Global Blood Therapeutics, Inc.
Form 424B4
June 21, 2016
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Filed Pursuant to Rule 424(b)(4)
Registration File No. 333-211976

Prospectus

6,400,000 Shares

COMMON STOCK

Global Blood Therapeutics, Inc. is offering 6,400,000 shares of common stock. Our common stock is listed on The NASDAQ Global Select Market under the symbol GBT. The last reported sale price of our common stock on The NASDAQ Global Select Market on June 20, 2016 was $18.94 per share.

We are an emerging growth company as that term is used in the Jumpstart Our Business Startups Act of 2012, as amended, and, as such, have elected to comply with certain reduced public company reporting requirements for this prospectus and future filings.

Investing in our common stock involves risks. See Risk Factors beginning on page 11.

PRICE $18.75 A SHARE

	Price to Public	Underwriting Discounts and Commissions [1]	Proceeds, before expenses, to Global Blood Therapeutics, Inc.
Per Share	$ 18.75	$ 1.1250	$ 17.6250
Total	$ 120,000,000	$ 7,200,000	$ 112,800,000

(1) The underwriters will receive compensation in addition to underwriting discounts and commissions. See Underwriting beginning on page 100 for additional information regarding underwriting compensation.

We have granted the underwriters an option to purchase up to 960,000 additional shares of our common stock from us at the public offering price, less underwriting discounts and commissions. The underwriters can exercise this option at any time within 30 days after the date of this prospectus.

Neither the Securities and Exchange Commission nor any state securities commission has approved or disapproved of these securities or determined if this prospectus is truthful or complete. Any representation to the contrary is a criminal offense.

The underwriters expect to deliver the shares of common stock to purchasers on or about June 24, 2016.

J.P. Morgan **Morgan Stanley**

Cowen and Company **Wedbush PacGrow**

June 20, 2016

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Prospectus

We and the underwriters have not authorized anyone to provide any information other than that contained or incorporated by reference in this prospectus or in any free writing prospectus prepared by or on behalf of us or to which we have referred you. We take no responsibility for, and can provide no assurance as to the reliability of, any other information that others may give you. We and the underwriters are not making an offer to sell these securities in any jurisdiction where the offer or sale is not permitted. You should assume that the information appearing or incorporated by reference in this prospectus is accurate only as of its date. Our business, financial condition, results of operations and prospects may have changed since the respective dates.

For investors outside of the United States: We have not, and the underwriters have not, done anything that would permit this offering or possession or distribution of this prospectus in any jurisdiction where action for that purpose is required, other than the United States. Persons outside of the United States who come into possession of this prospectus must inform themselves about, and observe any restrictions relating to, the offering of the shares of common stock and the distribution of this prospectus outside of the United States.

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PROSPECTUS SUMMARY

This summary highlights information contained elsewhere and incorporated by reference in this prospectus and does not contain all of the information that you should consider in making your investment decision. Before investing in our common stock, you should carefully read this entire prospectus, including the section titled Risk Factors and the information in our filings with the U.S. Securities and Exchange Commission, or the SEC, incorporated by reference in this prospectus. Unless the context suggests otherwise, all references to us, our, GBT, we, the Company and similar designations refer to Global Blood Therapeutics, Inc. and, where appropriate, our subsidiaries.

Global Blood Therapeutics, Inc.

Our Company

We are a clinical-stage biopharmaceutical company dedicated to discovering, developing and commercializing novel therapeutics to treat grievous blood-based disorders with significant unmet need. We are developing our initial product candidate, GBT440, as an oral, once-daily therapy for sickle cell disease, or SCD, and are currently evaluating GBT440 in SCD subjects in an ongoing Phase 1/2 clinical trial. SCD is a genetic disease 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. GBT440 inhibits abnormal hemoglobin polymerization, the underlying mechanism of RBC sickling. In our clinical trials of GBT440 in SCD subjects, we observed reduced markers of red blood cell destruction, improvements in anemia, improvements in markers of tissue oxygenation, reduced numbers of sickled RBCs, and reduced markers of inflammation. In addition to GBT440 for the treatment of SCD, we intend to evaluate GBT440 for the treatment of hypoxemic pulmonary disorders. In June 2016, we initiated clinical sites which began screening for a Phase 2a clinical trial of GBT440 in idiopathic pulmonary fibrosis, or IPF, and we expect to initiate a Phase 2b clinical trial of GBT440 in a hypoxemic pulmonary disorder in the second half of 2016. We are also engaged in other research and development activities targeted towards hereditary angioedema, or HAE. In 2015, we nominated GBT018713, a proprietary, small molecule kallikrein inhibitor, for development as an orally administered therapy intended for the prevention of HAE attacks. We plan to complete toxicology studies to enable the filing of an Investigational New Drug (IND) application, and subject to submission and clearance of the IND, we expect to initiate a Phase 1 clinical trial for GBT018713 in early 2017. We own or jointly own and have exclusively licensed rights to our portfolio of product candidates in the United States, Europe and other major markets. We own two issued U.S. patents that cover the composition of matter and method of use for GBT440, which are due to expire in 2032 and 2034, respectively (absent any applicable patent term extensions), and we own or co-own additional pending patent applications in the United States and selected foreign countries.

We have never been profitable and have incurred net losses in each year since inception. Our net losses were $16.6 million and $7.4 million for the three months ended March 31, 2016 and 2015, respectively. As of March 31, 2016 we had an accumulated deficit of $115.1 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. As of March 31, 2016, we had $134.0 million of cash and cash equivalents.

Overview of Sickle Cell Disease

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

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RBCs travel from the lung through blood vessels. Hemoglobin, the oxygen-carrying protein inside RBCs, releases oxygen at the tissues. In SCD, when oxygen is released at the tissues, HbS becomes sticky and aggregates into polymers, or long, rigid rods within an RBC, much like a sword within a balloon. The RBC assumes a sickled shape and becomes inflexible, which can cause blockage in small blood vessels. These polymers destroy RBCs and block blood flow, resulting in decreased oxygen delivery to tissues. 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. A 2014 publication noted that in the United States, SCD resulted in a shortened patient life expectancy by approximately 25 to 30 years even with available therapies.

Current treatment options for SCD are limited to hydroxyurea, or HU, blood transfusions and bone marrow transplantation. The utilization of these treatments is significantly limited due to their 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;
- 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.

Our Product Candidate

GBT440 s therapeutic approach was inspired by the natural activity of fetal hemoglobin, or HbF. HbF, which is present during fetal development and in early infancy until it is replaced with adult hemoglobin, 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 polymerization, and thereby prevents hemoglobin polymers from forming.

GBT440 is a novel, investigational drug that increases hemoglobin s affinity for oxygen by binding to the alpha-chain of hemoglobin. GBT440 has been observed to keep a proportion of sickle hemoglobin in its oxygenated state, which cannot participate in polymerization. Similar to HbF, by diluting total HbS with a proportion of GBT440-bound hemoglobin, GBT440 prevents hemoglobin polymer formation.

In December 2014, we initiated our randomized, placebo-controlled, double-blind, single and multiple ascending dose Phase 1/2 clinical trial of GBT440 in healthy subjects and subjects with SCD. The study is being conducted in three parts: 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

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days in SCD subjects). We are evaluating the safety, tolerability, pharmacokinetics, or PK, and pharmacodynamics, or PD, of GBT440, as well as exploratory markers of SCD activity, including anti-hemolytic effects and SCD-related clinical effects. We reported initial results from our Phase 1/2 clinical trial at the American Society of Hematology meeting in December 2015, and additional results from this trial at the European Hematological Association (EHA) meeting in June 2016. We believe the observations from the trial to date demonstrate a favorable safety profile and pharmaceutical properties, and the potential for GBT440 to serve as a disease-modifying therapy for SCD. In the third quarter of 2016, we intend to engage in discussions with U.S. and European regulatory authorities to define the future development plan for GBT440. In 2015, the FDA granted Fast Track Designation and Orphan Drug Designation for GBT440 for the treatment of SCD.

