appreciation in the price of our common stock.

We do not currently intend to pay any cash dividends on our common stock for the foreseeable future. We currently intend to invest our future earnings, if any, to fund our growth. Therefore, you are not likely to receive any dividends on your common stock for the foreseeable future. Since we do not intend to pay dividends, your ability to receive a return on your investment will depend on any future appreciation in the market value of our common stock. There is no guarantee that our common stock will appreciate or even maintain the price at which our holders have purchased it.

If securities or industry analysts do not publish research, or publish inaccurate or unfavorable research, about our business, our stock price and trading volume could decline.

The trading market for our common stock depends, in part, on the research and reports that securities or industry analysts publish about us or our business. Securities and industry analysts may not publish an adequate amount of research on our company, which may negatively impact the trading price for our stock. In addition, if one or more of the analysts who cover us downgrade our stock or publish inaccurate or unfavorable research about our business, our stock price would likely decline or increase in volatility. Further, if our operating results fail to meet the forecasts of analysts, our stock price would likely decline. If one or more of these analysts cease coverage of our company or fail to publish reports on us regularly, demand for our stock could decrease, which might cause our stock price and trading volume to decline.

We may be subject to adverse legislative or regulatory tax changes that could negatively impact our financial condition.

The rules dealing with U.S. federal, state and local income taxation are constantly under review by persons involved in the legislative process and by the IRS and the U.S. Treasury Department. Changes to tax laws (which changes may have retroactive application) could adversely affect our stockholders or us. In recent

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years, many such changes have been made and changes are likely to continue to occur in the future. For example, in December 2017, Congress passed the Tax Cuts and Jobs Act, which made broad and complex changes to the tax laws. We cannot predict whether, when, in what form, or with what effective dates, tax laws, regulations and rulings may be enacted, promulgated or decided, which could result in an increase in our, or our stockholders , tax liability or require changes in the manner in which we operate in order to minimize increases in our tax liability.

Item 1B. ***Unresolved Staff Comments***

None.

Item 2. ***Properties***

Our headquarters, where we have office and research and development laboratory space, is located in South San Francisco, California, where we lease 67,185 square feet of space pursuant to a noncancelable operating lease (the Lease). We believe that our existing facilities are sufficient for our current needs.

In August 2018, we entered into an amendment to the Lease to relocate from the current headquarters to a to-be constructed-building consisting of approximately 164,150 rentable square feet of space when the building is ready for occupancy. The building is expected to be ready to occupy in the first half of 2020 at which time we will vacate the currently occupied facility and will have no further obligations with respect to the current facility.

Item 3. ***Legal Proceedings***

As of the date of this annual report on Form 10-K, we are not party to any material legal proceedings. In the future, we may become subject to legal proceedings and claims arising in the ordinary course of business. Although the results of litigation and claims cannot be predicted with certainty, we do not believe we are party to any claim or litigation the outcome of which, if determined adversely to us, would individually or in the aggregate be reasonably expected to have a material adverse impact on our financial position, results of operations or cash flows. Regardless of the outcome, litigation can have an adverse effect on us because of defense and settlement costs, diversion of management resources and other factors.

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***

Market Information

Our common stock began trading on The NASDAQ Global Select Market on August 12, 2015 and trades under the symbol GBT . Prior to such time, there was no public market for our common stock.

Recent Sales of Unregistered Securities

During the year ended December 31, 2018, we did not issue or sell any unregistered securities not previously disclosed in a Quarterly Report on Form 10-Q or in a Current Report on Form 8-K.

Issuer Purchases of Equity Securities

We did not repurchase any securities during the quarter ended December 31, 2018.

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Holders of Common Stock

As of February 22, 2019, there were 10 holders of record of 56,322,257 outstanding shares of our common stock. We believe that the number of beneficial owners of our common stock at that date was substantially greater.

Securities Authorized for Issuance under Equity Compensation Plans

Information about our equity compensation plans is incorporated by reference to Item 12 of Part III of this Annual Report.

Dividend Policy

We have never declared or paid any cash dividends. We currently expect to retain all future earnings, if any, for use in the operation and expansion of our business, and therefore do not anticipate paying any cash dividends in the foreseeable future.

Performance Graph

The following is not deemed filed with the Securities and Exchange Commission and is not to be incorporated by reference into any filing we make under the Securities Act of 1933, as amended, whether made before or after the date hereof and irrespective of any general incorporation by reference language in such filing.

The graph below matches Global Blood Therapeutics, Inc. s cumulative 40-Month total shareholder return on common stock with the cumulative total returns of the NASDAQ Composite index, the NASDAQ Biotechnology index, and the NASDAQ Pharmaceutical index. The graph tracks the performance of a $100 investment in our common stock and in each index (with the reinvestment of all dividends) from 8/12/2015 to 12/31/2018.

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	8/12/15	12/15	12/16	12/17	12/18
Global Blood Therapeutics, Inc.	**100.00**	**74.99**	**33.52**	**91.28**	**95.22**
NASDAQ Composite	**100.00**	**98.20**	**106.49**	**137.61**	**132.60**
NASDAQ Biotechnology	**100.00**	**89.20**	**71.23**	**84.83**	**76.94**
NASDAQ Pharmaceutical	**100.00**	**88.11**	**70.17**	**79.70**	**72.88**

The stock price performance included in this graph is not necessarily indicative of future stock price performance.

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Item 6. ***Selected Financial Data***

The information set forth below for the three years ended December 31, 2018 is not necessarily indicative of results of future operations, and should be read in conjunction with Item 7, Management s Discussion and Analysis of Financial Condition and Results of Operations and the Consolidated Financial Statements and related notes thereto included in Item 8 of this Annual Report on Form 10-K to fully understand factors that may affect the comparability of the information presented below (in thousands, except for share and per share data):

	Years Ended December 31,		
	2018	**2017**	**2016**
Summary of Operations Data:			
Operating Expenses			
Research and development	$ 131,307	$ 87,807	$ 62,163
General and administrative	51,435	31,438	20,964
Total operating expenses	182,742	119,245	83,127
Loss from operations	(182,742)	(119,245)	(83,127)
Interest income, net	8,618	2,555	659
Other expenses, net	(69)	(334)	
Net loss	$ (174,193)	$ (117,024)	$ (82,468)
Basic and diluted net loss per common share	$ (3.41)	$ (2.76)	$ (2.48)
Weighted-average number of shares used in computing basic and diluted net loss per common share	51,150,728	42,323,686	33,207,382

	As of December 31,		
(in thousands)	**2018**	**2017**	**2016**
Selected Consolidated Balance Sheet Data:			
Cash and cash equivalents and marketable securities	$ 591,815	$ 329,432	$ 197,332
Working capital	452,007	298,048	134,254
Total assets	617,643	356,720	202,387
Accumulated deficit	(472,150)	(297,957)	(180,933)
Total stockholders equity	572,799	318,804	186,309

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

You should read the following discussion and analysis of our financial condition and results of operations together with the section of this annual report entitled Selected Financial Data and our consolidated financial statements and related notes included elsewhere in this annual report. This discussion and other parts of this annual report contain forward-looking statements that involve risk and uncertainties, such as statements of our plans, objectives, expectations, and intentions. In this annual report, words such as may, will, expect, anticipate, estimate, intend, and similar expressions (as well as other words or expressions referencing future events, conditions or circumstances) are intended to identify forward-looking statements, as described elsewhere herein. As a result of many factors, including those factors set forth in the Risk Factors section of this annual report, our actual results could differ materially from the results described in or implied by the forward-looking statements contained in the following discussion and analysis.

Overview

We are a clinical-stage biopharmaceutical company determined to discover, develop and deliver innovative treatments that provide hope to underserved patient communities. Our lead product candidate is voxelotor (previously known as GBT440), an oral, once-daily therapy that modulates hemoglobin s affinity for oxygen, which we believe inhibits hemoglobin polymerization in sickle cell disease, or SCD.

We are currently evaluating voxelotor in adult and adolescent patients with SCD in a Phase 3 clinical trial, which we call the HOPE Study. In June 2018, we completed a planned review of Part A of the HOPE Study. The primary endpoint (the proportion of patients with greater than 1 g/dL increase in hemoglobin versus baseline) showed a statistically significant increase at both the 1500 mg and 900 mg doses of voxelotor after 12 weeks of treatment versus placebo. The data also demonstrated corresponding improvements in other markers of hemolysis as well as a favorable safety and tolerability profile for voxelotor. Based upon these data and results in this planned preliminary review of Part A, we began discussions with the U.S. Food and Drug Administration, or FDA about seeking an accelerated approval pathway for voxelotor for SCD. In December 2018, we announced that the FDA agreed with our proposal to use the accelerated regulatory approval pathway under the FDA s Subpart H regulations, or Subpart H, for voxelotor for the treatment of SCD, and that we plan to submit a new drug application, or NDA, under this pathway to the FDA. The FDA grants accelerated approval under Subpart H for new drugs that address serious or life-threatening illnesses and that provide meaningful therapeutic benefit. We recently completed a pre-NDA meeting for the voxelotor program. Additionally, in December 2018, we announced updated efficacy and safety results from Part A of the Phase 3 HOPE Study of voxelotor at both the 1500 mg and 900 mg doses after 24 weeks of treatment versus placebo. These results, from approximately 150 patients with SCD treated with voxelotor for 24 weeks at both doses versus placebo, showed a statistically significant increase in the primary endpoint and showed improvements in other hemolysis measures. Voxelotor also continued to show a favorable safety and tolerability profile at 24 weeks.

We are also evaluating the safety and pharmacokinetics of single and multiple doses of voxelotor in adolescent and pediatric patients with SCD in a Phase 2a clinical trial, which we call the HOPE-KIDS 1 Study.

In October 2015, FDA granted Fast Track Designation for voxelotor for the treatment of SCD. In December 2015, the FDA granted Orphan Drug Designation for voxelotor for the treatment of SCD. In November 2016, voxelotor was granted Orphan Drug Designation in Europe for the treatment of SCD. In June 2017, the European Medicines Agency, or EMA, granted PRIME designation for voxelotor for the treatment of SCD. The PRIME program is a new regulatory mechanism that provides for early and proactive EMA support to medicine developers to help patients benefit as early as possible from innovative new products that have demonstrated the potential to significantly address an unmet medical need.

In August 2018, we entered into a license agreement with F. Hoffmann-La Roche Ltd. and Hoffmann-La Roche Inc. (together, Roche) pursuant to which Roche granted the company an exclusive and sublicensable worldwide license under certain patent rights and know-how to develop and commercialize inclacumab, a novel fully human monoclonal antibody against P-selectin, including any modified compounds targeting P-selectin and derived from inclacumab, for all indications and uses, except diagnostic use. Roche retained a non-exclusive,

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worldwide, perpetual, royalty-free license to inclacumab solely for any diagnostic use. We plan to develop inclacumab as a treatment for vaso-occlusive crises in patients with SCD.

SCD is marked by red blood cell, or RBC, destruction and occluded blood flow and hypoxia, leading to anemia, stroke, multi-organ failure, severe pain crises, and shortened patient life span. Voxelotor inhibits abnormal hemoglobin polymerization, the underlying mechanism that causes sickling of RBCs. In our clinical trials to date of voxelotor in SCD patients, we observed reduced markers of red blood cell destruction, improvements in anemia, improvements in markers of tissue oxygenation, and reduced numbers of sickled RBCs.

We own or jointly own and have exclusively licensed rights to our product candidates in the United States, Europe and other major markets. We are the sole owner of issued U.S. patents covering voxelotor, including its composition of matter, methods of use, and a polymorph of voxelotor. These issued patents covering voxelotor will expire between 2032 and 2035, absent any applicable patent term extensions. We own or co-own additional pending patent applications in the United States and multiple foreign countries relating to our lead product candidate voxelotor.

Beyond evaluation voxelotor in SCD, we are also engaged in other research and development activities, all of which are currently in earlier development stages. In addition, we regularly evaluate opportunities to in-license, acquire or invest in new business, technology or assets or engage in related discussions with other business entities.

Since our inception in 2011, we have devoted substantially all of our resources to identifying and developing our product candidates, including conducting clinical trials and nonclinical studies and providing general and administrative support for these operations.

We are not profitable and have incurred losses and negative cash flows from operations each year since our inception. We have financed our operations primarily through sale of equity securities. In January 2018, we completed a follow-on offering pursuant to which we issued an aggregate of 3,026,315 shares of our common stock at a price of $38.00 per share, including 2,631,579 shares sold at the initial closing in December 2017 and 394,736 shares sold pursuant to the exercise of the underwriter s over-allotment option in January 2018, resulting in aggregate proceeds of approximately $111.0 million, net of underwriting discounts and commissions, and offering expenses. In March 2018, we completed a follow-on offering and issued an aggregate of 4,600,000 shares of our common stock at a price of $54.00 per share, including 600,000 shares of common stock sold directly to the underwriters when they exercised their over-allotment option at the price of $54.00 per share. We received total proceeds of $240.6 million from the offering, net of underwriting discounts and commissions, and offering expenses. In January 2019, we completed a follow-on offering and issued an aggregate of 3,920,453 shares of our common stock at a price of $44.00 per share, including 3,409,090 shares sold at the initial closing in December 2018 and 511,363 shares sold pursuant to the exercise of the underwriter s over-allotment option in January 2019, resulting in aggregate proceeds of approximately $162.1 million from the offering, net of underwriting discounts and commissions, and estimated offering expenses.

Our net losses were $174.2 million for the year ended December 31, 2018, $117.0 million for the year ended December 31, 2017 and $82.5 million for the year ended December 31, 2016. As of December 31, 2018, we had an accumulated deficit of $472.2 million. To date, we have not generated any revenue. We do not expect to receive any revenue from any product candidates that we develop until we obtain regulatory approval and commercialize our products or enter into collaborative agreements with third parties. Substantially all of our net losses have resulted from costs incurred in connection with our research and development programs and from general and administrative costs associated with our operations. We had $275.4 million in cash and cash equivalents and $316.4 million in marketable securities as of December 31, 2018.

Critical Accounting Polices and Estimates

Our management s discussion and analysis of our financial condition and results of operations is based on our consolidated financial statements, which have been prepared in accordance with United States generally accepted accounting principles, or U.S. GAAP. The preparation of these consolidated financial statements

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requires us to make estimates and assumptions that affect the reported amounts of assets and liabilities and the disclosure of contingent assets and liabilities at the date of the consolidated financial statements, as well as the reported expenses incurred during the reporting periods. Our estimates are based on our historical experience and on various other factors that we believe are reasonable under the circumstances, the results of which form the basis for making judgments about the carrying value of assets and liabilities that are not readily apparent from other sources. Actual results may differ from these estimates under different assumptions or conditions. We believe that the accounting policies discussed below are critical to understanding our historical and future performance, as these policies relate to the more significant areas involving management s judgments and estimates.

Accrued Research and Development Costs

We record accrued expenses for estimated costs of our research and development activities conducted by third-party service providers, which include the conduct of nonclinical studies and clinical trials and contract manufacturing activities. We record the estimated costs of research and development activities based upon the estimated amount of services provided but not yet invoiced and include these costs in accrued liabilities in the balance sheet and within research and development expense in the consolidated statements of operations and comprehensive loss. These costs are a significant component of our research and development expenses. We record accrued expenses for these costs based on the estimated amount of work completed and in accordance with agreements established with these third parties.