Market Opportunity in SCD

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 90,000 to 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. The global incidence of SCD is estimated to be 250,000 to 300,000 births annually. One study estimated 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 cost exceeds $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.

Given a concentrated prescriber base for SCD and the small number of key opinion leaders who significantly influence the treatments for this patient population, we intend to promote GBT440 with a specialty sales force in the United States and Europe. We are also evaluating options for commercializing GBT440 in other significant markets due to the concentration of SCD patient populations in sub-Saharan Africa, the Middle East, South Asia and Latin America.

Additional Opportunities

Beyond SCD, building on data from preclinical models of hypoxemia, we initiated clinical sites which began screening for a Phase 2a clinical trial in IPF in June 2016, and we expect to initiate a Phase 2b clinical trial of GBT440 in a hypoxemic pulmonary disorder in the second half of 2016. Results from these clinical trials will guide further clinical development in IPF, as well as other chronic and acute hypoxemic pulmonary disorders. A 2012 publication estimated that there are approximately 90,000 patients with IPF in the United States.

Additionally, in 2015, we nominated GBT018713, a proprietary, small molecule kallikrein inhibitor, for development as an orally administered therapy intended for the prevention of HAE attacks. All currently marketed therapeutics for HAE must be administered intravenously or by subcutaneous injection. As a result, we believe that the availability of a safe and effective oral agent targeting a validated mechanism that prevents HAE attacks would have the potential to transform the treatment paradigm for this disease. We plan to complete toxicology studies to enable the filing of an IND application, and subject to submission and clearance of the IND, we expect to initiate a Phase 1 study for GBT018713 in early 2017.

Management

We have assembled a team of employees, directors and scientific founders 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 team has contributed to 18 drug approvals,

including Avastin, CellCept, Herceptin, INTEGRILIN, Kaletra, Kyprolis and Rituxan. We intend to leverage this expertise and experience to rapidly pursue the development of GBT440 and any other product candidates we may identify and develop.

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Our Strategy

Our strategy is to use our expertise in blood biology to build a multi-product company leading in the discovery, development and commercialization of novel medicines for grievous blood-based disorders. Key elements of our strategy include to:

- rapidly advance GBT440 for the treatment of SCD;
- explore the clinical development of GBT440 in IPF patients with hypoxemia, as well as in other chronic and acute hypoxemic pulmonary disorders;
- submit an Investigational New Drug application, or IND, and initiate clinical development for an oral kallikrein inhibitor in HAE; and
- evaluate opportunities to expand the scope of our product offerings.

Financial Overview

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. Our operating expenses increased during the first quarter of 2016 and we expect that they will increase during the remainder of 2016 and beyond, particularly as we continue the development of GBT440 in SCD, including the possible initiation of clinical trials in pediatric patients and pivotal clinical trials in adults and adolescents in the second half of 2016, and as we initiate clinical trials of GBT440 in IPF in the second quarter of 2016.

Our Development Pipeline

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

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Risks Associated with Our Business

Our ability to implement our business strategy is subject to numerous risks that you should be aware of before making an investment decision. These risks are described more fully in the section entitled Risk Factors in this prospectus. These risks include, among others:

- We are a clinical development-stage company with a limited operating history, have incurred significant losses since our inception, and anticipate that we will continue to incur significant losses for the foreseeable future;
- Even if this offering is successful, we will need to raise additional funding before we can expect to generate any revenues from product sales;
- If we are unable to obtain regulatory approval for GBT440 or any other product candidates that we may identify or develop, our business will be substantially harmed;
- We are heavily dependent upon the success of GBT440, which is in the early stages of clinical development;
- Results of earlier studies may not be predictive of future clinical trial results, and we may fail to establish an adequate safety or efficacy profile to conduct advanced clinical trials or obtain regulatory approval for GBT440 or any other product candidates that we may pursue;
- If we are unable to obtain and maintain sufficient intellectual property protection for GBT440, our technologies, or any future product candidates, we may not be able to compete effectively in our markets; and
- Our future success depends in part upon our ability to retain our key employees, consultants and advisors and to attract, retain and motivate other qualified personnel.

Implications of Being an Emerging Growth Company

We qualify as an emerging growth company as defined in the Jumpstart Our Business Startups Act of 2012, as amended, or the JOBS Act. As an emerging growth company, we have elected to take advantage of specified reduced disclosure and other requirements that are otherwise applicable generally to public companies. These provisions include:

- reduced disclosure about our executive compensation arrangements;

- no non-binding advisory votes on executive compensation or golden parachute arrangements; and

- exemption from the auditor attestation requirement in the assessment of our internal control over financial reporting.

We may take advantage of these exemptions for up to five years from our initial public offering or such earlier time that we are no longer an emerging growth company. We would cease to be an emerging growth company on the date that is the earliest of (i) the last day of the fiscal year in which we have total annual gross revenues of $1.0 billion or more; (ii) December 31, 2020; (iii) the date on which we have issued more than $1.0 billion in nonconvertible debt during the previous three years; or (iv) the last day of the fiscal year in which we are deemed to be a large accelerated filer under the rules of the Securities and Exchange Commission, or SEC, which means the market value of our common stock that is held by non-affiliates exceeds $700 million as of the prior June 30th. We may choose to take advantage of some but not all of these exemptions. We have taken advantage of reduced reporting requirements in this prospectus. Accordingly, the information contained herein may be different from the information you receive from other public companies in which you hold stock. Also, we have irrevocably elected to opt out of the exemption for the delayed adoption of certain accounting standards and, therefore, will be subject to the same new or revised accounting standards as other public companies that are not emerging growth companies.

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Corporate History and Information

We were incorporated under the laws of the State of Delaware in February 2011. Our principal executive office is located at 400 East Jamie Court, Suite 101, South San Francisco, California, and our telephone number is (650) 741-7700. Our website address is *www.globalbloodtx.com*. We do not incorporate the information on or accessible through our website into this prospectus, and you should not consider any information on, or that can be accessed through, our website as part of this prospectus.

We use various trademarks and trade names in our business, including without limitation our corporate name and logo. All other trademarks or trade names referred to in this prospectus are the property of their respective owners. Solely for convenience, the trademarks and trade names in this prospectus may be referred to without the ® and symbols, but such references should not be construed as any indicator that their respective owners will not assert, to the fullest extent under applicable law, their rights thereto.

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THE OFFERING

Common stock offered by us	6,400,000 shares
Common stock to be outstanding after this offering	35,936,449 shares
Underwriters option	We have granted the underwriters an option to purchase a maximum of 960,000 additional shares of common stock from us. The underwriters can exercise this option at any time within 30 days from the date of this prospectus.
Use of Proceeds	We estimate that we will receive net proceeds from the sale of shares of our common stock in this offering of approximately $112.3 million, or $129.2 million if the underwriters fully exercise their option to purchase additional shares, and after deducting underwriting discounts and commissions and estimated offering expenses payable by us. We intend to use the net proceeds from this offering and our existing cash and cash equivalents to fund our clinical development of GBT440 for the treatment of SCD, including the completion of our ongoing Phase 1/2 clinical trial, planned clinical pharmacology studies and through the initiation of a pivotal clinical trial, our planned clinical trials of GBT440 for the treatment of IPF and other hypoxemic pulmonary disorders, our completion and filing of an IND and commencement of clinical development of GBT018713 for the treatment of HAE, our other research and development activities, and for working capital and general corporate purposes. See Use of Proceeds for additional information.
Risk Factors	You should read carefully Risk Factors beginning on page 11 and other information included in, or incorporated by reference into, this prospectus for a discussion of factors that you should consider before deciding to invest in shares of our common stock.
NASDAQ Global Select Market symbol	GBT

The number of shares of common stock to be outstanding after this offering is based on 29,536,449 shares of common stock outstanding as of March 31, 2016 and excludes:

- 2,487,374 shares of common stock issuable upon exercise of outstanding options as of March 31, 2016 at a weighted average exercise price of $9.67 per share;

992,176 shares of restricted common stock which were subject to our right of repurchase as of March 31, 2016;

115,900 shares of common stock issuable upon exercise of options granted subsequent to March 31, 2016 at a weighted-average exercise price of $19.38 per share;

2,379,284 shares of common stock reserved for future issuance under our 2015 Stock Option and Incentive Plan, or the 2015 Plan, as of March 31, 2016; and

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112,100 shares of common stock reserved for future issuance under our 2015 Employee Stock Purchase Plan, or the 2015 ESPP, as of March 31, 2016.

Except as otherwise indicated, all information in this prospectus assumes no exercise by the underwriters of their option to purchase an additional 960,000 shares of our common stock in this offering.

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SUMMARY FINANCIAL DATA

The following tables present summary financial data for our business. We derived the following statements of operations data for the years ended December 31, 2015, 2014 and 2013 from our audited financial statements. We derived the statements of operations data for the three months ended March 31, 2016 and 2015 and the balance sheet data as of March 31, 2016 from our unaudited interim condensed financial statements. We have prepared the unaudited interim condensed financial statements on the same basis as our audited financial statements and, in the opinion of management, they reflect all adjustments, consisting only of normal recurring adjustments, that are necessary for the fair statement of our unaudited interim condensed financial statements. Our historical results are not necessarily indicative of the results that may be expected in the future, and our interim results are not necessarily indicative of the results to be expected for the full year or any other period. You should read this data together with the section titled Selected Quarterly Financial Information (unaudited) in our Annual Report on Form 10-K for the year ended December 31, 2015, the sections titled Management s Discussion and Analysis of Financial Condition and Results of Operations in our Annual Report on Form 10-K for the year ended December 31, 2015 and our Quarterly Report on Form 10-Q for the quarter ended March 31, 2016, and our financial statements and related notes included therein, each of which is incorporated by reference in this prospectus.

	Year Ended December 31,			Three Months Ended March 31,	
	2015	2014	2013	2016	2015
				(unaudited)	
	(in thousands, except share and per share data)				
Summary of Operations Data:					
Operating expenses:					
Research and development	$ 36,657	$ 16,324	$ 12,855	$ 12,415	$ 6,069
General and administrative	9,671	3,855	2,309	4,302	1,298
Related party expenses	65	332	499		53
Total operating expenses	46,393	20,511	15,663	16,717	7,420
Loss from operations	(46,393)	(20,511)	(15,663)	(16,717)	(7,420)
Change in fair value of Series A redeemable convertible preferred stock liability		(297)	(2,455)		
Interest income	33	1	2	117	3
Net loss	$ (46,360)	$ (20,807)	$ (18,116)	$ (16,600)	$ (7,417)
Net loss attributable to common stockholders	$ (50,540)	$ (23,772)	$ (19,851)	$ (16,600)	$ (8,657)
Net loss per share attributable to common stockholders, basic and diluted [1]	$ (3.95)	$ (14.20)	$ (16.14)	$ (0.56)	$ (4.22)
	12,806,697	1,673,919	1,230,241	29,441,404	2,052,874

Weighted-average number of shares used in computing net loss per share attributable to common stockholders, basic and diluted [(1)]	

(1) See Notes 2 and 13 to our audited financial statements and Notes 2 and 7 to our unaudited interim condensed financial statements incorporated by reference in this prospectus from our Annual Report on Form 10-K for the year ended December 31, 2015 and our Quarterly Report on Form 10-Q for the quarter ended March 31, 2016, respectively, for an explanation of the calculations of our basic and diluted net loss per share attributable to common stockholders and the weighted-average number of shares used in the computation of the per share amounts.

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	As of March 31, 2016	
	Actual	As Adjusted [1]
	(unaudited) (in thousands)	
Balance Sheet Data:		
Cash and cash equivalents	$ 133,984	$ 246,234
Working capital	125,043	237,293
Total assets	138,971	251,221
Additional paid-in capital	241,157	353,401
Accumulated deficit	(115,065)	(115,065)
Total stockholders equity	126,122	238,372

(1) The as adjusted column reflects the sale by us of 6,400,000 shares of our common stock in this offering at the public offering price of $18.75 per share, after deducting underwriting discounts and commissions and estimated offering expenses payable by us.

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RISK FACTORS

Investing in our common stock involves a high degree of risk. You should consider carefully the following risks, together with all the other information included and incorporated by reference in this prospectus, including our financial statements and notes thereto, before you invest in our common stock. If any of the following risks actually materializes, our operating results, financial condition and liquidity could be materially adversely affected. As a result, the trading price of our common stock could decline and you could lose all or part of your investment.

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, GBT440, which is our only product candidate in clinical development.

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, 2015, 2014 and 2013 were $46.4 million, $20.8 million and $18.1 million, respectively. Our net losses for the three months ended March 31, 2016 and 2015 were $16.6 million and $7.4 million, respectively. As of March 31, 2016, we had an accumulated deficit of $115.1 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 GBT440 in clinical development;
- establish and maintain manufacturing and supply relationships with third parties that can provide adequate supplies (in amount and quality) of GBT440 to support further clinical development and, if approved, commercialization;
- seek and obtain regulatory and marketing approvals for GBT440;
- build a sales and marketing organization or enter into selected collaborations to commercialize GBT440, if approved;

advance our other programs, including our programs for the clinical investigation of GBT440 in idiopathic pulmonary fibrosis (IPF) patients with hypoxemia and the development of a proprietary kallikrein inhibitor as an orally administered therapy intended for the prevention of hereditary angioedema (HAE) attacks, through preclinical and clinical development and commence development activities for any additional product candidates we may identify; and

expand our organization to support our research, development 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 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 achieve sustained profitability would depress the value of our company and could impair our ability to raise capital, expand our business, diversify our

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research and development pipeline, market GBT440 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.

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 GBT440 through clinical development and conducting preclinical research activities in our other programs. 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 GBT440 and other product candidates that we may identify and pursue in clinical trials. As of March 31, 2016, we had working capital of $125.0 million and capital resources consisting of cash and cash equivalents of $134.0 million. 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 GBT440 and any future product candidates.

In August 2015, we sold 6,900,000 shares of common stock in our initial public offering, or IPO, the net proceeds of which totaled $126.2 million, after deducting underwriting discounts and commissions and offering expenses incurred by us. We expect that our existing cash and cash equivalents will be sufficient to fund our operations through mid-2017. However, 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 GBT440 and 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 complete our ongoing clinical trial that we characterize as a Phase 1/2 trial of GBT440, to initiate and complete any registrational clinical trials of GBT440 and to pursue regulatory approvals for GBT440, and the costs of post-marketing studies that could be required by regulatory authorities;

- the progress and results of our Phase 1/2 clinical trial of GBT440;

- the progress, timing, scope and costs of our nonclinical studies, clinical trials and other related activities, including the ability to enroll subjects in a timely manner for our Phase 1/2 clinical trial of GBT440 and potential future clinical trials;

the costs of obtaining clinical and commercial supplies of GBT440 and any other product candidates we may identify and develop;

our ability to advance our other programs, including our program for the clinical investigation of GBT440 in IPF patients with hypoxemia and the development of a proprietary kallikrein inhibitor as an orally administered therapy intended for the prevention of HAE attacks, through preclinical and clinical development, and the timing and scope of these development activities;

our ability to successfully commercialize GBT440 and any other product candidates we may identify and develop;

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the manufacturing, selling and marketing costs associated with GBT440 and any other product candidates we may identify and develop, including the cost and timing of establishing our sales and marketing capabilities;

the amount and timing of sales and other revenues from GBT440 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;

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 the clinical development of GBT440 in SCD or one or more of our other research or development programs or the commercialization of any product candidates 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 GBT440 or any other 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 GBT440, and it is possible that neither GBT440 nor any other product candidates we may seek to develop in the future will ever obtain regulatory approval.