We estimate the amount of work completed through discussions with internal personnel and external service providers as to the progress or stage of completion of the services and the agreed-upon fee to be paid for such services. We make significant judgments and estimates in determining the accrued balance in each reporting period. As actual costs become known, we adjust our accrued estimates. Although we do not expect our estimates to be materially different from amounts actually incurred, our understanding of the status and timing of services performed, the number of subjects enrolled, and the rate of patient enrollment may vary from our estimates and could result in us reporting amounts that are too high or too low in any particular period. Our accrued expenses are dependent, in part, upon the receipt of timely and accurate reporting from clinical research organizations and other third-party service providers. To date, there have been no material differences between our accrued liabilities and actual expenses.

Stock-Based Compensation

We use the Black-Scholes-Merton option pricing model to estimate the fair value of options granted under our equity incentive plans and rights to acquire stock granted under our Employee Stock Purchase Plan (ESPP). The Black-Scholes-Merton option valuation model requires the use of assumptions, including the expected term of the award and the expected stock price volatility. We used the simplified method, which is based on the mid-point between the vesting date and the end of the contractual term, for the expected option term. We use peer company price volatility as well as the historical volatility of our own common stock to estimate expected stock price volatility due to the limited trading history for our common stock since our IPO in August 2015. The comparable companies were chosen based on their similar size, stage in life cycle, or area of specialty. We will continue to apply this process until a sufficient amount of historical information regarding the volatility of our stock price becomes available.

Restricted stock purchases (RSPs) and restricted stock units (RSUs) are measured based on the fair market values of the underlying stock on the dates of grant.

Stock-based compensation expense was calculated based on awards at the time of grant and is reduced for actual forfeitures at the time that the forfeitures occur.

The estimated fair value of stock options, RSPs and RSUs is expensed on a straight-line basis over the service period of the grant and the estimated fair value of performance-contingent options, RSUs and RSPs is expensed using an accelerated method over the term of the award once we determine that it is probable that those performance milestones will be achieved. Compensation expense for RSUs and RSPs that contain performance

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conditions is based on the grant date fair value of the award. Compensation expense is recorded over the requisite service period based on management s best estimate as to whether it is probable that the shares awarded are expected to vest. We assess the probability of the performance indicators being met on a continuous basis.

Fair value of each share of underlying common stock is based on the closing price of our common stock as reported on the date of grant.

Compensation expense for purchases under the ESPP is recognized based on the fair value of the common stock estimated based on the closing price of our common stock as reported on the date of offering, less the purchase discount percentage provided for in the plan.

Stock-based compensation expense was $30.1 million for the year ended December 31, 2018, $13.7 million for the year ended December 31, 2017 and $9.2 million for the year ended December 31, 2016. As of December 31, 2018, we had $70.7 million of total unrecognized stock-based compensation costs, which we expect to recognize over a weighted-average period of 2.4 years.

We have not recognized, and we do not expect to recognize in the near future, any tax benefit related to employee stock-based compensation expense as a result of the full valuation allowance on our deferred tax assets including deferred tax assets related to our net operating loss carryforwards.

Income Taxes

We use the asset and liability method of accounting for income taxes. Under this method, deferred tax assets and liabilities are determined based on the differences between the financial reporting and the tax basis of assets and liabilities and are measured using the enacted tax rates and laws that will be in effect when the differences are expected to reverse. We periodically assess the likelihood that the resulting deferred tax assets will be realized. A valuation allowance is provided when it is more likely than not that some portion or all of a deferred tax asset will not be realized.

On December 22, 2017, the President signed the Tax Cuts & Jobs Act (the Tax Act). The Tax Act, among other things, lowered the U.S. corporate income tax rate from 35% to 21% effective January 1, 2018. Consequently, our gross deferred tax assets as of December 31, 2017 were significantly reduced to reflect the estimated impact of the Tax Act. The significant reduction in our gross deferred tax assets are fully offset by a reduction in valuation allowance, resulting in no impact to our income tax expense. Our net operating loss (NOL) carryforwards have been trued up to correctly reflect our NOL balance at the end of 2018. The true up is as a result of the Tax Act and subsequent changes to our U.S. international tax structure.

As of December 31, 2018, our total deferred tax assets, less our total deferred tax liabilities, were $145.8 million. The deferred tax assets were primarily comprised of federal and state tax net operating losses and tax credit carryforwards. Due to our lack of earnings history and uncertainties surrounding our ability to generate future taxable income, the net deferred tax assets have been fully offset by a valuation allowance.

Utilization of the NOL carryforwards may be subject to a substantial annual limitation due to ownership changes that may have occurred or that could occur in the future, as required by Section 382 of the Internal Revenue Code of 1986, as amended, or the Code, and similar state provisions. These ownership change limitations may limit the amount of NOL carryforwards and other tax attributes that can be utilized annually to offset future taxable income and tax, respectively. In general, an ownership change as defined by Section 382 of the Code results from a transaction or series of transactions over a three-year period resulting in an ownership change of more than 50 percentage points (by

value) of the outstanding stock of a company by certain stockholders. Since our formation, we have raised capital through the issuance of capital stock on several occasions, which separately or combined with the purchasing stockholders subsequent disposition of those shares, may have resulted in such ownership changes, or could result in ownership changes in the future.

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Results of Operations

Comparison of the years ended December 31, 2018, 2017 and 2016

	Year Ended December 31,			Change			
				2018/2017		2017/2016	
(in thousands, except percentages)	**2018**	**2017**	**2016**	**$**	**%**	**$**	**%**
Operating expenses:							
Research and development	$ 131,307	$ 87,807	$ 62,163	$ 43,500	50%	$ 25,644	41%
General and administrative	51,435	31,438	20,964	19,997	64	10,474	50
Total operating expenses	182,742	119,245	83,127	63,497	54	36,118	43
Loss from operations	(182,742)	(119,245)	(83,127)	(63,497)	54	(36,118)	43
Interest income, net	8,618	2,555	659	6,063	238	1,896	288
Other expenses, net	(69)	(334)		265	(80)	(334)	*
Net loss	$ (174,193)	$ (117,024)	$ (82,468)	$ (57,169)	49%	$ (34,556)	42%

*Change is not meaningful

Research and development

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

- employee-related expenses, which include salaries, benefits and stock-based compensation;
- expenses incurred under agreements with consultants, third-party research and manufacturing organizations, and investigative clinical trial sites that conduct research and development activities on our behalf;
- the costs related to production of clinical supplies, including fees paid to contract manufacturers;
- laboratory and vendor expenses related to the execution of nonclinical studies and clinical trials;
- payments upon achievement of certain clinical development and regulatory milestones in relation with license agreement; and

facilities and other allocated expenses, which include expenses for rent and maintenance of facilities, depreciation and amortization expense and other supplies.

We expense all research and development costs in the periods in which they are 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 clinical sites. Nonrefundable advance payments for goods or services to be received in future periods for use in research and development activities are deferred and capitalized. The capitalized amounts are then expensed as the related goods are delivered and the services are performed.

The largest component of our total operating expenses is our investment in research and development activities, including the clinical development of voxelotor. We allocate research and development salaries, benefits, stock-based compensation and indirect costs to voxelotor, inclacumab and other product candidates that we may pursue on a program-specific basis.

We expect our research and development expenses will increase in future periods as we continue to invest in research and development activities related to developing our product candidates, and as programs advance into later stages of development and we begin to conduct larger clinical trials. The process of conducting the necessary clinical research to obtain regulatory approval is costly and time-consuming, and the successful development of our product candidates is highly uncertain. As a result, we are unable to determine the duration and completion costs of our research and development projects or when and to what extent we will generate revenue from the commercialization and sale of any of our product candidates.

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The following table summarizes our research and development expenses incurred during the respective periods (in thousands, except percentages):

	Years Ended December 31,			Change			
				2018/2017		2017/2016	
	2018	2017	2016	$	%	$	%
Costs incurred by development program:							
Voxelotor for the treatment of SCD	$ 103,613	$ 64,860	$ 39,039	$ 38,753	60%	$ 25,821	66%
Other preclinical programs	23,036	14,512	15,456	8,524	59	(944)	(6)
Inclacumab for the treatment of SCD	3,818			3,818	*		*
Voxelotor for the treatment of hypoxemic pulmonary disorders	840	8,435	7,668	(7,595)	(90)	767	10
Total research and development expenses	$ 131,307	$ 87,807	$ 62,163	$ 43,500	50%	$ 25,644	41%

*Change is not meaningful

Research and development expenses increased by $43.5 million, or 50%, to $131.3 million for the year ended December 31, 2018 from $87.8 million for the year ended December 31, 2017. The increase was primarily due to an increase of $38.8 million in internal and external costs related to our SCD program for voxelotor as we advanced this program, including expansion of our Phase 2a HOPE-KIDS 1 Study and our Phase 3 HOPE Study in 2018 as well as higher levels of manufacturing activities to support the program. In addition, there was an increase of $3.8 million in internal and external costs associated with inclacumab primarily driven by the upfront payment of $2.0 million under the License Agreement with Roche in August 2018. Furthermore, there was an increase of $8.5 million in internal and external costs associated with preclinical programs. The increase is partially offset by a $7.6 million decrease in expenses related to our former hypoxemic pulmonary disorders program that was discontinued in October 2017. Stock-based compensation expense was $12.7 million for the year ended December 31, 2018 and $5.9 million for the year ended December 31, 2017. The increase was primarily due to hiring additional personnel, stock price appreciation and vesting of market-condition stock awards.

Research and development expenses increased by $25.6 million, or 41%, to $87.8 million for the year ended December 31, 2017 from $62.2 million for the year ended December 31, 2016. The increase was primarily due to an increase of $25.8 million in internal and external costs related to our SCD program for voxelotor as we advanced this program, including expansion of our Phase 2a HOPE-KIDS 1 Study of adolescent and pediatric patients and incurred costs related to our Phase 3 HOPE Study in 2017. In addition, there was an increase of $0.8 million in internal and external costs associated with conducting our two Phase 2a clinical trials of voxelotor in IPF and our Phase 1 study in healthy volunteers that we refer to as our Basecamp study initiated in 2017. These increases were partially offset by a $0.9 million decrease in expenses related to preclinical efforts for our other research-stage programs, which is primarily due to our former hereditary angioedema, or HAE, program that was discontinued in September 2016. In October 2017, we ceased further development of voxelotor in hypoxemic pulmonary disorders.

General and administrative expenses

General and administrative expenses consist of personnel costs, allocated facilities costs and other expenses for outside professional services, including legal, patent, human resources, audit and accounting services. Personnel costs consist of salaries, benefits and stock-based compensation. Allocated expenses consist of expenses for rent and maintenance of facilities, depreciation and amortization expense and other supplies.

General and administrative expenses increased by $20.0 million, or 64%, to $51.4 million for the year ended December 31, 2018 from $31.4 million for the year ended December 31, 2017. The increase was primarily

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due to an increase of $9.6 million in stock-based compensation expense, as a result of our hiring additional personnel, stock price appreciation and vesting of market-condition restricted stock units, an increase of $4.9 million in salary and benefit costs due to higher headcounts, and an increase of $5.4 million in other general and administrative expenses, such as professional and consulting services, due to the growth of our operations.

General and administrative expenses increased by $10.5 million, or 50%, to $31.4 million for the year ended December 31, 2017 from $21.0 million for the year ended December 31, 2016. The increase was primarily due to an increase of $5.4 million in salaries and benefits, including $2.7 million of related stock-based compensation expense, as a result of our hiring additional personnel and grants of market-condition restricted stock units and an increase of $5.1 million in other general and administrative expenses, such as professional and consulting services, due to the growth of our operations.

Interest income, net

Interest income, net was $8.6 million in 2018 compared to $2.6 million in 2017. The $6.0 million increase was due to the additional income earned from higher investment balances following our public equity offerings in 2017 and 2018 as well as higher interest rates in 2018.

Interest income, net was $2.6 million in 2017 compared to $0.7 million in 2016. The $1.9 million increase was due to the additional income earned from higher investment balances following our public equity offerings in 2017.

Income Taxes

As of December 31, 2018, we had federal net operating loss carryforwards of approximately $381.9 million to offset future federal taxable income, with $208.9 million available through 2037 and $173.0 million available indefinitely. We also had state net operating loss carryforwards of approximately $151.7 million that may offset future state taxable income, through 2036. Current federal and state tax laws include substantial restrictions on the utilization of net operating losses and tax credits in the event of an ownership change. Even if the carryforwards are available, they may be subject to annual limitations, lack of future taxable income, or future ownership changes that could result in the expiration of the carryforwards before they are utilized. At December 31, 2018, we recorded a 100% valuation allowance against our deferred tax assets of approximately $145.8 million, as at that time our management believed it was uncertain that they would be fully realized. If we determine in the future that we will be able to realize all or a portion of our net operating loss carryforwards, an adjustment to our net operating loss carryforwards would increase net income in the period in which we make such a determination.

Liquidity and Capital Resources

We are not profitable and have incurred losses and negative cash flows from operations each year since our inception. We have financed our operations primarily through sale of equity securities. In January 2018, we completed a follow-on offering pursuant to which we issued an aggregate of 3,026,315 shares of our common stock at a price of $38.00 per share, including 2,631,579 shares sold at the initial closing in December 2017 and 394,736 shares sold pursuant to the exercise of the underwriter s over-allotment option in January 2018, resulting in aggregate proceeds of approximately $111.0 million, net of underwriting discounts and commissions, and offering expenses. In March 2018, we completed a follow-on offering and issued an aggregate of 4,600,000 shares of our common stock at a price of $54.00 per share, including 600,000 shares of common stock sold directly to the underwriters when they exercised their over-allotment option at the price of $54.00 per share. We received total proceeds of $240.6 million from the offering, net of underwriting discounts and commissions, and offering expenses. In January 2019, we completed a follow-on offering and issued an aggregate of 3,920,453 shares of our common stock at a price of $44.00 per share,

including 3,409,090 shares sold at the initial closing in December 2018 and 511,363 shares sold pursuant to the exercise of the underwriter s over-allotment option in January 2019, resulting in aggregate proceeds of approximately $162.1 million from the offering, net of underwriting discounts and commissions, and estimated offering expenses.

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Our primary use of cash is to fund operations, which consist primarily of research and development expenditures. Cash used to fund operations is impacted by the timing of when we pay these expenses, as reflected in the change in our outstanding accounts payable and accrued expenses.