Applications for GBT440 or any other product candidates we may develop could fail to receive regulatory approval for many reasons, including but not limited to:

our inability to demonstrate to the satisfaction of the FDA or comparable foreign regulatory authorities that GBT440 or any other product candidate we may develop is safe and effective for each of its intended indications;

the FDA or comparable foreign regulatory authorities may disagree with our plans regarding the pathways for approval or the design or implementation of our clinical trials;

the population studied in the clinical program may not be sufficiently broad or representative to assure safety in the full population for which we seek approval;

the FDA or comparable foreign regulatory authorities may require additional preclinical studies or clinical trials beyond those we anticipate;

the FDA or comparable foreign regulatory authorities may disagree with our interpretation of data from nonclinical studies or clinical trials;

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- the data collected from clinical trials of GBT440 and 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 other submission for regulatory approval in the United States or elsewhere;

- 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 fail to approve the manufacturing processes, test procedures and specifications, or facilities of third-party manufacturers with which we contract for clinical and commercial supplies; and

- the approval policies or regulations of the FDA or comparable foreign regulatory authorities may change in a manner that renders our clinical trial design or data insufficient for approval.

The lengthy approval process, as well as the unpredictability of the results of clinical trials, may result in our failing to obtain regulatory approval to market GBT440 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.

We are heavily dependent on the success of our lead product candidate, GBT440, and all of our other programs are still in the preclinical development stage. If we are unable to successfully complete clinical development, obtain regulatory approval for, or commercialize GBT440, 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 preclinical and clinical development of GBT440, including conducting preclinical studies and clinical trials and providing general and administrative support for these operations. Our future success is dependent on our ability to successfully develop, obtain regulatory approval for, and commercialize GBT440. Before we can generate any revenues from sales of GBT440, we will be required to conduct additional clinical development, including, among other things, additional toxicology studies that may be required before we can conduct longer-term clinical trials and a larger registrational clinical trial if our ongoing clinical trial of GBT440 is successful, seek and obtain regulatory approval, secure adequate manufacturing supply to support larger clinical trials and commercial sales and build a commercial organization. Further, the success of GBT440 will depend on patent and trade secret protection, acceptance of GBT440 by patients, the medical community and third-party payors, its ability to compete with other therapies, healthcare coverage and reimbursement, and maintenance of an acceptable safety profile following approval, among other factors. If we do not achieve one or more of these factors in a timely manner or at all, we could experience significant delays or an inability to successfully commercialize GBT440, which would materially harm our business. GBT440 is currently our only product candidate to have advanced into what we characterize as a Phase 1/2 clinical trial, and it may be years before GBT440 can advance into a registrational study, if at all. All of our other programs are in an early stage of research and development. Although we have nominated for Investigational New Drug application, or IND, enabling toxicology studies a novel, small molecule, orally available kallikrein inhibitor product candidate for the prevention of angioedema attacks associated with HAE, the data generated in these studies may not be adequate to support the filing of an IND or for clinical evaluation, and we have not yet selected any other product candidates that would enable the filing of an IND. We cannot be certain that GBT440 will be successful in clinical trials or receive regulatory approval. If we do not receive regulatory approval for, or otherwise fail to successfully commercialize, GBT440 or any other product candidate, we may need to spend significant additional time and resources to identify other product candidates, advance them through preclinical and clinical development and apply for regulatory approvals, which

would adversely affect our business, prospects, financial condition and results of operations.

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The development of GBT440 as a potential disease-modifying anti-sickling agent represents a novel therapeutic approach to SCD treatment, and there is a risk that the outcome of our clinical trials will not be favorable.

We have concentrated our therapeutic product research and development efforts on developing novel, mechanism-based therapeutics for the treatment of grievous blood-based disorders with significant unmet need, including SCD, and our future success depends on the successful development of this therapeutic approach. The clinical trial requirements of the FDA and other regulatory agencies and the criteria these regulators use to determine the safety and efficacy of a product candidate vary substantially according to the type, complexity, novelty and intended use and market of the potential product. At the moment, there is only one approved therapy for SCD, hydroxyurea, and there are no approved therapeutics 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 that targets this mechanism in SCD are subject to unknown risks, and we may experience setbacks with our ongoing or planned clinical trials of GBT440 because of the limited clinical experience with its mechanism of action in SCD patients. In particular, regulatory authorities in the United States have not issued definitive guidance as to how to measure and achieve efficacy in SCD. Although we are evaluating exploratory endpoints, including anti-sickling and anti-hemolytic effects, changes in hemoglobin levels, and reticulocyte counts, for GBT440 in our Phase 1/2 clinical trial, regulators have not determined that such data signifies a clinically meaningful result in SCD patients or can support advancement into registrational trials or regulatory approval. We may not achieve our pre-specified endpoints in our Phase 1/2 clinical trial or in other clinical trials where there is limited or no regulatory guidance regarding appropriate clinical endpoints, which would decrease the probability of obtaining marketing approval for GBT440 or any other product candidate we may develop. Any inability to design clinical trials with protocols and endpoints acceptable to applicable regulatory authorities, and to obtain regulatory approvals for GBT440 and 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 GBT440 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 and preclinical studies and clinical trials of GBT440 and other 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 do not necessarily predict final results. For example, our preclinical studies and clinical trials of GBT440 to date have involved only one genotype of SCD, HbSS, and the results of these studies may not be replicated in other genotypes of SCD or in subsequent clinical trials. Additionally, any positive results generated in our Phase 1/2 clinical trial of GBT440 in adults would not ensure that we will achieve similar results in larger, registrational clinical trials or in clinical trials of GBT440 in pediatric populations or in other indications, such as hypoxemic pulmonary disorders. In addition, preclinical and clinical data are often susceptible to various interpretations and analyses, and many companies that have believed their product candidates performed satisfactorily in preclinical studies and clinical trials have nonetheless failed to obtain marketing approval. Product candidates in later stages of clinical trials 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. Even if early stage clinical trials are successful, we may need to conduct additional clinical trials for product candidates in additional patient populations or under different treatment conditions before we are able to seek approvals from the FDA and regulatory authorities outside the United States to market and sell these product candidates. Our failure to demonstrate the required characteristics to support marketing approval for GBT440 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.

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Before we are able to submit GBT440 for marketing approval, the FDA and comparable foreign regulatory authorities will require that we conduct additional clinical trials and may impose additional requirements, the scope of which are not known at this time.

Before we can submit an NDA to the FDA for GBT440, we must successfully complete our ongoing clinical trial and one or more additional larger clinical trials. The FDA typically requires at least two pivotal, well-controlled clinical trials as a condition to the submission of an NDA and does not consider a single 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 patient reported outcomes and a confirmatory study would have been difficult to conduct on ethical grounds. Although we characterize our current clinical trial of GBT440 as a Phase 1/2 clinical trial because it is designed to evaluate exploratory endpoints that we believe may be clinically relevant to SCD patients, it is possible that, even if we achieve favorable results in our first clinical trial of GBT440, the FDA may require us to conduct one or more additional clinical trials, possibly involving a larger sample size or a different clinical trial design, before we can initiate a pivotal trial. The FDA may also require that we conduct additional toxicology studies before evaluating GBT440 in longer term clinical trials or impose a longer follow-up period for subjects treated with GBT440 prior to accepting an NDA submission.