We believe that our existing capital resources will be sufficient to fund our planned operations for at least the next twelve months. We have based this estimate on assumptions that may prove to be wrong, and we could utilize our available capital resources sooner than we currently expect. We will continue to require additional financing to advance voxelotor through any completion of clinical development, to develop other potential product candidates from our research programs and to fund operations for the foreseeable future. We will continue to seek funds through equity or debt financings, collaborative or other arrangements with corporate sources, or through other sources of financing. Adequate additional funding may not be available to us on acceptable terms, or at all. Our failure to raise capital as and when needed could have a negative impact on our financial condition and our ability to pursue our business strategies. Our future funding requirements will depend on many factors, including:

- the time and cost necessary to evaluate our completed Phase 3 HOPE Study and conduct and complete our ongoing Phase 2a HOPE-KIDS 1 Study of voxelotor for the potential treatment of SCD;

- the time and cost necessary to conduct and complete any additional clinical studies required to pursue regulatory approvals for voxelotor for SCD or any other indications, and the costs of post-marketing studies that could be required by regulatory authorities for any indications;

- the progress, data and results of our Phase 3 HOPE Study and Phase 2a HOPE-KIDS 1 Study, as well as potential other clinical trials of voxelotor for the potential treatment of SCD and our potential future clinical trials;

- the progress, timing, scope and costs of our nonclinical studies, our clinical trials and other related activities, including our ability to enroll subjects in a timely manner for our potential future clinical trials of voxelotor for SCD or for inclacumab or any other product candidates that we may identify and develop;

- the costs of obtaining clinical and commercial supplies of voxelotor, inclacumab and any other product candidates we may identify and develop;

- our ability to advance our development programs, including our program for the clinical investigation of voxelotor in SCD patients through nonclinical and clinical development, as well as inclacumab and any other potential product candidate programs we may identify and pursue, the timing and scope of these development activities, and the availability of accelerated approval for voxelotor and of any approval for any of our other product candidates;

our ability to successfully obtain any regulatory approvals from any regulatory authorities, and the scope of any such regulatory approvals, to market and sell voxelotor, inclacumab and any other product candidates we may identify and develop in any territory(ies);

our ability to successfully commercialize voxelotor, inclacumab and any other product candidates we may identify and develop in any territories;

the manufacturing, selling and marketing costs associated with the potential commercialization of voxelotor, inclacumab and any other product candidates we may identify and develop, including the cost and timing of establishing our sales and marketing capabilities in any territory(ies);

the amount and timing of sales and other revenues from voxelotor and any other product candidates we may identify and develop, including the sales price and the availability of adequate third-party reimbursement;

the cash requirements of any future acquisitions or discovery of product candidates;

the time and cost necessary to respond to technological and market developments;

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the extent to which we may acquire or in-license other product candidates and technologies and the costs and timing associated with any such acquisitions or in-licenses;

our ability to attract, hire, and retain qualified personnel; and

the costs of maintaining, expanding, and protecting our intellectual property portfolio.

Further, our operating plan may change, and we may need additional funds to meet operational needs and capital requirements for clinical trials and other research and development expenditures. We currently have no credit facility or committed sources of capital. Because of the numerous risks and uncertainties associated with the development and commercialization of our product candidate, we are unable to estimate the amounts of increased capital outlays and operating expenditures associated with our current and anticipated clinical studies and research and development activities.

The following table summarizes our cash flows for the periods indicated:

	Year Ended December 31,		
(in thousands)	**2018**	**2017**	**2016**
Cash used in operating activities	$ (135,375)	$ (93,022)	$ (67,723)
Cash used in investing activities	(184,157)	(35,000)	(106,852)
Cash provided by financing activities	397,906	235,188	118,145
Net increase (decrease) in cash, cash equivalents and restricted cash	$ 78,374	$ 107,166	$ (56,430)

Cash flows from operating activities

Net cash used in operating activities was $135.4 million for the year ended December 31, 2018, consisting of a net loss of $174.2 million, which was partially offset by non-cash charges of $30.1 million for stock-based compensation and $4.0 million for depreciation and amortization expense. The change in our net operating assets and liabilities was due primarily to an increase of $2.5 million of prepaid expenses due to advance payments made in connection with our Phase 3 HOPE Study and our Phase 2a HOPE-KIDS 1 Study, an increase of $8.0 million of accrued liabilities related to higher research and development activities and higher professional and consulting services due to the growth of our operations, an increase of $1.5 million of accrued compensation related to higher headcounts and a decrease of $1.3 million of accounts payable due to timing of payments. The remainder of changes in operating assets and liabilities are primarily related to continuous growth of our operations.

Net cash used in operating activities was $93.0 million for the year ended December 31, 2017, consisting of a net loss of $117.0 million, which was partially offset by non-cash charges of $13.7 million for stock-based compensation and $2.4 million for depreciation and amortization expense. The change in our net operating assets and liabilities was due primarily to an increase of $3.6 million of accrued compensation related to higher headcounts, an increase of $3.3 million of accrued liabilities along with an increase of $2.8 million of accounts payable related to an increase in our research and development activities and an increase in professional and consulting services due to the growth of our operations.

Net cash used in operating activities was $67.7 million for the year ended December 31, 2016, consisting of a net loss of $82.5 million, which was offset by non-cash charges for stock-based compensation of $9.2 million, and for depreciation and amortization expense of $1.2 million. The change in our net operating assets and liabilities was due primarily to increases in accrued expenses related to an increase in our research and development activities and an increase in professional and consulting services of $1.8 million due to the growth of our operations, in accounts payable as a result of timing of payments of $1.1 million, and in accrued compensation related to our headcount of $2.7 million.

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Cash flows from investing activities

Net cash used in investing activities for the year ended December 31, 2018 was $184.2 million, primarily consisting of the purchase of marketable securities of $361.4 million, and purchase of property and equipment for our office and laboratory facility of $4.8 million, which are partially offset by maturities of marketable securities of $182.0 million.

Net cash used in investing activities for the year ended December 31, 2017 was $35.0 million, primarily consisting of the purchase of marketable securities of $127.7 million, and purchase of property and equipment for our office and laboratory facility of $3.1 million, which are partially offset by maturities of marketable securities of $96.0 million.

Net cash used in investing activities for the year ended December 31, 2016 was $106.9 million related to the purchase of marketable securities of $105.5 million and the purchase of property and equipment for our office and laboratory facilities of $1.4 million.

Cash flows from financing activities

Cash provided by financing activities was $397.9 million for the year ended December 31, 2018. The cash provided by financing activities in 2018 was primarily from net proceeds of $396.5 million from the issuance of common stock in connection with our follow-on offerings completed in January 2018, March 2018 and December 2018, and to a lesser extent, proceeds of $7.7 million from the issuance of common stock to participants in the employee stock purchase plan and exercise of stock options, which are partially offset by $6.3 million of taxes paid related to net shares settlement of equity awards.

Net cash provided by financing activities was $235.2 million for the year ended December 31, 2017. The cash provided by financing activities in 2017 was primarily from net proceeds of $232.0 million from the issuance of common stock in connection with our follow-on offerings completed during 2017 and to a lesser extent, proceeds of $3.9 million from the issuance of common stock to participants in the employee stock purchase plan and exercise of stock options.

Net cash provided by financing activities was $118.1 million for the year ended December 31, 2016 and $128.3 million for the year ended December 31, 2015. The cash provided by financing activities in 2016 was primarily related to net proceeds of $117.0 million from our follow-on offering in July 2016 and proceeds of $1.2 million from the issuance of common stock to participants in the employee stock purchase plan and exercise of stock options.

Off-Balance Sheet Arrangements

As of December 31, 2018, we had no off-balance sheet arrangements as defined in Item 303(a)(4) of Regulation S-K as promulgated by the SEC.

Contractual Obligations and Other Commitments

In August 2018, we entered into an amendment to our Lease (the Lease Amendment) to relocate and expand our leased premises to a to-be-constructed-building consisting of approximately 164,150 rentable square feet of space (the Substitute Premises) when the Substitute Premises are ready for occupancy (the Substitute Premises Commencement Date). The Lease Amendment has a contractual term of 10 years from the Substitute Premises Commencement Date. The Lease Amendment grants us an option to extend the Lease Amendment for an additional 10-year period. We intend to vacate our current headquarters (the Existing Premises) and surrender and deliver the Existing Premises to

the landlord on or before the date which is sixty days after the Substitute Premises Commencement Date, upon which time we will have no further obligations with respect to the Existing Premises.

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The following table summarizes our contractual obligations under the new and existing operating leases as of December 31, 2018 (in thousands):

		Payments Due by Period				
	Total	2019	2020	2021	2022	Thereafter
Operating lease obligations[1]	$ 137,357	$ 4,406	$ 6,513	$ 11,642	$ 12,020	$ 102,776
Total contractual obligations	$ 137,357	$ 4,406	$ 6,513	$ 11,642	$ 12,020	$ 102,776

(1) The table above is prepared under the assumption that the Substitute Premises Commencement Date is June 30, 2020.

We have excluded from the above table $16.2 million in contractual obligations related to uncertain tax positions as we cannot make a reasonably reliable estimate of the period of cash settlement.

In August 2018, we entered into a license agreement (the License Agreement) with F. Hoffmann-La Roche Ltd. and Hoffmann-La Roche Inc. (together, Roche) pursuant to which Roche granted us an exclusive and sublicensable worldwide license under certain patent rights and know-how to develop and commercialize inclacumab for all indications and uses. Roche retained a non-exclusive, worldwide, perpetual, royalty-free license to inclacumab solely for any diagnostic use. As of December 31, 2018, we have paid Roche an upfront payment of $2.0 million. We are subject to contingent payments totaling approximately $125.5 million upon achievement of certain clinical development and regulatory milestones for inclacumab and commercial sales milestones if they occur before certain dates in the future. We are also subject to royalty payments to Roche based on tiered percentages ranging from low double-digit for the first annual net sales of inclacumab tier up to mid double-digit for annual net sales over $1.0 billion.

Recent Accounting Pronouncements

From time to time, new accounting pronouncements are issued by the Financial Accounting Standards Board (FASB) or other standards setting bodies that are adopted by us as of the specified effective date. Unless otherwise discussed, we believe that the impact of recently issued standards that are not yet effective will not have a material impact on our consolidated financial statements upon adoption.

Leases (Topic 842)

In February 2016, the FASB issued ASU No. 2016-02, *Leases (Topic 842)*. The new standard requires lessees to record a right-of-use asset and a lease liability for all leases with a term of greater than 12 months regardless of their classification. As originally issued, Topic 842 required companies to adopt the standard using a modified retrospective approach with a cumulative adjustment to equity as of the beginning of the earliest comparative period presented. This provision also required companies to recast prior period comparative financial statements including providing the updated disclosure requirements in those periods. The standard is effective for interim and annual periods beginning after December 15, 2018, with early adoption permitted.

During 2018, the FASB issued ASU No. 2018-11, *Leases (Topic 842) Targeted Improvements*, which provided an entity with an alternative transition methodology to adopt the provisions of Topic 842 using a modified retrospective

approach with a cumulative adjustment to accumulated deficit as of the effective date. This approach does not require an entity to recast comparative period financial statements or provide the updated disclosure requirements during those periods. We expect to adopt the new standard on January 1, 2019 and use the effective date as our date of initial application.

The new standard also provides a number of optional practical expedients for the transition from *ASC 840 Leases (Topic 840)* to Topic 842 that allow entities to not (i) reassess whether any expired or existing contracts are considered or contain leases; (ii) reassess the lease classification for any expired or existing leases; and (iii) reassess initial direct costs for any existing leases. These practical expedients, if elected, must be elected as a package and applied consistently by an entity to all of its leases. We plan to elect the use of practical expedients as a package.

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We expect that this standard will have a material effect on our consolidated financial statements. While we continue to evaluate the provisions of ASC 842 to determine the impact the adoption will have on our consolidated financial statements, we currently believe the most significant effects relate to the recognition of new right-of-use (ROU) assets and lease liabilities on our consolidated balance sheet related to our office and equipment operating leases. We do not expect a significant change in our leasing activities between now and adoption. On adoption, we currently expect to recognize additional lease liabilities of approximately $25.9 million and corresponding ROU assets of approximately $14.2 million, which reflect lease incentives previously received of approximately $11.7 million that are currently recorded as deferred rent liabilities on our consolidated balance sheet.

The new standard also provides practical expedients for an entity s ongoing accounting. We currently expect to elect the short-term lease recognition exemption for all leases that qualify. This means, for those leases that qualify, we will not recognize ROU assets or lease liabilities, and this includes not recognizing ROU assets or lease liabilities for existing short-term leases of those assets in transition. We also currently expect to elect the practical expedient to not separate lease and non-lease components for all of our leases.

Other recent accounting pronouncements

In February 2018, the FASB issued ASU No. 2018-02, *Income Statement Reporting Comprehensive Income (Topic 220): Reclassification of Certain Tax Effects from Accumulated Other Comprehensive Income*. The amendment of ASU No. 2018-02 states an entity may elect to reclassify the income tax effects of the Tax Cuts and Jobs Act of 2017 (the Tax Cuts and Jobs Act) on items within accumulated other comprehensive income to retained earnings. The amendments in this update are effective for annual periods, and interim periods within those annual periods, beginning after December 15, 2018. Early adoption is permitted. We believe that the adoption of this new standard will have no material impact on our consolidated financial position or results of operations and have not elected to early adopt the amendment.

In August 2018, the FASB issued ASU No. 2018-13, *Fair Value Measurement (Topic 820)*. The new standard modifies the disclosure requirements on fair value measurements in Topic 820, Fair Value Measurement, including removals of, modification to, and additional disclosure requirements from Topic 820. The amendment of ASU No. 2018-13 removes disclosure requirements from Topic 820 in the areas of (1) the amount of and reasons for transfers between Level 1 and Level 2 of the fair value hierarchy; (2) the policy for timing of transfers between levels, and (3) the valuation processes for Level 3 fair value measurements. The amendments in this update are effective for fiscal years, and interim periods within those fiscal years, beginning after December 15, 2019. Except for certain amendments related to Level 3 fair value measurements, all the other amendments should be applied retrospectively to all periods presented upon their effective date. Early adoption is permitted upon issuance of the ASU No. 2018-13. We believe that the adoption of this new standard will have no material impact on our consolidated financial position or results of operations and have not elected to early adopt the amendment.

In August 2018, the FASB issued ASU No. 2018-15, *Intangibles Goodwill and Other Internal-Use Software (Subtopic 350-40), Customer s Accounting for Implementation Costs Incurred in a Cloud Computing Arrangement That Is a Service Contract* (or ASU 2018-15). ASU No. 2018-15 requires a customer that is a party to a cloud computing service contract to follow the internal-use software guidance in Subtopic 350-40 to determine which implementation costs to capitalize and which costs to expense. The amendments in this update are effective for annual reporting periods beginning after December 15, 2019, and interim periods within those fiscal years. Early adoption of the amendments in this update is permitted. The amendments in this update should be applied either retrospectively or prospectively to all implementation costs incurred after the date of adoption. We believe that the adoption of this new standard will have no material impact on our consolidated financial position or results of operations and have not elected to early adopt the amendment.

Accounting Pronouncements Adopted

In August 2016, the FASB issued ASU No. 2016-15, *Classification of Certain Cash Receipts and Cash Payments*. The new standard provides guidance on eight specific cash flow classification issues. The standard is

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effective for annual periods beginning after December 15, 2017, and interim periods within those annual periods. We adopted ASU No. 2016-15 in the first quarter of 2018. The adoption of this new standard did not have a material impact on our consolidated financial statements.

In November 2016, the FASB issued ASU No. 2016-18, *Restricted Cash*. The new standard requires that a statement of cash flows explain the change during the period in the total of cash, cash equivalents, and amounts generally described as restricted cash or restricted cash equivalents. Therefore, amounts generally described as restricted cash and restricted cash equivalents should be included with cash and cash equivalents when reconciling the beginning-of-period and end-of-period total amounts shown on the statement of cash flows. The standard is effective for annual periods beginning after December 15, 2017, and interim periods within those annual periods. We adopted ASU No. 2016-18 in the first quarter of 2018 using a retrospective transition method to each period presented. The adoption of this new standard did not have a material impact on our consolidated financial statements.

In May 2017, the FASB issued ASU No. 2017-09, *Compensation Stock Compensation (Topic 718)*, which is intended to clarify and reduce the diversity in practice and cost and complexity when applying the guidance in Topic 718, Compensation Stock Compensation, to a change to the terms or conditions of a share-based payment award. The new standard is effective for annual periods, and interim periods within those annual periods, beginning after December 15, 2017. We adopted ASU No. 2017-09 in the first quarter of 2018. The adoption of this new standard did not have a material impact on our consolidated financial statements.

In March 2018, the FASB issued ASU No. 2018-04, *Investments Debt Securities (Topic 320) and Regulated Operations (Topic 980): Amendments to SEC Paragraphs Pursuant to SEC Staff Accounting Bulletin No. 117 and SEC Release No. 33-9273.* The amendment of ASU No. 2018-04 adds, amends and supersedes various paragraphs that contain SEC guidance in ASC 320, *Investments-Debt Securities* and ASC 980, *Regulated Operations*. The amendments in this update were effective upon issuance in March 2018. The adoption of this new standard did not have a material impact on our consolidated financial statements.

In March 2018, the FASB issued ASU No. 2018-05, *Income Taxes (Topic 740): Amendments to SEC Paragraphs Pursuant to SEC Staff Accounting Bulletin No. 118*. The amendment of ASU No. 2018-05 adds various paragraphs that contain SEC guidance in ASC 740, *Income Taxes* and SEC Staff Accounting Bulletin No. 118. The amendments in this update were effective upon issuance in March 2018. We believe that the adoption of this new standard did not have a material impact on our consolidated financial statements.

In June 2018, the FASB issued ASU No. 2018-07, *Compensation Stock Compensation (Topic 718), Improvements to Nonemployee Share-Based Payment Accounting*, which is intended to improve the usefulness of the information provided to the users of financial statements while reducing cost and complexity in financial reporting. Under the new standard, nonemployee share-based payment awards within the scope of Topic 718 are measured at grant-date fair value of the equity instruments that an entity is obligated to issue when conditions necessary to earn the right to benefit from the instruments have been satisfied. These equity-classified non-employee share-based payment awards are measured at the grant date. Consistent with the accounting for employee share-based payment awards, an entity considers the probability of satisfying performance conditions when nonemployee share-based payment awards contain such conditions. The new standard also eliminates the requirement to reassess classification of such awards upon vesting. The new standard is effective for annual periods, and interim periods within those annual periods, beginning after December 15, 2018. Early adoption is permitted, but no earlier than an entity s adoption date of Topic 606. We early adopted ASU No. 2018-07 effective January 1, 2018. The adoption of this new standard did not have a material impact on our consolidated financial statements.

Item 7A. ***Quantitative and Qualitative Disclosures about Market Risk***

Interest Rate Sensitivity

We are exposed to market risks in the ordinary course of our business. These risks primarily include interest rate sensitivities. We have invested primarily in money market funds, negotiable certificates of deposit,

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U.S. treasury notes, federal agency notes and corporate debt securities. The fair value of our investments, including those included in cash and cash equivalents and marketable securities, was $591.7 million as of December 31, 2018 and $316.9 million as of December 31, 2017. We had no outstanding debt as of December 31, 2018 and 2017.

Our investment policy is to limit credit exposure through diversification and investment in highly rated securities. We, along with our investment advisors, actively review current investment ratings, company specific events, and general economic conditions in managing our investments.

We performed a sensitivity analysis to determine the impact a change in interest rates would have on the value of our investment portfolio. Based on our investment positions as of December 31, 2018, a hypothetical 100 basis point increase in interest rate would result in a $2.4 million decline in the fair market value of our portfolio. Such losses would only be realized if we sold the investments prior to maturity.

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Item 8. ***Financial Statements and Supplementary Data***

GLOBAL BLOOD THERAPEUTICS, INC.

INDEX TO CONSOLIDATED FINANCIAL STATEMENTS

Years Ended December 31, 2018 and 2017

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Report of Independent Registered Public Accounting Firm

To the Stockholders and Board of Directors

Global Blood Therapeutics, Inc.:

Opinions on the Consolidated Financial Statements and Internal Control over Financial Reporting

We have audited the accompanying consolidated balance sheets of Global Blood Therapeutics, Inc. and subsidiaries (the Company) as of December 31, 2018 and 2017, the related consolidated statements of operations and comprehensive loss, stockholders equity, and cash flows for each of the years in the three-year period ended December 31, 2018, and the related notes (collectively, the consolidated financial statements). We also have audited the Company s internal control over financial reporting as of December 31, 2018, based on criteria established in *Internal Control Integrated Framework (2013)* issued by the Committee of Sponsoring Organizations of the Treadway Commission.

In our opinion, the consolidated financial statements referred to above present fairly, in all material respects, the financial position of the Company as of December 31, 2018 and 2017, and the results of its operations and its cash flows for each of the years in the three-year period ended December 31, 2018, in conformity with U.S. generally accepted accounting principles. Also in our opinion, the Company maintained, in all material respects, effective internal control over financial reporting as of December 31, 2018, based on criteria established in *Internal Control Integrated Framework (2013)* issued by the Committee of Sponsoring Organizations of the Treadway Commission.

Basis for Opinions

The Company s management is responsible for these consolidated financial statements, for maintaining effective internal control over financial reporting, and for its assessment of the effectiveness of internal control over financial reporting, included in the accompanying Management s Annual Report on Internal Control Over Financial Reporting in Item 9A. Our responsibility is to express an opinion on the Company s consolidated financial statements and an opinion on the Company s internal control over financial reporting based on our audits. We are a public accounting firm registered with the Public Company Accounting Oversight Board (United States) (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 audits to obtain reasonable assurance about whether the consolidated financial statements are free of material misstatement, whether due to error or fraud, and whether effective internal control over financial reporting was maintained in all material respects.

Our audits of the consolidated financial statements included performing procedures to assess the risks of material misstatement of the consolidated 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 consolidated 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 consolidated financial statements. Our audit of internal control over financial reporting included obtaining an understanding of internal control over financial reporting, assessing the risk that a material weakness exists, and testing and evaluating the design and operating effectiveness of internal control based on the assessed risk. Our audits also included performing such other procedures as we considered necessary in the circumstances. We believe that our audits provide

a reasonable basis for our opinions.

Definition and Limitations of Internal Control over Financial Reporting

A company s internal control over financial reporting is a process designed to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in

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accordance with generally accepted accounting principles. A company s internal control over financial reporting includes those policies and procedures that (1) pertain to the maintenance of records that, in reasonable detail, accurately and fairly reflect the transactions and dispositions of the assets of the company; (2) provide reasonable assurance that transactions are recorded as necessary to permit preparation of financial statements in accordance with generally accepted accounting principles, and that receipts and expenditures of the company are being made only in accordance with authorizations of management and directors of the company; and (3) provide reasonable assurance regarding prevention or timely detection of unauthorized acquisition, use, or disposition of the company s assets that could have a material effect on the financial statements.

Because of its inherent limitations, internal control over financial reporting may not prevent or detect misstatements. Also, projections of any evaluation of effectiveness to future periods are subject to the risk that controls may become inadequate because of changes in conditions, or that the degree of compliance with the policies or procedures may deteriorate.

/s/ KPMG LLP

We have served as the Company s auditor since 2014.

San Francisco, California

February 27, 2019

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GLOBAL BLOOD THERAPEUTICS, INC.

Consolidated Balance Sheets

(In thousands, except share and per share amounts)

	December 31,	
	2018	**2017**
Assets		
Current assets:		
Cash and cash equivalents	$ 275,357	$ 198,332
Short-term marketable securities	202,177	116,493
Prepaid expenses	6,337	3,839
Other assets, current	1,909	5,648
Total current assets	485,780	324,312
Property and equipment, net	14,981	16,571
Long-term marketable securities	114,281	14,607
Restricted cash	2,395	1,046
Other assets, noncurrent	206	184
Total assets	$ 617,643	$ 356,720
Liabilities and Stockholders Equity		
Current liabilities:		
Accounts payable	$ 6,046	$ 7,177
Accrued liabilities	16,792	10,135
Accrued compensation	10,036	8,579
Other liabilities, current	899	373
Total current liabilities	33,773	26,264
Other liabilities, noncurrent	11,071	11,652
Total liabilities	44,844	37,916
Commitments and contingencies (Note 10)		
Stockholders equity:		
Preferred stock, $0.001 par value, 5,000,000 shares authorized at December 31, 2018 and 2017, respectively, and none issued and outstanding as of December 31, 2018 and 2017.		
Common stock, $0.001 par value, 150,000,000 shares authorized at December 31, 2018 and 2017, respectively; 55,640,299 and 46,131,723 shares issued and outstanding at December 31, 2018 and 2017, respectively.	56	46

Additional paid-in capital	1,044,941	617,051
Accumulated other comprehensive loss	(48)	(336)
Accumulated deficit	(472,150)	(297,957)
Total stockholders equity	572,799	318,804
Total liabilities and stockholders equity	$ 617,643	$ 356,720

See accompanying notes.

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GLOBAL BLOOD THERAPEUTICS, INC.

Consolidated Statements of Operations and Comprehensive Loss

(In thousands, except share and per share amounts)

	Year Ended December 31,		
	2018	**2017**	**2016**
Operating expenses:			
Research and development	$ 131,307	$ 87,807	$ 62,163
General and administrative	51,435	31,438	20,964
Total operating expenses	182,742	119,245	83,127
Loss from operations	(182,742)	(119,245)	(83,127)
Interest income, net	8,618	2,555	659
Other expenses, net	(69)	(334)	
Net loss	(174,193)	(117,024)	(82,468)
Other comprehensive loss:			
Net unrealized gain (loss) on marketable securities, net of tax	288	(170)	(166)
Comprehensive loss	$ (173,905)	$ (117,194)	$ (82,634)
Basic and diluted net loss per common share	$ (3.41)	$ (2.76)	$ (2.48)
Weighted-average number of shares used in computing basic and diluted net loss per common share	51,150,728	42,323, 686	33,207,382

See accompanying notes.

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GLOBAL BLOOD THERAPEUTICS, INC.

Consolidated Statements of Stockholders Equity

(In thousands, except share amounts)

	Common Stock		Additional Paid-In Capital	Accumulated Other Comprehensive Loss	Accumulated Deficit	Total Stockholders Equity
	Shares	Amount				
Balance at December 31, 2015	29,359,800	29	239,231		(98,465)	140,795
Issuance of common stock upon equity offering, net of issuance costs	6,667,228	7	116,988			116,995
Issuance of common stock upon exercise of stock options	147,126		222			222
Issuance of common stock pursuant to ESPP purchases	65,252		1,018			1,018
Vesting of restricted stock purchases	398,750	1	677			678
Stock-based compensation expense			9,235			9,235
Net unrealized gain (loss) on marketable securities				(166)		(166)
Net loss					(82,468)	(82,468)
Balance at December 31, 2016	36,638,156	$ 37	$ 367,371	$ (166)	$ (180,933)	$ 186,309
Issuance of common stock upon equity offerings, net of issuance costs	8,498,926	8	231,947			231,955
Issuance of common stock upon exercise of stock options	578,455	1	2,815			2,816
Issuance of common stock upon vesting of restricted share units, net of shares withheld for	33,212		(238)			(238)

employee taxes						
Issuance of common stock pursuant to ESPP purchases	76,585		1,050			1,050
Vesting of restricted stock purchases	306,389		424			424
Stock-based compensation expense			13,682			13,682
Net unrealized gain (loss) on marketable securities				(170)		(170)
Net loss					(117,024)	(117,024)
Balance at December 31, 2017	46,131,723	$ 46	$ 617,051	$ (336)	$ (297,957)	$ 318,804
Issuance of common stock upon equity offerings, net of issuance costs	8,403,826	8	396,026			396,034
Issuance of common stock upon exercise of stock options	596,434	1	6,021			6,022
Issuance of common stock upon vesting of restricted share units, net of shares withheld for employee taxes	255,039	1	(6,253)			(6,252)
Issuance of common stock pursuant to ESPP purchases	61,031		1,647			1,647
Vesting of restricted stock purchases	192,246		369			369
Stock-based compensation expense			30,080			30,080
Net unrealized gain (loss) on marketable securities				288		288
Net loss					(174,193)	(174,193)
Balance at December 31, 2018	55,640,299	$ 56	$ 1,044,941	$ (48)	$ (472,150)	$ 572,799

See accompanying notes.

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GLOBAL BLOOD THERAPEUTICS, INC.

Consolidated Statements of Cash Flows

(In thousands)

	Year Ended December 31,		
	2018	**2017**	**2016**
CASH FLOWS FROM OPERATING ACTIVITIES:			
Net loss	$ (174,193)	$ (117,024)	$ (82,468)
Adjustments to reconcile net loss to net cash used in operating activities:			
Depreciation and amortization	4,607	1,658	1,160
Amortization (accretion) of premium (discount) on marketable securities	(661)	704	75
Stock-based compensation	30,080	13,682	9,235
Loss from disposal of fixed assets, net	45		
Changes in operating assets and liabilities:			
Prepaid expenses	(2,500)	(1,856)	(761)
Other assets, current	(1,278)	(162)	(512)
Accounts payable	(1,285)	2,771	1,066
Accrued liabilities	8,031	3,280	1,794
Accrued compensation	1,457	3,612	2,725
Other liabilities, current	742	(63)	23
Other liabilities, noncurrent	(420)	376	(60)
Net cash used in operating activities	(135,375)	(93,022)	(67,723)
CASH FLOWS FROM INVESTING ACTIVITIES:			
Purchases of property and equipment	(4,824)	(3,101)	(1,352)
Sale of property and equipment	75		
Purchases of marketable securities	(361,405)	(127,724)	(105,500)
Maturities of marketable securities	181,997	96,000	
Purchases of other assets		(175)	
Net cash used in investing activities	(184,157)	(35,000)	(106,852)
CASH FLOWS FROM FINANCING ACTIVITIES:			
Proceeds from issuance of common stock, net of issuance costs	396,501	231,955	116,995
Proceeds from issuance of common stock in settlement of employee stock purchase plan and exercise of stock options	7,669	3,892	1,240
Repurchases of unvested restricted stock purchases	(12)	(421)	(90)
Taxes paid related to net share settlement of equity awards	(6,252)	(238)	
Net cash provided by financing activities	397,906	235,188	118,145

Net increase (decrease) in cash, cash equivalents and restricted cash	78,374	107,166	(56,430)
Cash, cash equivalents and restricted cash at beginning of period	199,378	92,212	148,642
Cash, cash equivalents and restricted cash at end of period	$ 277,752	$ 199,378	$ 92,212
SUPPLEMENTAL DISCLOSURES OF NON-CASH FINANCING INFORMATION:			
Accrued issuance costs	$ 467	$	$
Leasehold improvements paid for by landlord	$	$ 11,086	$
Accrued purchase of property and equipment	$ 48	$ 1,536	$ 114

See accompanying notes.

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GLOBAL BLOOD THERAPEUTICS, INC.

Notes to Consolidated Financial Statements

1. Organization and Basis of Presentation

Global Blood Therapeutics Inc. (the Company , we , us , and our) was incorporated in Delaware in February 2011 an commenced operations in May 2012. We are a clinical-stage biopharmaceutical company determined to discover, develop and deliver innovative treatments that provide hope to underserved patient communities. Our primary activities have been establishing our facilities, recruiting personnel, conducting development of our product candidates, including clinical trials, establishing commercial operations and raising capital. Our principal operations are based in South San Francisco, California, and we operate in one segment.

Follow-on Offerings

In December 2017, we completed a follow-on offering and issued 2,631,579 shares of common stock at a price of $38.00 per share with proceeds of $96.4 million net of underwriting costs and commissions and offering expenses. In addition, in January 2018, we sold an additional 394,736 shares of our common stock directly to the underwriters when they exercised their over-allotment option at the price of $38.00 per share for proceeds of $14.6 million net of underwriting costs and commissions.

In March 2018, we completed a follow-on offering and issued an aggregate of 4,600,000 shares of our common stock at a price of $54.00 per share, including 600,000 shares of our common stock sold directly to the underwriters when they exercised their over-allotment option at the price of $54.00 per share. We received total proceeds of $240.6 million from the offering, net of underwriting discounts and commissions, and offering expenses.