It is possible that the FDA or the comparable foreign authorities may not consider the results of our ongoing and planned clinical trials to be sufficient for approval of GBT440 for SCD or IPF. If the FDA or comparable foreign regulatory authorities require additional clinical trials or data beyond that which we currently anticipate, we would incur increased costs and 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 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 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 our product candidates.

Before obtaining marketing approval from regulatory authorities for the sale of our product candidates, we must conduct extensive clinical trials to demonstrate the safety and efficacy of the product candidates in humans. Clinical testing is expensive, time-consuming and uncertain as to the outcome. We cannot guarantee that any clinical trials 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 in reaching, or any failure to reach, a consensus with regulatory agencies on study design;

- delays in reaching, or any failure to reach, 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, approval at 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 regulatory agencies, after an inspection of our clinical trial operations or study sites;

failure by our CROs, other third parties or us to adhere to clinical trial, regulatory or legal requirements;

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failure to perform in accordance with the FDA s good clinical practices, or GCP, or applicable regulatory guidelines in other countries;

delays in the testing, validation, manufacturing and delivery of sufficient quantities of our product candidates to the clinical sites;

delays in having patients complete participation in a study or return for post-treatment follow-up;

clinical trial sites or patients 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;

occurrence of serious adverse events or other safety concerns associated with the product candidate that are viewed to outweigh its potential benefits; or

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

We could also encounter delays if a clinical trial is suspended or terminated by us, by the IRBs 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. Such authorities may suspend or terminate a clinical trial due to a number of factors, including failure to conduct the clinical trial in accordance with regulatory requirements or our clinical protocols, inspection of the clinical trial operations or trial site by the FDA or other regulatory authorities resulting in the imposition of a clinical hold, unforeseen safety issues or adverse side effects, and failure to demonstrate a benefit from using a drug. In addition, if we make manufacturing or formulation changes to our product candidates, we may need to conduct additional studies to bridge our modified product candidates to earlier versions.

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 and jeopardize our ability to obtain regulatory approvals, 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 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 the regulatory approvals necessary to commercialize our product candidates.

Identifying and qualifying patients to participate in our ongoing and planned clinical trials of GBT440 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. Accordingly, there are limited patient pools from which to draw for clinical trials. For example, according to CDC estimates, the prevalence of SCD, for which GBT440 is being studied, is 90,000 to 100,000 individuals in the United States. Although genetic screening for SCD is mandatory for newborns in the United States, we may not be able to identify, recruit, and enroll a sufficient number of subjects to complete our clinical trials of GBT440 because of the perceived risks and benefits of GBT440, 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. Further, if subjects in our clinical trials fail to comply with our dosing regimens, we may not be able to generate clinical data acceptable to the FDA in our trials. If patients are unwilling to participate in our studies for any reason, the timeline for recruiting subjects, conducting studies and obtaining regulatory approval of potential products may be delayed.

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If we experience difficulties or delays in enrollment or are otherwise unable to successfully complete any clinical trial of GBT440 or our other product candidates, our costs may 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 a sample of the potential patient population. Our Phase 1/2 clinical trial of GBT440 is designed to enroll between 96 and 128 subjects. Any rare and severe side effects of GBT440 may be uncovered only in later stages of our Phase 1/2 trial or only in any larger, subsequent trials that we may conduct. 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 preclinical toxicology study with GBT440 in non-humans and clinical trials involving other hemoglobin modifiers have shown a decrease in oxygen delivery to tissue when the percentage of modified hemoglobin is significant. Hemoglobin modifiers, by increasing HbS s affinity for oxygen, can cause a shift in oxygen levels, potentially resulting in tissue hypoxia. If GBT440 or any product candidates that we may develop are associated with tissue hypoxia or undesirable side effects in clinical trials or have characteristics that are unexpected, we may need to abandon their development or limit their development to more narrow uses or subpopulations in which the undesirable side effects or other characteristics are less prevalent, less severe or more acceptable from a risk-benefit perspective, which could adversely affect our business, prospects, financial condition and results of operations.

Although we intend to pursue expedited regulatory approval pathways for GBT440, it may not qualify for expedited development or, if it does qualify for expedited development, it may not actually lead to a faster development or regulatory review or approval process.

Although we believe there may be an opportunity to accelerate the development of GBT440 through one or more of the FDA s expedited programs, such as fast track, breakthrough therapy, accelerated approval or priority review, and we intend to pursue one or more of these expedited programs, we cannot be assured that GBT440 or any other product candidates that we may develop will qualify for such programs.

In October 2015, the FDA designated our investigation of GBT440 for the treatment of SCD as a Fast Track development program. Fast Track is a process designated to facilitate the development and expedite the review of drugs to treat serious conditions and that 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 approval for GBT440 will occur on an expedited basis.

In addition, a drug may be eligible for designation 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. Although breakthrough designation or access to any other expedited program may expedite the development or approval process, it does not change the standards for approval. If we apply for breakthrough therapy designation or any other expedited program for GBT440, the FDA may determine that GBT440, our proposed target indication or other aspects of our clinical development plans do not qualify for such expedited program. Even if we are successful in obtaining a breakthrough therapy designation or access to any other expedited program, we may not experience faster development timelines or achieve faster review or approval compared to conventional FDA procedures.

Furthermore, access to an expedited program may also be withdrawn by the FDA if it believes that the designation is no longer supported by data from our clinical development program. Additionally, qualification for Fast Track or any other expedited review procedure does not ensure that we will ultimately obtain regulatory approval for GBT440 or any other product candidate that we may develop in a timely manner, or at all.

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Although the FDA has granted orphan drug designation to GBT440 for the treatment of SCD, we may not receive orphan drug designation for GBT440 in other jurisdictions or for other indications that we may pursue, or for 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 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 European Medicines Agency, or EMA, grants orphan drug designation to promote the development of 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 (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 is authorized or, if a method exists, the product would be of significant benefit to those affected by the condition. In December 2015, the FDA granted orphan drug designation for GBT440 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 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 has granted orphan drug designation to GBT440 for the treatment of SCD, we may apply for orphan drug designation for GBT440 in other jurisdictions or for other indications, or for other product candidates we may develop, and applicable regulatory authorities may not grant us these additional designations. In addition, the exclusivity granted under any orphan drug designations that we have received or may receive may not effectively protect the product candidate from competition because different drugs can be approved for the same condition. 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, in that it is shown to be safer, more effective or makes a major contribution to patient care. 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.

Even if we receive regulatory approval for GBT440 or any other product candidate that we may develop, we will be subject to ongoing regulatory obligations and scrutiny and may be subject to product labeling and other post-marketing restrictions.

Even if a product candidate is approved, regulatory authorities may still impose significant restrictions on its indicated uses or marketing or impose ongoing requirements for potentially costly post-marketing studies. Furthermore, any new legislation addressing drug safety issues could result in delays or increased costs to assure compliance. If GBT440 or any other product candidates that we may develop are approved, they will each be subject to 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 our product candidates. For example, the

development of GBT440 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 the desired age ranges, our business may 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. As such, we and our contract manufacturers are subject to continual review and periodic inspections to assess compliance with cGMP 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 to comply with requirements concerning advertising and promotion for our products. The timing of our obligation to report adverse events would be triggered by the date we become aware of the adverse event as well as the nature of the event. We may fail to report adverse events we become aware of within the prescribed timeframe. We may also fail to appreciate that we have become aware of a reportable adverse event, especially if it is not reported to us as an adverse event or if it is an adverse event that is unexpected or removed in time from the use of our products. Promotional communications with respect to prescription drugs are subject to a variety of legal and regulatory restrictions and must be consistent with the information in the product s approved label. As such, we may not promote our products for indications or uses for which they do not have FDA approval.