In December 2018, we completed a follow-on offering and issued 3,409,090 shares of common stock at a price of $44.00 per share with proceeds of $140.9 million net of underwriting costs and commissions, and estimated offering expenses. In addition, in January 2019, we sold an additional 511,363 shares of our common stock directly to the underwriters when they exercised their over-allotment option at the price of $44.00 per share for proceeds of $21.2 million net of underwriting costs and commissions.

Need for Additional Capital

In the course of our development activities, we have sustained operating losses and we expect such losses to continue over the next several years. Our ultimate success depends on the outcome of our research and development activities. As of December 31, 2018, we had an accumulated deficit of $472.2 million. We expect to incur additional losses in the future to conduct product research and development and we anticipate the need to raise additional capital to fully implement our business plan. We intend to raise such capital through the issuance of additional equity, potentially through borrowings, and strategic alliances with partner companies. However, if such financing is not available at adequate levels or when it will be required, we will need to reevaluate our operating plans. We believe that our existing capital resources consisting of cash and cash equivalent and marketable securities will be sufficient to fund our operations for at least the next twelve months from the date of issuance of these financial statements.

2. Summary of Significant Accounting Policies

Basis of Presentation

The accompanying consolidated financial statements have been prepared in accordance with accounting principles generally accepted in the United States of America (U.S. GAAP).

Use of Estimates

The preparation of the accompanying consolidated financial statements in accordance with U.S. GAAP requires us to make estimates and assumptions that affect the reported amounts of assets and liabilities, the

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disclosure of contingent assets and liabilities at the date of the consolidated financial statements, and the reported amounts of costs and expenses during the reporting period. We base our estimates and assumptions on historical experience when available and on various factors that we believe to be reasonable under the circumstances. We evaluate our estimates and assumptions on an ongoing basis. Our actual results could differ from these estimates under different assumptions or conditions.

Principles of Consolidation

The accompanying consolidated financial statements include the accounts of the Company and its wholly-owned subsidiaries. All significant intercompany transactions and balances have been eliminated upon consolidation.

Segment Reporting

We have determined that we operate in a single segment based upon the way the business is organized for making operating decisions and assessing performance. The Company has only one operating segment related to the development of pharmaceutical products. All property and equipment is maintained in the United States.

Cash and Cash Equivalents

We consider all highly liquid investments with original maturities of three months or less at the time of purchase to be cash equivalents. Cash equivalents, which consist primarily of amounts invested in money market accounts, are stated at fair value.

Concentration of Credit Risk

We invest in a variety of financial instruments and, by our policy, limit the amount of credit exposure with any one issuer, industry or geographic area for investments other than instruments backed by the U.S. federal government.

Investments in Marketable Securities

We invest in marketable securities, primarily money market funds, corporate debt securities, government securities, government agency securities, and certificates of deposits. We classify our marketable securities as available-for-sale securities and report them at fair value in cash equivalents or marketable securities on the consolidated balance sheets with related unrealized gains and losses included within accumulated other comprehensive income (loss) on the consolidated balance sheet. The amortized cost of debt securities is adjusted for amortization of premiums and accretion of discounts to maturity, which is included in interest income on the consolidated statements of operations and comprehensive loss. Realized gains and losses and declines in value judged to be other-than-temporary, if any, on available-for-sale securities are included in interest and other income (loss). The cost of securities sold is based on the specific identification method. Interest and dividends on securities classified as available-for-sale are included in interest income.

We regularly review all of our investments for other-than-temporary declines in estimated fair value. Our review includes the consideration of the cause of the impairment, including the creditworthiness of the security issuers, the number of securities in an unrealized loss position, the severity and duration of the unrealized losses, whether we have the intent to sell the securities and whether it is more likely than not that we will be required to sell the securities before the recovery of their amortized cost basis. When we determine that the decline in estimated fair value of an investment is below the amortized cost basis and the decline is other-than-temporary, we reduce the carrying value of the security and record a loss for the amount of such decline.

Fair Value Measurement

The carrying amounts of certain financial instruments, including cash and cash equivalents, other receivables as included in other assets, current, restricted cash, accounts payable and accrued liabilities approximate fair value due to their relatively short maturities.

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Property and Equipment, Net

Property and equipment are stated at cost, less accumulated depreciation and amortization. Depreciation is provided using the straight-line method over the estimated useful lives of the assets, three years for computer equipment and five years for laboratory equipment. Leasehold improvements are amortized over the shorter of the lease term or the estimated useful life of the improvements. Depreciation and amortization begins at the time the asset is placed in service. Maintenance and repairs are charged as expense in the statements of operations and comprehensive loss as incurred. Upon sale or retirement of assets, the cost and related accumulated depreciation and amortization are removed from the consolidated balance sheet and any resulting gain or loss is reflected in operations.

Impairment of Long-Lived Assets

We evaluate our long-lived assets, including property and equipment, for impairment whenever events or changes in circumstances indicate that the carrying value of these assets may not be recoverable. Recoverability of these assets is measured by comparison of the carrying amount of each asset to the future undiscounted cash flows the asset is expected to generate over its remaining life. If the asset is considered to be impaired, the amount of any impairment is measured as the difference between the carrying value and the fair value of the impaired asset. There have been no impairments of our long-lived assets for the periods presented.

Restricted Cash

Restricted cash consists of cash deposits held by our financial institution as collateral for our letter of credit under our facility lease.

Accruals of Research and Development Costs

We record accruals for estimated costs of research, nonclinical and clinical studies and manufacturing development. These costs are a significant component of our research and development expenses. A substantial portion of our ongoing research and development activities are conducted by third-party service providers, including contract research organizations and contract manufacturing organizations. We accrue the costs incurred under our agreements with these third parties based on actual work completed in accordance with agreements established with these third parties. We determine the actual costs through discussions with internal personnel and external service providers as to the progress or stage of completion of the services and the agreed-upon fee to be paid for such services. We make judgments and estimates in determining the accrual balance in each reporting period. As actual costs become known, we adjust our accruals. We have not experienced any material deviations between accrued clinical trial expenses and actual clinical trial expenses. However, actual services performed, number of subjects enrolled, and the rate of subject enrollment may vary from our estimates, resulting in adjustments to clinical trial expense in future periods. Changes in these estimates that result in material changes to our accruals could materially affect our results of operations.

Leases

We enter into lease agreements for our office and laboratory facilities. These leases are classified as operating leases. Rent expense is recognized on a straight-line basis over the noncancelable term of the lease and, accordingly, we record the difference between cash rent payments and the recognition of rent expense as a deferred rent liability, which is included within other liabilities on the consolidated balance sheet. Incentives granted under our facilities leases, including rent holiday and allowances to fund leasehold improvements, are deferred and are recognized as adjustments to rental expense on a straight-line basis over the noncancelable term of the lease.

Comprehensive Income (Loss)

Comprehensive income (loss) is defined as a change in equity of a business enterprise during a period, resulting from transactions from non-owner sources. Our comprehensive income (loss) is comprised of net loss and changes in unrealized gains and losses on our marketable securities.

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Research and Development

Research and development costs are expensed as incurred and consist of salaries and benefits, stock-based compensation expense, lab supplies and facility costs, as well as fees paid to other nonemployees and entities that conduct certain research and development activities on our behalf. Amounts incurred in connection with license agreements are also included in research and development expense. Nonrefundable advance payments for goods or services to be received in the future for use in research and development activities are capitalized and then expensed as the related goods are delivered or the services are performed.

Stock-Based Compensation

We measure and recognize stock-based compensation expense, including employee and non-employee equity awards, based on fair value at the grant date. We use the Black-Scholes option-pricing model to calculate fair value. Stock-based compensation expense recognized in the consolidated statements of operations is based on stock awards ultimately vested, taking into consideration actual forfeitures.

Income Taxes

We use the asset and liability method of accounting for income taxes. Under this method, deferred tax assets and liabilities are determined based on the differences between the financial reporting and the tax bases of assets and liabilities and are measured using the enacted tax rates and laws that will be in effect when the differences are expected to reverse. We must then assess the likelihood that the resulting deferred tax assets will be realized. A valuation allowance is provided when it is more likely than not that some portion or all of a deferred tax asset will not be realized. Due to our lack of earnings history, the net deferred tax assets have been fully offset by a valuation allowance.

We recognize benefits of uncertain tax positions if it is more likely than not that such positions will be sustained upon examination based solely on their technical merits, as the largest amount of benefit that is more likely than not to be realized upon the ultimate settlement. It is our policy to include penalties and interest expense related to income taxes as a component of other expense and interest expense, respectively, as necessary. To date, there have been no interest or penalties incurred in relation to the unrecognized tax benefits.

Net Loss per Share

Basic net loss per share is calculated by dividing the net loss by the weighted average number of shares of common stock outstanding during the period, without consideration of common stock equivalents. Diluted net loss per share is the same as basic net loss per share, since the effects of potentially dilutive securities are antidilutive given our net loss.

Recent Accounting Pronouncements

Leases (Topic 842)

In February 2016, the FASB issued ASU No. 2016-02, *Leases (Topic 842)*. The new standard requires lessees to record a right-of-use asset and a lease liability for all leases with a term of greater than 12 months regardless of their classification. As originally issued, Topic 842 required companies to adopt the standard using a modified retrospective approach with a cumulative adjustment to equity as of the beginning of the earliest comparative period presented. This provision also required companies to recast prior period comparative financial statements including providing the

updated disclosure requirements in those periods. The standard is effective for interim and annual periods beginning after December 15, 2018, with early adoption permitted.

During 2018, the FASB issued ASU No. 2018-11, *Leases (Topic 842) Targeted Improvements*, which provided an entity with an alternative transition methodology to adopt the provisions of Topic 842 using a modified retrospective approach with a cumulative adjustment to accumulated deficit as of the effective date. This approach does not require an entity to recast comparative period financial statements or provide the updated

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disclosure requirements during those periods. We expect to adopt the new standard on January 1, 2019 and use the effective date as our date of initial application.

The new standard also provides a number of optional practical expedients for the transition from *ASC 840 Leases (Topic 840)* to Topic 842 that allow entities to not (i) reassess whether any expired or existing contracts are considered or contain leases; (ii) reassess the lease classification for any expired or existing leases; and (iii) reassess initial direct costs for any existing leases. These practical expedients, if elected, must be elected as a package and applied consistently by an entity to all of its leases. We plan to elect the use of practical expedients as a package.

We expect that this standard will have a material effect on our consolidated financial statements. While we continue to evaluate the provisions of ASC 842 to determine the impact the adoption will have on our consolidated financial statements, we currently believe the most significant effects relate to the recognition of new right-of-use (ROU) assets and lease liabilities on our consolidated balance sheet related to our office and equipment operating leases. We do not expect a significant change in our leasing activities between now and adoption. On adoption, we currently expect to recognize additional lease liabilities of approximately $25.9 million and corresponding ROU assets of approximately $14.2 million, which reflect lease incentives previously received of approximately $11.7 million that are currently recorded as deferred rent liabilities on our consolidated balance sheet.

The new standard also provides practical expedients for an entity s ongoing accounting. We currently expect to elect the short-term lease recognition exemption for all leases that qualify. This means, for those leases that qualify, we will not recognize ROU assets or lease liabilities, and this includes not recognizing ROU assets or lease liabilities for existing short-term leases of those assets in transition. We also currently expect to elect the practical expedient to not separate lease and non-lease components for all of our leases.

Other recent accounting pronouncements

In February 2018, the FASB issued ASU No. 2018-02, *Income Statement Reporting Comprehensive Income (Topic 220): Reclassification of Certain Tax Effects from Accumulated Other Comprehensive Income*. The amendment of ASU No. 2018-02 states an entity may elect to reclassify the income tax effects of the Tax Cuts and Jobs Act of 2017 (the Tax Cuts and Jobs Act) on items within accumulated other comprehensive income to retained earnings. The amendments in this update are effective for annual periods, and interim periods within those annual periods, beginning after December 15, 2018. Early adoption is permitted. We believe that the adoption of this new standard will have no material impact on our consolidated financial position or results of operations and have not elected to early adopt the amendment.

In August 2018, the FASB issued ASU No. 2018-13, *Fair Value Measurement (Topic 820)*. The new standard modifies the disclosure requirements on fair value measurements in Topic 820, Fair Value Measurement, including removals of, modification to, and additional disclosure requirements from Topic 820. The amendment of ASU No. 2018-13 removes disclosure requirements from Topic 820 in the areas of (1) the amount of and reasons for transfers between Level 1 and Level 2 of the fair value hierarchy; (2) the policy for timing of transfers between levels, and (3) the valuation processes for Level 3 fair value measurements. The amendments in this update are effective for fiscal years, and interim periods within those fiscal years, beginning after December 15, 2019. Except for certain amendments related to Level 3 fair value measurements, all the other amendments should be applied retrospectively to all periods presented upon their effective date. Early adoption is permitted upon issuance of the ASU No. 2018-13. We believe that the adoption of this new standard will have no material impact on our consolidated financial position or results of operations and have not elected to early adopt the amendment.

In August 2018, the FASB issued ASU No. 2018-15, *Intangibles Goodwill and Other Internal-Use Software (Subtopic 350-40), Customer s Accounting for Implementation Costs Incurred in a Cloud Computing Arrangement That Is a Service Contract* (or ASU 2018-15). ASU No. 2018-15 requires a customer that is a party to a cloud computing service contract to follow the internal-use software guidance in Subtopic 350-40 to determine which implementation costs to capitalize and which costs to expense. The amendments in this update are effective for annual reporting periods beginning after December 15, 2019, and interim periods within those fiscal years. Early adoption of the amendments in this update is permitted. The amendments in this update should

be applied either retrospectively or prospectively to all implementation costs incurred after the date of adoption. We believe that the adoption of this new standard will have no material impact on our consolidated financial position or results of operations and have not elected to early adopt the amendment.

Accounting Pronouncements Adopted

In August 2016, the FASB issued ASU No. 2016-15, *Classification of Certain Cash Receipts and Cash Payments*. The new standard provides guidance on eight specific cash flow classification issues. The standard is effective for annual periods beginning after December 15, 2017, and interim periods within those annual periods. We adopted ASU No. 2016-15 in the first quarter of 2018. The adoption of this new standard did not have a material impact on our consolidated financial statements.

In November 2016, the FASB issued ASU No. 2016-18, *Restricted Cash*. The new standard requires that a statement of cash flows explain the change during the period in the total of cash, cash equivalents, and amounts generally described as restricted cash or restricted cash equivalents. Therefore, amounts generally described as restricted cash and restricted cash equivalents should be included with cash and cash equivalents when reconciling the beginning-of-period and end-of-period total amounts shown on the statement of cash flows. The standard is effective for annual periods beginning after December 15, 2017, and interim periods within those annual periods. We adopted ASU No. 2016-18 in the first quarter of 2018 using a retrospective transition method to each period presented. The adoption of this new standard did not have a material impact on our consolidated financial statements.

In May 2017, the FASB issued ASU No. 2017-09, *Compensation Stock Compensation (Topic 718)*, which is intended to clarify and reduce the diversity in practice and cost and complexity when applying the guidance in Topic 718, Compensation Stock Compensation, to a change to the terms or conditions of a share-based payment award. The new standard is effective for annual periods, and interim periods within those annual periods, beginning after December 15, 2017. We adopted ASU No. 2017-09 in the first quarter of 2018. The adoption of this new standard did not have a material impact on our consolidated financial statements.

In March 2018, the FASB issued ASU No. 2018-04, *Investments Debt Securities (Topic 320) and Regulated Operations (Topic 980): Amendments to SEC Paragraphs Pursuant to SEC Staff Accounting Bulletin No. 117 and SEC Release No. 33-9273.* The amendment of ASU No. 2018-04 adds, amends and supersedes various paragraphs that contain SEC guidance in ASC 320, *Investments-Debt Securities* and ASC 980, *Regulated Operations*. The amendments in this update were effective upon issuance in March 2018. The adoption of this new standard did not have a material impact on our consolidated financial statements.

In March 2018, the FASB issued ASU No. 2018-05, *Income Taxes (Topic 740): Amendments to SEC Paragraphs Pursuant to SEC Staff Accounting Bulletin No. 118*. The amendment of ASU No. 2018-05 adds various paragraphs that contain SEC guidance in ASC 740, *Income Taxes* and SEC Staff Accounting Bulletin No. 118. The amendments in this update were effective upon issuance in March 2018. We believe that the adoption of this new standard did not have a material impact on our consolidated financial statements.

In June 2018, the FASB issued ASU No. 2018-07, *Compensation Stock Compensation (Topic 718), Improvements to Nonemployee Share-Based Payment Accounting*, which is intended to improve the usefulness of the information provided to the users of financial statements while reducing cost and complexity in financial reporting. Under the new standard, nonemployee share-based payment awards within the scope of Topic 718 are measured at grant-date fair value of the equity instruments that an entity is obligated to issue when conditions necessary to earn the right to benefit from the instruments have been satisfied. These equity-classified non-employee share-based payment awards are measured at the grant date. Consistent with the accounting for employee share-based payment awards, an entity

considers the probability of satisfying performance conditions when nonemployee share-based payment awards contain such conditions. The new standard also eliminates the requirement to reassess classification of such awards upon vesting. The new standard is effective for annual periods, and interim periods within those annual periods, beginning after December 15, 2018. Early adoption is permitted, but no earlier than an entity s adoption date of Topic 606. We early adopted ASU No. 2018-07 effective January 1, 2018. The adoption of this new standard did not have a material impact on our consolidated financial statements.

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3. Fair Value Measurements

Fair value accounting is applied for all financial assets and liabilities that are recognized or disclosed at fair value in the consolidated financial statements on a recurring basis (at least annually). Our financial instruments consist of cash and cash equivalents, marketable securities, other receivables as included in other assets, current, restricted cash, accounts payable and accrued liabilities. Cash and cash equivalents, marketable securities and restricted cash are reported at their respective fair values on our Consolidated Balance Sheets. The remaining financial instruments are reported on our Consolidated Balance Sheets at cost that approximate current fair values due to their relatively short maturities.

Assets and liabilities recorded at fair value on a recurring basis in the consolidated balance sheets are categorized based upon the level of judgment associated with the inputs used to measure their fair values. Fair value is defined as the exchange price that would be received for an asset or an exit price that would be paid to transfer a liability in the principal or most advantageous market for the asset or liability in an orderly transaction between market participants on the measurement date. The authoritative guidance on fair value measurements establishes a three-tier fair value hierarchy for disclosure of fair value measurements as follows:

Level 1 Inputs are unadjusted, quoted prices in active markets for identical assets or liabilities at the measurement date;

Level 2 Inputs are observable, unadjusted quoted prices in active markets for similar assets or liabilities, unadjusted quoted prices for identical or similar assets or liabilities in markets that are not active, or other inputs that are observable or can be corroborated by observable market data for substantially the full term of the related assets or liabilities; and

Level 3 Unobservable inputs that are significant to the measurement of the fair value of the assets or liabilities that are supported by little or no market data.

The following table summarizes our financial assets measured at fair value on a recurring basis (in thousands):

	December 31, 2018			
	Total	**Level 1**	**Level 2**	**Level 3**
Financial Assets:				
Money market funds	$ 275,234	$ 275,234	$	$
Corporate debt securities	110,027		110,027	
U.S. government agency securities	88,028		88,028	
Certificates of deposits	6,675		6,675	
U.S. government securities	111,728		111,728	
Total financial assets	$ 591,692	$ 275,234	$ 316,458	$

	December 31, 2017			
	Total	**Level 1**	**Level 2**	**Level 3**
Financial Assets:				
Money market funds	$ 185,824	$ 185,824[1]	$	$

Corporate debt securities	46,977		46,977	
U.S. government agency securities	54,989		54,989	
Certificates of deposits	9,129		9,129	
U.S. government securities	20,007		20,007	
Total financial assets	$ 316,926	$ 185,824	$ 131,102	$

(1) *In 2017, some balances have been reclassified from cash to money market funds in the above table.*

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We estimate the fair values of our investments in corporate debt securities, government and government related securities and certificates of deposits by taking into consideration valuations obtained from third-party pricing services. The fair value of our marketable securities classified within Level 2 is based upon observable inputs that may include benchmark yields, reported trades, broker/dealer quotes, issuer spreads, two-sided markets, benchmark securities, bids, offers and reference data including market research publications. At December 31, 2018, the weighted average remaining contractual maturities of our Level 2 investments was less than one year and all of these investments are rated A-1/P-1/F1 or A/A2, or higher by Moody s and S&P. There were no transfers between Level 1 and Level 2 during the periods presented.

4. Available-for-Sale Securities

Estimated fair values of available-for-sale securities are generally based on prices obtained from commercial pricing services. The following table is a summary of available-for-sale securities recorded in cash and cash equivalents, restricted cash, or marketable securities in our Consolidated Balance Sheets (in thousands):

	December 31, 2018				December 31, 2017			
	Amortized Cost	Unrealized Gains	Unrealized (Losses)	Estimated Fair Value	Amortized Cost	Unrealized Gains	Unrealized (Losses)	Estimated Fair Value
Financial Assets:								
Money market funds	$ 275,234	$	$	$ 275,234	$ 185,824	$	$	$ 185,824[1]
Corporate debt securities	110,053	69	(95)	110,027	47,108		(131)	46,977
U.S. government agency securities	88,042	40	(54)	88,028	55,170		(181)	54,989
Certificates of deposits	6,681	1	(7)	6,675	9,142		(13)	9,129
U.S. government securities	111,730	60	(62)	111,728	20,018		(11)	20,007
Total	$ 591,740	$ 170	$ (218)	$ 591,692	$ 317,262	$	$ (336)	$ 316,926

(1) *In 2017, some balances have been reclassified from cash to money market funds in the above table.*

The following table summarizes the classification of the available-for-sale securities on our Consolidated Balance Sheets (in thousands):

	December 31, 2018	December 31, 2017
Cash and cash equivalents	$ 275,234	$ 185,826[1]
Short-term marketable securities	202,177	116,493
Long-term marketable securities	114,281	14,607
Total	$ 591,692	$ 316,926

(1) *In 2017, some balances have been reclassified from cash to money market funds in the above table.*

We do not intend to sell the investments that are in an unrealized loss position, and it is unlikely that we will be required to sell the investments before recovery of their amortized cost basis, which may be maturity. We have determined that the gross unrealized losses on our marketable securities at December 31, 2018 were temporary in nature. All unrealized losses from all marketable securities at December 31, 2018 are not material.

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5. Balance Sheet Components

Property and Equipment

Property and equipment consist of the following (in thousands):

	December 31,	
	2018	2017
Laboratory equipment	$ 7,363	$ 5,715
Computer equipment	1,501	1,594
Leasehold improvements	13,785	12,642
Construction-in-progress	239	419
Total property and equipment	22,888	20,370
Less: accumulated depreciation and amortization	(7,907)	(3,799)
Property and equipment, net	$ 14,981	$ 16,571

Depreciation expense was $4.7 million for the year ended December 31, 2018, $1.7 million for the year ended December 31, 2017 and $1.2 million for the year ended December 31, 2016. Refer to Note 10 Commitments and Contingencies for details on acceleration of depreciation expenses recognized during the year ended December 31, 2018.

Accrued Liabilities

Accrued liabilities consist of the following (in thousands):

	December 31,	
	2018	2017
Accrued clinical and manufacturing expenses	$ 15,121	$ 8,035
Accrued professional and consulting services	1,016	1,007
Other	655	1,093
Total accrued liabilities	$ 16,792	$ 10,135

Other liabilities, current and noncurrent

Other liabilities consist of the following (in thousands):

	December 31,	
	2018	2017
Restricted shares subject to repurchase, current	$ 157	$ 373

Deferred rent, current	712	
Other payable, current	30	
Total other liabilities, current	$ 899	$ 373
Restricted shares subject to repurchase, noncurrent	$	$ 161
Deferred rent, noncurrent	11,041	11,491
Other payable, noncurrent	30	
Total other liabilities, noncurrent	$ 11,071	$ 11,652

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6. Stockholders Equity

Common Stock Reserved for Issuance

We have reserved sufficient shares of common stock for issuance upon the exercise of stock options, vesting of restricted stock units and restricted shares subject to future vesting. Common stockholders are entitled to dividends if and when declared by the board of directors, subject to the prior rights of any preferred stockholders. As of December 31, 2018, no common stock dividends had been declared by the board of directors.

We have reserved shares of common stock, on an as-converted basis, for future issuance as follows:

	December 31,	
	2018	**2017**
Restricted shares subject to future vesting	47,051	241,617
Restricted stock units	975,419	820,713
Options issued and outstanding	3,243,551	2,945,901
Shares available for future grant under the 2015 Plan and 2017 Inducement Equity Plan	3,003,454	1,708,680
Employee stock purchase plan	240,935	186,033
Total	7,510,410	5,902,944

Restricted Stock

We have issued restricted stock awards to employees under our 2012 Stock Option and Grant Plan (the 2012 Plan). Under the related stock purchase agreements, we have the right to repurchase the common stock at the lower of fair market value and the stockholders original purchase price which right lapses according to individual vesting schedules. In order to vest, the holders are required to provide continued service to us. Upon vesting, the appropriate amounts are transferred from liabilities to additional paid-in capital. If the employment or other service relationship of the holder of any unvested restricted common stock is terminated for any reason, we have the right to repurchase the unvested shares at the lower of fair market value or the stockholder s original purchase price. As such, the shares subject to future vesting are not deemed outstanding for accounting purposes until the shares vest.

Restricted shares subject to repurchase were as follows:

	December 31,	
	2018	**2017**
Restricted shares subject to repurchase:		
Shares issued pursuant to the 2012 Stock Option and Grant Plan	47,051	241,617
Total restricted shares subject to repurchase	47,051	241,617

7. Share-based Compensation

2017 Inducement Equity Plan

In January 2017, we adopted the 2017 Inducement Equity Plan (the 2017 Inducement Plan). Under the 2017 Inducement Plan, shares of our common stock are reserved for the issuance of non-qualified stock options and other equity-based awards to induce highly-qualified prospective officers and employees who are not currently employed by us or our subsidiaries to become employed with our company. The number of shares initially reserved for grant is subject to adjustment for reorganization, recapitalization, stock dividend, stock split, or similar changes in our capital stock. As of December 31, 2018, there were 458,350 shares reserved for the future issuance of equity awards under the 2017 Inducement Plan.

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2015 Stock Option and Incentive Plan

In July 2015, we adopted the 2015 Stock Option and Incentive Plan (the 2015 Plan). Under the 2015 Plan, shares of our common stock are reserved for the issuance of stock options, restricted stock, and other equity-based awards to employees, non-employee directors, and consultants under terms and provisions established by the Board of Directors and approved by our stockholders at inception. Awards granted under the 2015 Plan expire no later than 10 years from the date of grant. For incentive stock options and non-statutory stock options, the option price shall not be less than 100% of the fair market value on the day of grant. If at the time we grant an option and the optionee directly or by attribution owns stock possessing more than 10% of the total combined voting power of all our classes of stock, the option price is required to be at least 110% of the fair market value on the day of grant. Options granted typically vest over a 4-year period but may be granted with different vesting terms. As of December 31, 2018, there were 2,545,104 shares reserved for the future issuance of equity awards under the 2015 Plan.

2012 Stock Option and Grant Plan

In 2012, the Company adopted the 2012 Stock Option and Grant Plan (the 2012 Plan) under which our Board of Directors was authorized to grant incentive stock options to employees, including officers and members of the Board of Directors who are also employees of ours, and non-statutory stock options (options that do not qualify as incentive options) and/or our restricted stock and other equity-based awards to employees, officers, directors, or consultants of ours. Previously, we had initially reserved 2,785,713 shares of common stock for issuance under the 2012 Plan. On April 9, 2015 we increased the number of shares available under the 2012 Plan by 1,000,000 to a total of 3,785,713 shares. Awards granted under the 2012 Plan expire no later than 10 years from the date of grant. Upon adoption of the 2015 Plan, no new awards or grants are permitted under the 2012 Plan.

Stock Option Activity

The following table summarizes activity under the Company s stock option plans, including the 2017 Inducement Plan, 2015 Plan and the 2012 Plan and related information (in thousands, except share and per share amounts and term):

	Number of Options	Weighted-Average Exercise Price	Weighted-Average remaining contractual term (years)	Aggregate Intrinsic Value
Outstanding December 31, 2017	2,945,901	$ 17.50	8.25	
Options granted	1,102,208	52.80		
Options exercised	(596,434)	10.10		
Options canceled	(208,124)	34.84		
Outstanding December 31, 2018	3,243,551	$ 29.74	7.96	$ 49,373
Vested and exercisable December 31, 2018	1,553,778	$ 21.80	7.31	$ 32,305

The aggregate intrinsic value was calculated as the difference between the exercise price of the options and the fair value of our common stock as of December 31, 2018. The total intrinsic value of options exercised was $23.4 million for the year ended December 31, 2018, $11.3 million for the year ended December 31, 2017 and $2.4 million for the

year ended December 31, 2016. The weighted-average estimated fair value of stock options granted was $33.58 for the year ended December 31, 2018, $16.19 for the year ended December 31, 2017 and $11.74 for the year ended December 31, 2016.

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Stock Options Granted to Employees with Service-based Vesting Valuation Assumptions

The fair values of stock options granted to employees were calculated using the following assumptions:

	Year Ended December 31,		
	2018	2017	2016
Expected term (in years)	5.3-6.1	5.3-6.1	5.3-6.1
Volatility	68.7%-71.8%	68.9%-75.6%	70.6%-82.3%
Risk-free interest rate	2.6%-3.0%	1.8%-2.3%	1.1%-2.1%
Dividend yield			

In determining the fair value of the options granted, we used the Black-Scholes-Merton option-pricing model and assumptions discussed below.

Expected Term Our expected term represents the period that the options granted are expected to be outstanding and is determined using the simplified method (based on the mid-point between the vesting date and the end of the contractual term). We have very limited historical information to develop reasonable expectations about future exercise patterns and post-vesting employment termination behavior for our stock option grants.

Expected Volatility We use peer company price volatility as well as the historical volatility of our own common stock to estimate expected stock price volatility due to the limited trading history for our common stock since our IPO in August 2015. When selecting comparable publicly traded biopharmaceutical companies on which we have based our expected stock price volatility, we selected companies with comparable characteristics to us, including enterprise value, risk profiles, position within the industry, and with historical share price information sufficient to meet the expected life of the stock-based awards. The historical volatility data was computed using the daily closing prices for the selected companies shares during the equivalent period of the calculated expected term of the stock-based awards. We will continue to apply this process until a sufficient amount of historical information regarding the volatility of our own stock price becomes available.

Risk-Free Interest Rate The risk-free interest rate is based on the U.S. Treasury zero coupon issues in effect at the time of grant for periods corresponding with the expected term of option.

Expected Dividend We have never paid dividends on our common stock and have no plans to pay dividends on our common stock. Therefore, we used an expected dividend yield of zero.