If a regulatory agency discovers previously unknown problems with a product, such as adverse events of unanticipated severity or frequency, or problems with the facility where the product is manufactured, or disagrees with the promotion, marketing, or labeling of a product, a regulatory agency may impose restrictions or sanctions on that product or us, including requiring withdrawal of the product from the market. If we fail to comply with applicable regulatory requirements, a regulatory agency or enforcement authority may:

- issue untitled or warning letters;
- impose civil or criminal penalties;
- impose injunctions;
- suspend regulatory approval;
- suspend any of our ongoing clinical trials;
- impose product recalls and 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.

Any government investigation of alleged violations of law could require us to expend significant time and resources in response, and could generate negative publicity. Any failure to comply with ongoing regulatory requirements may significantly and adversely affect our ability to commercialize and generate revenues from GBT440 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 harmed.

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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 CRO who monitors our Phase 1/2 clinical trial of GBT440, to monitor and manage data for some of our ongoing nonclinical and all of our clinical programs. We rely on these parties for execution of our 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 cGMP or GCP, and Good Laboratory Practices, or GLP, 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, and other contractors. If we or any of our CROs or 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 approval process.

In addition, the execution of preclinical studies and clinical trials, and the subsequent compilation and analysis of the data produced, 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 as little as 30 days prior written notice of a material breach by us that is not cured within 30 days. Many of these agreements may also be terminated by such third parties under certain other circumstances, including our failure to comply with applicable laws. If any of our relationships with our third-party CROs terminates, we may not be able to enter into arrangements with alternative CROs or do so on commercially reasonable terms. In addition, our CROs are not our employees, and except for remedies available to us under our agreements with such CROs, we cannot control whether they devote sufficient time and resources to our programs. Furthermore, these third party CROs may also have relationships with other entities, some of which may be our competitors. If CROs 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 they obtain is compromised due to the failure to adhere to our protocols, regulatory requirements, or for other reasons, our development activities may be extended, delayed, or terminated and we may not be able to obtain regulatory approval for or successfully commercialize our product candidates. Switching or adding CROs involves additional cost, time and management resources and focus. CROs may also generate higher costs than anticipated.

Accordingly, our dependence on third-party CROs and other 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 our product candidates for preclinical studies and clinical trials and expect to continue to do so for commercialization. Our business could be harmed if those third parties fail to provide us with sufficient quantities of drug product, or fail to do so at acceptable quality 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 Phase 1/2 clinical trial of GBT440 or any future clinical trials that we may conduct, and we

lack the resources to manufacture any of our product candidates on a commercial scale. We rely, and expect to continue to rely, on third-party manufacturers to produce our product candidates for our clinical trials, as well as for commercial manufacture if any of our product candidates receives marketing

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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 also expect to rely on third parties for the manufacture of commercial supplies of GBT440 or any other product candidates, if approved.

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

- reliance on the third party for regulatory compliance and quality assurance;
- the possible breach of the manufacturing agreement by the third party;
- the possible misappropriation of our proprietary information, including our trade secrets and know-how; and
- the possible termination or non-renewal of the agreement by the third party at a time that is costly or inconvenient for us.

Furthermore, all of our contract manufacturers are engaged with other companies to supply and/or manufacture materials or products for such companies, which exposes our manufacturers to regulatory risks for the production of such materials and products. As a result, failure to meet the regulatory requirements for the production of those materials and products may affect the regulatory clearance of our contract manufacturers facilities generally. If the FDA or a comparable foreign regulatory agency does not approve these facilities for the manufacture of our product candidates or if any agency withdraws its approval in the future, we may need to find alternative manufacturing facilities, which would negatively impact our ability to develop, obtain regulatory approval for or market our product candidates, if approved.

GBT440 and any future product candidates that we may develop 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. We are currently manufacturing GBT440 through third parties and have adequate supplies to conduct our ongoing Phase 1/2 clinical trial, but we have not yet begun to produce the clinical supply of GBT440 for any larger registrational trials that we may conduct. 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 commercialization activities. Our current and anticipated future dependence upon others for the manufacturing of our product candidates or 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 our product candidates, 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 cGMP, 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 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 our product candidates.

We or our contract manufacturers must supply all necessary documentation in support of an NDA or MAA on a timely basis and must adhere to GLP and cGMP regulations enforced by the FDA and other regulatory agencies through their facilities inspection program. Some of our contract manufacturers have never produced a commercially approved pharmaceutical product and therefore have not obtained the requisite regulatory authority approvals to do so. 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 of our product candidates or any of our other potential products. In addition, the regulatory authorities may, at any time, audit or inspect a manufacturing facility involved with the preparation of our product candidates or our other potential products or the associated quality systems for compliance with the regulations applicable to the activities being conducted. 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 the regulatory requirements. If these facilities do not pass a pre-approval plant inspection, regulatory approval of the products may not be granted or may be substantially delayed until any violations are corrected to the satisfaction of the regulatory authority, if ever.

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

Additionally, if supply from one approved manufacturer is interrupted, an alternative manufacturer would need to be qualified through an NDA supplement or MAA variation, or equivalent foreign regulatory filing, which could result in further delay. The regulatory agencies may also require additional studies if a new manufacturer is relied upon for commercial production. Switching manufacturers may involve substantial costs and is likely to result in a delay in our desired clinical and commercial timelines.

These factors could cause 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, which increases the possibility that a competitor will discover them or that our trade secrets will be misappropriated or disclosed.

Because we rely on third parties to manufacture GBT440 and conduct other aspects of our clinical development activities, we must, at times, share trade secrets with them. We seek to protect our proprietary technology in part by entering into confidentiality agreements and, if applicable, material transfer agreements, collaborative research agreements, consulting agreements or other similar agreements with 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, such as trade secrets. Despite the contractual provisions employed when working with third parties, the need to share trade secrets and other confidential

information increases the risk that such trade secrets become known by our

competitors, are inadvertently incorporated into the technology of others, or are disclosed or used in violation of these agreements. Given that our proprietary position is based, in part, on our know-how and trade secrets, a competitor s discovery of our trade secrets or other unauthorized use or disclosure would impair our competitive position and may have a material adverse effect on our business.

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

Risks Related to Our 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 GBT440 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 we may exclusively license or own solely and jointly with others, particularly patents, in the United States and other countries with respect to our product candidates and technology. 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 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.

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 highly uncertain. Our pending and future patent applications may not result in patents being issued that protect our 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.

Moreover, we may be subject to a third-party preissuance submission of prior art to the United States Patent and Trademark Office, or 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 current or 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 recently 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, or the Leahy-Smith Act, enacted on September 16, 2011, the United States has moved to a first to file system. The Leahy-Smith Act also includes a number of significant changes that affect the way patent applications will be 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 act and new regulations on specific patents discussed herein have not been determined and would need to be reviewed. Accordingly, it is not clear what, if any, impact the Leahy-Smith Act will have on the operation of our business. However, the Leahy-Smith Act 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.

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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 GBT440 or any future product candidates that we may develop.

We cannot assure that GBT440 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 GBT440 or any 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 GBT440 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 intellectual property rights with respect to our 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 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 products 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 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 patent litigation in the United States, defendant counterclaims alleging invalidity and/or unenforceability are commonplace. Grounds for a validity challenge could be an alleged failure to meet any of several statutory requirements, including lack of novelty, obviousness, written description or non-enablement. Grounds for an unenforceability assertion could be an allegation that someone connected with prosecution of the patent withheld relevant information from the USPTO, or made a misleading statement, during prosecution. The outcome following legal assertions of invalidity and unenforceability is 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. Our defense of litigation or 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 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.