Restricted Stock Units

In January 2017, the Compensation Committee of our Board of Directors approved the commencement of granting restricted stock units (RSUs) to our employees. RSUs are share awards that entitle the holder to receive freely tradable shares of our common stock upon the completion of a specific period of continued service. RSUs are generally subject to forfeiture if employment terminates prior to the release of vesting restrictions. RSUs granted are valued at the market price of our common stock on the date of grant. We recognize noncash compensation expense for the fair value of RSUs on a straight-line basis over the requisite service period of these awards.

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The following table summarizes activity of RSUs granted to employees with service-based vesting under the 2017 Inducement Plan and 2015 Plan and related information (in thousands, except share, per share amounts and vesting period):

		Number of RSUs	Weighted-Average Grant Date Fair Value	Weighted-Average Remaining Vesting Period (years)	Aggregate Intrinsic Value
Non-vested units	December 31, 2017	467,463	$ 24.93	1.71	$ 18,395
RSUs granted		625,765	54.48		
RSUs vested		(179,772)	34.38		
RSUs forfeited		(97,287)	41.89		
Non-vested units	December 31, 2018	816,169	$ 43.34	1.54	$ 33,504

Restricted Stock Purchases

When Restricted Stock Purchases (RSPs) are granted, the individual purchases the shares at the grant date fair value of the underlying common stock. The purchase of the stock is subject to forfeiture prior to vesting at the lower of fair value and the original purchase price. The award is treated similarly to an early exercise of stock options for accounting purposes.

A summary of our unvested restricted stock for the year ended December 31, 2018 is as follows:

		Number of RSPs	Weighted Average Grant Date Fair Value per Share
Outstanding	December 31, 2017	241,617	$ 1.46
RSPs vested		(192,246)	1.26
Repurchased by Company		(2,320)	2.27
Outstanding	December 31, 2018	47,051	$ 2.24

Market-Condition Awards Granted to Employees

On August 11, 2017, our Board of Directors approved awards up to an aggregate of 365,250 RSUs to certain of our senior management team under the 2015 Plan, the vesting of which are contingent upon a combination of continued employment and achieving certain market capitalization milestones. The market-condition awards do not vest until the achievement of their respective market capitalization milestones, which must occur on or before December 31, 2019. The grant date fair value of these market-condition awards was estimated using a Monte Carlo simulation model. The derived service periods, which are the estimated periods of time that would be required to satisfy the market conditions, are also determined at the grant date. We record expense on a straight-line basis over the applicable derived service periods.

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The following table summarizes activity of the market-condition awards under the 2015 Plan and related information (in thousands, except share, per share amounts and vesting period):

	Number of units	Weighted-Average Grant Date Fair Value	Weighted-Average Remaining Vesting Period (years)	Aggregate Intrinsic Value
Non-vested market-condition awards December 31, 2017	353,250	$ 15.15	0.73	$ 13,900
Granted				
Vested	(188,400)	18.22		
Forfeited	(5,600)	11.64		
Non-vested market-condition awards December 31, 2018	159,250	$ 11.64	0.04	$ 6,537

The following table summarizes the assumptions used to estimate the fair value of the market-condition awards during the year ended December 31, 2017:

Valuation date stock price	$ 28.55
Volatility	65.6%
Risk-free interest rate	1.4%
Dividend yield	

At December 31, 2018, total unrecognized compensation expense related to unvested market-condition awards was $36,500, which is expected to be recognized over their respective remaining derived service periods. The remaining weighted average derived service period is 0.04 year as of December 31, 2018. We recognized $3.1 million and $2.2 million in stock-based compensation expense related to the market-condition awards for the year ended December 31, 2018 and December 31, 2017 respectively.

Employee Stock Purchase Plan

In July 2015, we adopted the 2015 Employee Stock Purchase Plan (the 2015 ESPP). Under the 2015 ESPP our employees may purchase common stock through payroll deductions at a price equal to 85% of the lower of the fair market value of the stock at the beginning of the offering period or at the end of each applicable purchase period. The 2015 ESPP provided for offering periods of six months in duration. As approved by the Compensation Committee of the Board of Directors in December 2017, the 2015 ESPP provides for offering periods of two years in duration with purchase periods occurring every six months during an offering period. The purchase periods end on either January 31 or July 31. Contributions under the 2015 ESPP are limited to a maximum of 15% of an employee s eligible compensation. ESPP purchases are settled with common stock from the ESPP s previously authorized and available pool of shares. During the year ended December 31, 2018, 61,031 shares were issued under the ESPP for $1.6 million.

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The fair values of the rights granted under the 2015 ESPP were calculated using the following assumptions:

	Year Ended December 31, 2018	Year Ended December 31, 2017
Expected term (in years)	0.5 2.0	0.5
Volatility	59.2-65.4%	60.1-63.5%
Risk-free interest rate	1.6-2.7%	0.7-1.2%
Dividend yield	%	%

Stock-Based Compensation Expense

Total stock-based compensation recognized by functions was as follows (in thousands):

	Year Ended December 31,		
	2018	2017	2016
Research and development	$ 12,747	$ 5,905	$ 4,153
General and administrative	17,333	7,777	5,082
Total stock-based compensation expense	$ 30,080	$ 13,682	$ 9,235

During the year ended December 31, 2016, we recorded charges of $1.5 million relating to the fair value of stock options which were modified for two terminated employees. $0.9 million of these charges were classified as research and development expenses and the remaining $0.6 million of these charges were classified as general and administrative expenses.

Unrecognized Stock-Based Compensation Expense and Weighted-Average Remaining Amortization Period

As of December 31, 2018 the unrecognized stock-based compensation cost, and the estimated weighted-average amortization period, using the straight-line attribution method, was as follows (in thousands, except amortization period):

	Unrecognized Compensation Cost	Weighted-average remaining amortization period (years)
Options	$ 37,467	1.3
Restricted stock purchases	56	
Restricted stock units	31,466	1.1
ESPP	1,709	

Total unrecognized stock-based compensation expense	$	70,698	2.4

8. Defined Contribution Plan

In 2013, we began to sponsor a 401(k) retirement plan, in which substantially all of our full-time employees are eligible to participate. Eligible participants may contribute a percentage of their annual compensation to this plan, subject to statutory limitations. We made contributions to the Plan for eligible participants, and recorded contribution expenses of $0.8 million for the year ended December 31, 2018, $0.3 million for the year ended December 31, 2017 and $0.2 million for the year ended December 31, 2016.

9. Income Taxes

On December 22, 2017, the President signed the Tax Cuts and Jobs Act (the Tax Act). The Tax Act, among other things, lowered the U.S. corporate income tax rate from 35% to 21% effective January 1, 2018. Consequently, our gross deferred tax assets as of December 31, 2017 were significantly reduced to reflect the

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estimated impact of the Tax Act. Due to our lack of earnings history and uncertainties surrounding our ability to generate future taxable income, the net deferred tax assets have been fully offset by a valuation allowance. The significant reduction in our gross deferred tax assets are fully offset by a reduction in valuation allowance, resulting in no impact to our income tax expense.

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

	Year Ended December 31,		
	2018	2017	2016
Loss before provision for income taxes:			
United States	$ (174,190)	$ (101,288)	$ (70,103)
International		(15,736)	(12,365)
	$ (174,190)	$ (117,024)	$ (82,468)

No provision for income taxes was recorded for the years ended December 31, 2018, December 31, 2017 and December 31, 2016. We have incurred net operating losses for all the periods presented. We have not reflected any benefit of such net operating loss (NOL) carryforwards in the accompanying consolidated financial statements. We have established a full valuation allowance against the related deferred tax assets due to the uncertainty surrounding the realization of such assets. Our net operating loss carryforwards have been trued up to correctly reflect our NOL balance at the end of 2018. The true up is as a result of the Tax Act and subsequent changes to our U.S. international tax structure.

The effective tax rate of the provision for income taxes differs from the federal statutory rate as follows:

	Year Ended December 31,		
	2018	2017	2016
Federal statutory income tax rate	21.0%	34.0%	34.0%
State taxes	1.3		
Federal and state tax credits	7.1	7.3	8.3
Change in valuation allowance	(33.3)	(14.8)	(41.1)
Foreign rate differential	1.7	(4.6)	(5.1)
Officer compensation limitation	(0.7)	(0.9)	
Stock based compensation/Non-deductible changes in fair value	2.9	0.7	3.9
Tax reform tax rate change		(21.7)	
Provision for Taxes	0.0%	0.0%	0.0%

The components of the deferred tax assets and liabilities are as follows (in thousands):

	December 31,

	2018	2017
Deferred tax assets:		
Net operating loss carryforwards	$ 90,861	$ 51,448
Tax credits	47,375	32,732
Property and equipment	760	116
Accruals and reserves	1,954	1,668
Stock based compensation	4,838	1,915
Gross deferred tax assets	145,788	87,879
Valuation allowance	(145,788)	(87,879)
Net deferred tax assets	$	$

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Realization of the deferred tax assets is dependent upon future taxable income, if any, the amount and timing of which are uncertain. We have established a valuation allowance to offset deferred tax assets as of December 31, 2018 and 2017 due to the uncertainty of realizing future tax benefits from our net operating loss carryforwards and other deferred tax assets. The valuation allowance increased approximately $57.9 million, $17.8 million, and $34.0 million during the years ended December 31, 2018, 2017, and 2016, respectively. The increase in the valuation allowance is mainly related to the increase in net operating loss carryforwards and the increase in tax credits generated during the respective taxable years.

As of December 31, 2018, we had federal net operating loss carryforwards of approximately $381.9 million to offset future federal taxable income, with $208.9 million available through 2037 and $173.0 million available indefinitely. We also had state net operating loss carryforwards of approximately $151.7 million that may offset future state taxable income through 2036. Current federal and state tax laws include substantial restrictions on the utilization of net operating losses and tax credits in the event of an ownership change. Even if the carryforwards are available, they may be subject to annual limitations, lack of future taxable income, or future ownership changes that could result in the expiration of the carryforwards before they are utilized. At December 31, 2018, we recorded a 100% valuation allowance against our deferred tax assets of approximately $145.8 million, as at that time our management believed it was uncertain that they would be fully realized. If we determine in the future that we will be able to realize all or a portion of our net operating loss carryforwards, an adjustment to valuation allowance would increase net income in the period in which we make such a determination.

In general, if we experience a greater than 50 percentage point aggregate change in ownership over a three-year period (a Section 382 ownership change), utilization of our pre-change NOL carryforwards are subject to an annual limitation under Section 382 of the Internal Revenue Code (California has similar laws). The annual limitation generally is determined by multiplying the value of our stock at the time of such ownership change (subject to certain adjustments) by the applicable long-term tax-exempt rate. Such limitations may result in expiration of a portion of the NOL carryforwards that were generated prior to 2018 before utilization. The NOL carryforwards that were generated during and after 2018 can be carried forward indefinitely and are able to offset up to 80% of taxable income in each future year. We have not utilized any NOL carryovers through December 31, 2018. In addition, our deferred tax assets are subject to full valuation allowance, and thus no benefit for deferred tax assets are recorded on our books. Our ability to use the remaining NOL carryforwards may be further limited if we experience a Section 382 ownership change as a result of future changes in our stock ownership.

No liability related to uncertain tax positions is recorded on the consolidated financial statements. All uncertain tax positions are currently recorded as a reduction to our deferred tax asset. It is our policy to include penalties and interest expense related to income taxes as a component of other expense and interest expense, respectively, as necessary.

A reconciliation of the beginning and ending amount of unrecognized tax benefits is as follows (in thousands):

	December 31,	
	2018	2017
Balance at beginning of year	$ 11,150	$ 5,296
Additions based on tax positions related to current year	5,144	6,346
Decreased for prior period positions	(62)	(492)
Unrecognized tax benefit - December 31	$ 16,232	$ 11,150

We do not expect that our uncertain tax positions will materially change in the next twelve months. The reversal of the uncertain tax benefits will not impact our effective tax rate as we continue to maintain a full valuation allowance against our deferred tax assets.

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We file income tax returns in the United States, California and other states. We are not currently under examination by income tax authorities in federal, state or other jurisdictions. All tax returns will remain open for examination by the federal and state authorities for three and four years, respectively, from the date of utilization of any net operating loss or credits.

10. Commitments and Contingencies

Facilities

In March 2017, we entered into a noncancelable operating lease (the Lease) for approximately 67,185 square feet of space in South San Francisco, California (the Existing Premises). The date on which we became responsible for paying rent under the Lease was December 15, 2017 (the Rent Commencement Date). The Lease expires 10 years after the Rent Commencement Date. The Lease grants us an option to extend the Lease for an additional 10-year period. Future minimum rental payments under the Lease during the 10-year term are $48.3 million in the aggregate. The Lease further provides that we are obligated to pay to the landlord certain costs, including taxes and operating expenses. The Lease term commenced in November 2017 as we gained control over physical access to the Existing Premises. We have acquired $11.1 million of leasehold improvements at our Existing Premises with the tenant inducement allowance provided under the Lease. We are required to repay $1.7 million of the tenant inducement allowance to the landlord in the form of additional monthly rent with interest applied over the term of the Lease.

In August 2018, we entered into an amendment to the Lease (the Lease Amendment) to relocate the leased premises from the Existing Premises to a to-be-constructed-building consisting of approximately 164,150 rentable square feet of space (the Substitute Premises) when the Substitute Premises are ready for occupancy (the Substitute Premises Commencement Date). The Lease Amendment has a contractual term (the Substitute Premises Term) of 10 years from the Substitute Premises Commencement Date. The Lease Amendment grants us an option to extend the Lease for an additional 10-year period. Future minimum rental payments under the Lease Amendment during the 10-year term are $121.5 million in the aggregate. Under the Lease Amendment, we are obligated to pay to the landlord certain costs, including taxes and operating expenses. The Lease Amendment also provides a tenant inducement allowance of up to $27.9 million, of which $4.1 million, if utilized, would be repaid to the landlord in the form of additional monthly rent with interest applied.

In March 2017, we provided a standby letter of credit of $0.9 million as security for our obligations under the Lease on our Existing Premises. The security deposit was increased to $2.4 million under the Lease Amendment. This standby letter of credit is classified as restricted cash.

We intend to vacate the Existing Premises and surrender and deliver the Existing Premises to landlord on or before the date which is sixty days after the Substitute Premises Commencement Date, upon which time we will have no further obligations with respect to the Existing Premises. Upon signing of the Lease Amendment, we re-evaluated the remaining useful life of the leasehold improvements at our Existing Premises and started to amortize the leasehold improvements over the remaining period of expected use, resulting in an acceleration of depreciation expenses of $2.3 million during the year ended December 31, 2018.

Future annual minimum lease payments due under the Lease and Lease Amendment at December 31 of each year are as follows (in thousands):

Year ending December 31,	Amount[1]

2019	4,406
2020	6,513
2021	11,642
2022	12,020
Thereafter	102,776
Total	$ 137,357

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(1) *The table above is prepared under the assumption that the Substitute Premises Commencement Date is June 30, 2020.*

Rent expense was $3.6 million for the year ended December 31, 2018, $2.0 million for the year ended December 31, 2017 and $1.3 million for the year ended December 31, 2016. The operating leases require us to share in prorated operating expenses and property taxes based upon actual amounts incurred; those amounts are not fixed for future periods and, therefore, are not included in the future commitments listed above.

Indemnifications

We indemnify each of our directors and officers for certain events or occurrences, subject to certain limits, while the director is or was serving at our request in such capacity, as permitted under Delaware law and in accordance with its certificate of incorporation and bylaws. The term of the indemnification period lasts as long as a director may be subject to any proceeding arising out of acts or omissions of such director in such capacity. The maximum amount of potential future indemnification is unlimited; however, we currently hold director liability insurance. This insurance allows the transfer of risk associated with our exposure and may enable us to recover a portion of any future amounts paid. We believe that the fair value of these indemnification obligations is minimal. Accordingly, we have not recognized any liabilities relating to these obligations for any period presented.

Contingencies

In the ordinary course of business, we may be subject to legal claims and regulatory actions that could have a material adverse effect on our business or financial position. We assess our potential liability in such situations by analyzing potential outcomes, assuming various litigation, regulatory and settlement strategies. If we determine a loss is probable and its amount can be reasonably estimated, we accrue an amount equal to the estimated loss.

No losses and no provision for a loss contingency have been recorded to date.

Contingent Payments

In August 2018, we entered into a license agreement (the License Agreement) with F. Hoffmann-La Roche Ltd. and Hoffmann-La Roche Inc. (together, Roche) pursuant to which Roche granted us an exclusive and sublicensable worldwide license under certain patent rights and know-how to develop and commercialize inclacumab for all indications and uses, except diagnostic use. Roche retained a non-exclusive, worldwide, perpetual, royalty-free license to inclacumab solely for any diagnostic use. As of December 31, 2018, we have paid Roche an upfront payment of $2.0 million. We are obligated to make contingent payments to Roche totaling approximately $125.5 million upon achievement of certain clinical development and regulatory milestones for inclacumab and commercial sales milestones if they occur before certain dates in the future. We are also obligated to make royalty payments to Roche based on tiered percentages ranging from low double-digit for the first annual net sales of inclacumab tier up to mid double-digit for annual net sales over $1.0 billion.

11. Net Loss per Share

Basic net loss per share is computed by dividing net loss by the weighted-average number of common shares outstanding for the period. Since we were in a loss position for all periods presented, diluted net loss per share is the same as basic net loss per share for all periods as the inclusion of all potential common shares outstanding would have been anti-dilutive.

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The following securities were not included in the diluted net loss per share calculations because their effect was anti-dilutive:

	December 31,		
	2018	2017	2016
Options to purchase common stock	3,243,551	2,945,901	2,769,702
Restricted shares subject to future vesting	47,051	241,617	672,112
Restricted stock units	975,419	820,713	
Common stock potentially issuable for ESPP purchases			8,386
Total	4,266,021	4,008,231	3,450,200

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Selected Quarterly Financial Information (unaudited)

The following table provides the selected consolidated quarterly financial data for 2018 and 2017:

	Quarter Ended							
(in thousands, except per share amounts)	**December 31, 2018**	**September 30, 2018**	**June 30, 2018**	**March 31, 2018**	**December 31, 2017**	**September 30, 2017**	**June 30, 2017**	**March 31, 2017**
Loss from operations	$ (52,084)	$ (45,476)	$ (42,487)	$ (42,695)	$ (41,915)	$ (29,180)	$ (24,430)	$ (23,721)
Net loss	$ (49,201)	$ (43,068)	$ (40,368)	$ (41,556)	$ (41,252)	$ (28,557)	$ (23,883)	$ (23,332)
Basic and diluted net loss per common share	$ (0.93)	$ (0.83)	$ (0.78)	$ (0.87)	$ (0.95)	$ (0.66)	$ (0.55)	$ (0.60)

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

None.

Item 9A. ***Controls and Procedures***

Evaluation of Disclosure Controls and Procedures

Our management carried out an evaluation, with the participation of our Chief Executive Officer and our Chief Financial Officer, of the effectiveness of our disclosure controls and procedures (as defined in Rules 13a-15(e) and 15d-15(e) of the Exchange Act) as of the end of the period covered by this Annual Report on Form 10-K. In connection with that evaluation, our Chief Executive Officer and our Chief Financial Officer concluded that our disclosure controls and procedures were effective. Disclosure controls and procedures means controls and procedures designed to ensure that information required to be disclosed by us in the reports that we file or submit is recorded, processed, summarized and reported within the time periods specified in the SEC s rules and forms. These disclosure controls and procedures include, without limitation, controls and procedures designed to ensure that information

required to be disclosed by us in the reports that we file or submit is accumulated and communicated to management, including our principal executive officer and principal financial officer, as appropriate to allow timely decisions regarding required disclosure.

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 defined in Rule 13a-15(f) and 15d-15(f) under the Securities Exchange Act of 1934, as amended). Our management, including our Chief Executive Officer and our Chief Financial Officer assessed the effectiveness of our internal control over financial reporting using the criteria set forth by the Committee of Sponsoring Organizations of the Treadway Commission (COSO) in Internal Control 2013 Integrated Framework. Based on that assessment, our management concluded that our internal control over financial reporting was effective as of December 31, 2018. The effectiveness of our internal control over financial

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reporting as of December 31, 2018 has been audited by KPMG LLP, an independent registered public accounting firm, as stated in its report which is included in Item 8 of this Annual Report on Form 10-K.

Changes in Internal Control over Financial Reporting

There have been no changes in our internal control over financial reporting (as defined in Rules 13a-15(f) and 15d-15(f) under the Exchange Act) during the quarter ended December 31, 2018 that have materially affected, or are reasonably likely to materially affect, our internal control over financial reporting.

Inherent Limitations on Effectiveness of Controls

Internal control over financial reporting may not prevent or detect all errors and all fraud. A control system, no matter how well conceived and operated, can provide only reasonable, not absolute, assurance that the objectives of the control system are met. Also, projections of any evaluation of effectiveness of internal control 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. Accordingly, our disclosure controls and procedures are designed to provide reasonable, not absolute, assurance that the objectives of our disclosure control system are met.

Item 9B. ***Other Information***

None.

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PART III

Item 10. ***Directors, Executive Officers and Corporate Governance***

Except as set forth below, the information required by this item is incorporated by reference from our definitive Proxy Statement to be filed with the SEC in connection with our 2019 Annual Meeting of Stockholders within 120 days after the end of the fiscal year ended December 31, 2018.

We have adopted a Code of Business Conduct and Ethics that applies to all of our directors, officers and employees, including our principal executive officer and principal financial officer. The Code of Business Conduct and Ethics is posted on our website at http://www.ir.globalbloodtx.com.

We intend to satisfy the disclosure requirement under Item 5.05 of Form 8-K regarding an amendment to, or waiver from, a provision of this Code of Business Conduct and Ethics by posting such information on our website, at the address and location specified above and, to the extent required by the listing standards of The NASDAQ Stock Market, by filing a Current Report on Form 8-K with the SEC, disclosing such information.

Item 11. ***Executive Compensation***

The information required by this item is incorporated by reference from our definitive Proxy Statement to be filed with the SEC in connection with our 2019 Annual Meeting of Stockholders within 120 days after the end of the fiscal year ended December 31, 2018.

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

The information required by this item is incorporated by reference from our definitive Proxy Statement to be filed with the SEC in connection with our 2019 Annual Meeting of Stockholders within 120 days after the end of the fiscal year ended December 31, 2018.

Item 13. ***Certain Relationships and Related Transactions and Director Independence***

The information required by this item is incorporated by reference from our definitive Proxy Statement to be filed with the SEC in connection with our 2019 Annual Meeting of Stockholders within 120 days after the end of the fiscal year ended December 31, 2018.

Item 14. ***Principal Accounting Fees and Services***

The information required by this item is incorporated by reference from our definitive Proxy Statement to be filed with the SEC in connection with our 2019 Annual Meeting of Stockholders within 120 days after the end of the fiscal year ended December 31, 2018.

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PART IV

Item 15. ***Exhibits and Financial Statement Schedules***

(a) The following documents are filed as part of this report:

(1) CONSOLIDATED FINANCIAL STATEMENTS

The consolidated financial statements filed as part of this Annual Report on Form 10-K are listed in the Index to Consolidated Financial Statements under Part II, Item 8 of this Annual Report on Form 10-K.

(2) CONSOLIDATED FINANCIAL STATEMENT SCHEDULES

Consolidated financial statement schedules have been omitted in this Annual Report on Form 10-K because they are not applicable, not required under the instructions, or the information requested is set forth in the consolidated financial statements or related notes thereto.

(3) EXHIBITS

The exhibits listed in the accompanying Exhibit Index are filed as part of, or incorporated by reference into, this Annual Report on Form 10-K.

Item 16. ***Form 10-K Summary***

None.

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Exhibit Index

Exhibit Number	Exhibit Description	Incorporated by Reference			Filed Herewith
		Form	Date	Number	
3.1	Restated Certificate of Incorporation.	S-1/A	7/31/2015	3.2	
3.2	Amended and Restated Bylaws.	S-1/A	7/31/2015	3.4	
4.1	Specimen Common Stock Certificate.	S-1/A	7/31/2015	4.1	
4.2	Amended and Restated Investors Rights Agreement by and among the Registrant and certain of its stockholders dated December 22, 2014	S-1	7/8/2015	4.2	
4.3	First Amendment to Amended and Restated Investors Rights Agreement by and among the Registrant and certain of its stockholders dated January 26, 2016	10-K	3/29/2016	4.3	
10.1#	2012 Stock Option and Grant Plan and forms of award agreements thereunder	S-1	7/8/2015	10.1	
10.2#	2015 Stock Option and Incentive Plan and forms of award agreements thereunder	S-8	1/25/2017	99.1	
10.3#	Employment Offer Letter Agreement by and between the Registrant and Ted W. Love, M.D., dated May 19, 2014	S-1	7/8/2015	10.3	
10.4#	Employment Offer Letter Agreement by and between the Registrant and Jeffrey Farrow, dated February 19, 2016	8-K	4/4/2016	10.1	
10.5	Form of Indemnification Agreement by and between the Registrant and each of its directors and officers	S-1/A	7/31/2015	10.8	
10.6#	2015 Employee Stock Purchase Plan	S-8	8/12/2015	99.3	
10.7#	Senior Executive Cash Incentive Bonus Plan	8-K	1/12/2016	10.1	
10.8#	Amended and Restated 2017 Inducement Equity Plan	S-8	7/2/2018	99.1	
10.9#	Form of Non-Qualified Stock Option Agreement under Global Blood Therapeutics, Inc. 2017 Inducement Equity Plan	S-8	1/25/2017	99.4	
10.10#	Form of Restricted Stock Unit Award Agreement under Global Blood Therapeutics, Inc. 2017 Inducement Equity Plan	S-8	1/25/2017	99.5	
10.11#		10-K	3/13/2017	10.17	

	Employment Offer Letter by and between the Registrant and Patricia Suvari, dated October 7, 2016			
10.12	Lease by and between the Company and HCP Oyster Point III LLC, dated March 17, 2017	8-K	3/22/2017	10.1
10.13	Sales Agreement by and between the Company and Cowen and Company, LLC, dated August 23, 2017	S-3ASR	8/23/2017	1.2
10.14#	Change in Control Policy	8-K	8/1/2017	10.1

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Exhibit Number	Exhibit Description	Incorporated by Reference			Filed Herewith
		Form	Date	Number	
10.15#	Employment Offer Letter by and between the Registrant and David Johnson, dated February 21, 2018	10-Q	5/7/2018	10.4	
10.16+	License Agreement by and between the Company and F. Hoffmann-La Roche Ltd. and Hoffmann-La Roche Inc., dated August 22, 2018	10-Q	11/6/2018	10.1	
10.17	First Amendment to Lease by and between the Company and HCP Oyster Point III LLC, dated August 29, 2018	8-K	8/30/2018	10.1	
10.18#	Non-Employee Director Compensation Policy				X
10.19#	Employment Offer Letter by and between the Registrant and Brian Cathers, Ph.D., dated January 21, 2019				X
21.1	Subsidiaries of the Registrant	S-1	6/10/2016	21.1	
23.1	Consent of KPMG LLP, Independent Registered Public Accounting Firm				X
24.1	Power of Attorney (included on signature page to this Annual Report)				X
31.1	Certification of Principal Executive Officer required by Rule 13a-14(a) and Rule 15d-14(a) of the Securities Exchange Act of 1934, as adopted pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.				X
31.2	Certification of Principal Financial Officer required by Rule 13a-14(a) and Rule 15d-14(a) of the Securities Exchange Act of 1934, as adopted pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.				X
32.1*	Certification of Principal Executive Officer pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.				X
32.2*	Certification of Principal Financial Officer pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.				X
101.INS	XBRL Instance Document				X
101.SCH	XBRL Taxonomy Extension Schema Document				X
101.CAL	XBRL Taxonomy Extension Calculation Linkbase				X

	Document	
101.DEF	XBRL Taxonomy Extension Definition Linkbase Document.	X
101.LAB	XBRL Taxonomy Extension Label Linkbase Document.	X
101.PRE	XBRL Taxonomy Extension Presentation Linkbase Document.	X

Represents management compensation plan, contract or arrangement.

+ Confidential treatment has been requested for certain information contained in this Exhibit (indicate by asterisks). Such information has been omitted and filed separately with the SEC.

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* The certifications attached as Exhibit 32.1 and 32.2 that accompany this Annual Report on Form 10-K are not deemed filed with the SEC and are not to be incorporated by reference into any filing of the registrant under the Securities Act of 1933, as amended, or the Securities Exchange Act of 1934, as amended, whether made before or after the date of this Form 10-K, irrespective of any general incorporation language contained in such filing.

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SIGNATURES

Pursuant to the requirements 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.

GLOBAL BLOOD THERAPEUTICS, INC.

By: /s/ Ted W. Love
Ted W. Love, M.D.
President and Chief Executive Officer (Principal Executive Officer)

Date: February 27, 2019

POWER OF ATTORNEY

KNOW ALL PERSONS BY THESE PRESENTS, that each person whose signature appears below constitutes and appoints Ted W. Love, M.D. and Jeffrey Farrow, and each of them, his true and lawful attorneys-in-fact, with full power of substitution, for him in any and all capacities, to sign any and all amendments to this Annual Report on Form 10-K, and to file the same, with exhibits thereto and other documents in connection therewith with the Securities and Exchange Commission, hereby ratifying and confirming all that said attorneys-in-fact or any of them or their substitute or substitutes may lawfully do or cause to be done by virtue thereof.

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 in the capacities and on the dates indicated:

Signature	Title	Date
/s/ Ted W. Love Ted W. Love, M.D.	President, Chief Executive Officer and Director *(Principal Executive Officer)*	February 27, 2019
/s/ Jeffrey Farrow Jeffrey Farrow	Chief Financial Officer *(Principal Financial Officer)*	February 27, 2019
/s/ Lesley A. Calhoun Lesley A. Calhoun	Senior Vice President of Finance and Chief Accounting Officer *(Principal Accounting Officer)*	February 27, 2019
/s/ Willie L. Brown, Jr. Willie L. Brown, Jr.	Director	February 27, 2019

/s/ Charles Homcy	Director	February 27, 2019
Charles Homcy, M.D.		
/s/ Scott W. Morrison	Director	February 27, 2019
Scott W. Morrison		
/s/ Deval L. Patrick	Director	February 27, 2019
Deval L. Patrick		

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Signature	Title	Date
/s/ Mark L. Perry	Director	February 27, 2019
Mark L. Perry		
/s/ Glenn F. Pierce	Director	February 27, 2019
Glenn F. Pierce, M.D., Ph.D.		
/s/ Philip A. Pizzo	Director	February 27, 2019
Philip A. Pizzo, M.D.		
/s/ Dawn Svoronos	Director	February 27, 2019
Dawn Svoronos		
/s/ Wendy Yarno	Director	February 27, 2019
Wendy Yarno		