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. 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, in September 2015 we secured exclusive rights from the Regents of the University of California, or the Regents, for certain patents and patent applications that they jointly own related to GBT440 and GBT440 analogs. 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.

If we are unable to protect the confidentiality of our trade secrets, 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. 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.

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

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 outside the United States, or from selling or importing products made using our inventions in and into the United States or other jurisdictions. Competitors may use our technologies in jurisdictions where we have not obtained patent protection to develop their own products and may also export infringing products to territories where we have patent protection, but enforcement is not as strong as

that in the United States. These products may compete with our products and our patents or other intellectual property rights may not be effective or sufficient to prevent them from competing.

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Many companies have encountered significant problems in protecting and defending intellectual property rights in foreign jurisdictions. The legal systems of certain countries, particularly certain developing countries, do not favor the enforcement of patents, trade secrets, and other intellectual property protection, particularly those relating to biotechnology products, which could make it difficult for us to stop the infringement of our patents or marketing of competing products in violation of our proprietary rights generally. Proceedings to enforce our patent rights in foreign jurisdictions, 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.

Risks Related to Commercialization

Even if GBT440 or any other product candidate that we may develop receives marketing approval, their commercial success will depend upon the degree of market acceptance by physicians, patients, third-party payors and others in the medical community.

If GBT440 or other product candidates that we may pursue receives marketing approval, they may nonetheless fail to gain sufficient market acceptance by physicians, patients, third-party payors and others in the medical community. If our product candidates do 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 these target indications, also provide incremental health benefits to patients. 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 number of factors, including:

- the efficacy and potential advantages compared to alternative treatments, such as, in the case of GBT440, hydroxyurea;
- our ability to offer our drugs for sale at competitive prices;
- the convenience and ease of administration compared to alternative treatments, including future alternative treatments;
- the willingness of the target patient population to try new therapies and of physicians to prescribe these therapies;
- the availability of products and their ability to meet market demand, including a reliable supply for long-term daily treatment;

the strength of marketing and distribution support;

the availability of third-party coverage and adequate reimbursement;

the clinical indications for which the product is approved;

the prevalence and severity of any side effects and overall safety profile; and

any restrictions on the use of our drugs 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 when approved by health authorities.

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

have no marketing or sales organization. To successfully commercialize any products that may result from our development programs, we will need to develop these 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 expensive, difficult 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.

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 may be unable to compete successfully against these 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 and extent of reimbursement by governmental and private payors is essential for most patients to be able to afford expensive treatments, such as ours, 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 health maintenance, managed care, pharmacy benefit and similar healthcare management organizations, or reimbursed by government health administration authorities, private health coverage insurers and other third-party payors. 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 products. In the United States, the principal decisions about reimbursement for new medicines are typically 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 Medicaid or Medicare. However, 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 requires state agency approval to qualify a doctor s prescription for reimbursement.

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. 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.

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. 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.

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 EU, 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. If reimbursement of our product candidates is unavailable or limited in scope or amount, or if pricing is set at unsatisfactory levels, our business could be harmed, possibly materially, based on the large population of patients with SCD who reside in foreign countries.

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 initiatives to contain healthcare costs. For example, in March 2010, the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act, or the Health Care Reform Law, 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 Health Care Reform Law, among other things, 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 promoted a new Medicare Part D coverage gap discount program.

In addition, other legislative changes have been proposed and adopted in the United States since the Health Care Reform Law was enacted. On August 2, 2011, 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. This includes aggregate reductions of Medicare payments to providers up to 2% per fiscal year. On January 2,

2013, President Obama signed into law the American Taxpayer Relief Act of 2012, which, among other things, delayed for another two months the budget cuts mandated by these sequestration provisions of the Budget Control Act of 2011. On March 1, 2013, the President signed an executive order implementing sequestration, and on April 1, 2013, the 2% Medicare payment reductions went into effect. We expect that additional state and federal healthcare reform measures will be adopted in the future, any of which could limit the amounts that federal and state governments will pay for healthcare products and services, which could result in reduced demand for our product candidates or additional pricing pressures.

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 our product candidates, including those described in this prospectus under Business Competition. 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 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.

We focus our research and product development on treatments for chronic blood diseases, with an initial focus on SCD. Our projections of both the number of people who have these diseases, as well as the subset of people with these diseases who have the potential to benefit from treatment with our product candidates, are based on 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 these diseases. 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 each of 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. 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.

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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 and clinical 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 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 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 GBT440, 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. With the exception of GBT440, all of our other potential product candidates

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remain in the preclinical development stage. 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 or other characteristics that indicate it is unlikely to be effective or otherwise does not meet applicable regulatory criteria;
- 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 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 GBT440.

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 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 FDA warnings on product labels;

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; however, 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; however, 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 could subject us to costly litigation, require us to pay substantial amounts of money to injured patients, delay, negatively impact or end our opportunity to receive or maintain regulatory approval to market our product candidates, if approved, or require us to suspend or abandon our commercialization efforts of any approved product candidates. Even in a circumstance in which we do not believe that an adverse event is related to our products, the investigation into the circumstance may be time-consuming or inconclusive. These investigations 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 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 certain programs or product candidates or for indications that later prove to have greater commercial potential. 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 GBT440, 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 GBT440 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. We will face, to the extent that we decide to enter into collaboration agreements, significant competition in seeking appropriate collaborators. Whether we reach a definitive agreement for a 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 do so 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 our collaborators. Collaborators generally have significant discretion in determining the efforts and resources that they will apply to these 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, termination of the collaboration arrangement. These disagreements can be difficult to resolve if neither of the parties has final decision-making authority under the collaboration agreement. Collaborations with pharmaceutical or biotechnology companies and other third parties often are terminated or allowed to expire by the other party. Any such termination or expiration would adversely affect us financially and could harm our business reputation.

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.

We currently have no international operations, but our business strategy incorporates potential international expansion as we seek to obtain regulatory approval for, and commercialize, GBT440 in patient populations outside the United States. If GBT440 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:

multiple, conflicting, and changing laws and regulations such as privacy regulations, 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 use of our products in various countries;

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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 of these factors could significantly harm our future international expansion and operations and, consequently, our results of operations.

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

Our results of operations could be adversely affected by general conditions in the global economy and in the global financial markets which biotechnology companies such as ourselves rely upon for sources of capital. In the past, global financial crises caused extreme volatility and disruptions in the capital and credit markets. 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 suppliers, possibly resulting in supply disruption. 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.

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 CROs, CMOs, or other contractors or consultants, 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 CROs, CMOs, and other contractors and consultants are vulnerable to damage from computer viruses, unauthorized access, natural disasters, terrorism, war and telecommunication and electrical failures. While we have not experienced any such system failure, accident or security breach to date, 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 preclinical 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 and This Offering

If we fail to maintain proper and effective systems of disclosure controls and internal controls over financial reporting to the extent required under applicable regulations, 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, Section 404, or Section 404, of the Sarbanes-Oxley Act of 2002, or Sarbanes Oxley, and the rules and regulations of The NASDAQ Stock Market. Section 404 generally requires our management and independent registered public accounting firm to report on the effectiveness of our internal control over financial reporting. Company responsibilities required by Sarbanes Oxley include establishing and maintaining corporate oversight and adequate internal control over financial reporting and disclosure controls and procedures. Effective internal controls are necessary for us to produce reliable financial reports and are important to help prevent financial fraud.

Beginning with the annual report on Form 10-K for the fiscal year ending December 31, 2016, Section 404 requires an annual management assessment of the effectiveness of our internal control over financial reporting. Once we are no longer an emerging growth company under the JOBS Act or, if prior to such date, we opt to no longer take advantage of the applicable exemption, we will be required to include an opinion from our independent registered public accounting firm on the effectiveness of our internal control over financial reporting. We expect to incur substantial additional professional fees and internal costs to expand our accounting and finance functions and to expend significant management efforts in order to comply with these requirements. Previously we have never been required to test our internal controls within a specified period and, as a result, we may experience difficulty in meeting these reporting requirements in a timely manner.

To date, we have never conducted a review of our internal control over financial reporting for the purpose of providing the reports required by Section 404. In connection with the audit of our financial statements as of and for the years ended December 31, 2014 and 2013, we identified a material weakness in our internal control over financial reporting that related to a lack of sufficient number of qualified personnel within our accounting function to adequately segregate duties, a lack of sufficient review and approval of manual journal entries posted to the general ledger and a lack of adequate review procedures over general ledger account reconciliations. Although we have remediated this material weakness, during the course of our subsequent review and testing, we may identify additional material weaknesses or significant deficiencies and 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 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, as a public company we are required to file accurate and timely quarterly and annual reports with the SEC under the Exchange Act. Any failure to report our financial results on an accurate and timely basis could result in sanctions, lawsuits, delisting of our shares from The NASDAQ Global Select Market or other adverse consequences that would materially harm our business.

We are an emerging growth company, and will be able to avail ourselves of reduced disclosure requirements applicable to emerging growth companies, which could make our common stock less attractive to investors.

We are an emerging growth company as defined in the Jumpstart Our Business Startups Act of 2012, as amended, or the JOBS Act, and we have elected to take advantage of some of the exemptions from reporting requirements that are applicable to other public companies that are not emerging growth companies, including not being required to comply with the auditor attestation requirements of Section 404(b) of the Sarbanes-Oxley Act, reduced disclosure obligations regarding executive compensation in our periodic reports and proxy statements, and exemptions from the requirements of holding a nonbinding advisory vote on executive compensation and shareholder approval of any golden parachute payments not previously approved. We will remain an emerging growth company until the earliest of (1) December 31, 2020, (2) the last day of the fiscal year in which we have total annual gross revenue of at least $1.0 billion, (3) the last day of the fiscal year in which we are deemed to be a large accelerated filer, which means the market value of our common stock that is held by non-affiliates exceeds $700 million as of the prior June 30th and (4) the date on which we have issued more than $1.0 billion in non-convertible debt during the prior three-year period. We cannot predict if investors will find our common stock less attractive because we may rely on certain reporting exemptions available to emerging growth companies. If some investors find our common stock less attractive as a result, there may be a less active trading market for our common stock and our stock price may be more volatile.

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 IPO 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 our preclinical studies or clinical trials;
- reports of adverse events in other treatments for SCD or other indications that we may pursue, or clinical trials of such products;
- any delay in filing an IND or NDA for any of our 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 GBT440 or any other product candidates that we may develop;
- adverse regulatory decisions affecting our product candidates or development programs;

inability to obtain additional funding;

our failure to prosecute, maintain or enforce our intellectual property rights;

changes in laws or regulations applicable to future products;

inability to obtain adequate product supply for 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 strategic collaborations;

failure to meet or exceed any financial projections that we or the investment community may provide;

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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;

disputes or other developments relating to proprietary rights, including patents, litigation matters and our ability to obtain patent protection for our technologies;

additions or departures of key scientific or management personnel;

significant lawsuits, including patent or stockholder litigation;

changes in the market valuations of similar companies;

sales of our common stock by us or our stockholders in the future;

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

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; 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 revenue or operating results fall below the expectations of analysts or investors or below any forecasts we may provide to the market, or if the forecasts we provide to the market are below the expectations of analysts or investors, the price of our common stock could decline substantially. Such a stock price decline could occur even when we have met any previously publicly stated revenue and/or earnings guidance we may provide.

If you purchase our common stock in this offering, you will incur immediate and substantial dilution in the book value of your shares.

Investors purchasing shares of common stock in this offering will pay a price per share that substantially exceeds the pro forma book value per share of our tangible assets after subtracting our liabilities as of March 31, 2016. As a result, investors purchasing shares of common stock in this offering will incur immediate dilution of $12.12 per share, based on the public offering price of $18.75 per share.

Further, investors purchasing shares of common stock in this offering will contribute approximately 35% of the total amount invested by stockholders since our inception (or 38% of such total amount if the underwriters option is exercised), but will own only approximately 18% of the shares of common stock outstanding (or 20% of the shares of common stock outstanding if the underwriters option is exercised). For information on how the foregoing amounts were calculated, see Dilution.

This dilution is due to the substantially lower price paid by our investors who purchased shares prior to this offering as compared to the price offered to investors in this offering, and the exercise price of stock options granted to our employees. The exercise of any of these options would result in additional dilution. As a result of the dilution to investors purchasing shares in this offering, investors may receive significantly less than the purchase price paid in this offering, if anything, in the event of our liquidation.

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 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.

Pursuant to our 2015 Stock Option and Incentive Plan, or the 2015 Plan, we are authorized to grant stock options and other equity-based awards to our employees, directors and consultants. The number of shares available for future grant

under the 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, 50,000 shares of our common stock were initially reserved for future issuance pursuant to our 2015

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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 by the maximum amount each year, 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 affiliates. 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 and executive officers may in the future establish programmed selling plans under Rule 10b5-1 of the Securities Exchange Act of 1934, as amended, 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 69.1% of our outstanding voting stock as of May 31, 2016, based on the latest publicly available information and, upon closing of this offering, the same group will beneficially own approximately 57.3% of our outstanding voting stock. 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 will have broad discretion in the use of proceeds from this offering and may invest or spend the proceeds in ways with which you do not agree or in ways that ultimately may not increase the value of your investment.

We will have broad discretion over the use of proceeds from this offering. You may not agree with our decisions, and our use of the proceeds may not yield any return on your investment. We expect to use the net proceeds to us from this offering to continue the clinical development of GBT440, to fund the research and development of our other

programs, and for working capital and general corporate purposes. Our failure to apply the net proceeds from this offering effectively could compromise our ability to pursue our growth strategy and

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we might not be able to yield a significant return, if any, on our investment of these net proceeds. In addition, the net proceeds from this offering may not be sufficient for our anticipated uses, and we may need additional resources to progress our product candidates to the stage we expect. You will not have the opportunity to influence our decisions on how to use our net proceeds from this offering.

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 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

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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, however we do not believe that this ownership change 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 this 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.

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.

We will continue to incur significant costs as a result of operating as a public company, and our management will devote substantial time to compliance initiatives.

As a public company, we incur significant legal, accounting, and other expenses that we did not incur as a private company. In addition, the Sarbanes-Oxley Act, as well as rules subsequently implemented by the SEC and The NASDAQ Global Select Market have imposed various requirements on public companies. In July 2010, the Dodd-Frank Wall Street Reform and Consumer Protection Act, or the Dodd-Frank Act, was enacted. There are significant corporate governance and executive compensation related provisions in the Dodd-Frank Act that require the SEC to adopt additional rules and regulations in these areas such as say on pay and pay parity. Recent legislation permits smaller emerging growth companies to implement many of these requirements over a longer period and up to five years from the pricing of our IPO. We have elected to take advantage of this legislation but cannot guarantee that we will not be required to implement these requirements sooner than budgeted or planned and thereby incur unexpected expenses. Stockholder activism, the current political environment, and the current high level of government intervention and regulatory reform may lead to substantial new regulations and disclosure obligations, 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 these compliance initiatives. Moreover, these 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 the Sarbanes-Oxley Act and rules adopted by the SEC and by NASDAQ, would likely result in increased costs to us as we respond to their requirements.

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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. 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.

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CAUTIONARY NOTE REGARDING FORWARD-LOOKING STATEMENTS

This prospectus and the documents incorporated by reference contain 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. The forward-looking statements are contained principally in the sections titled Prospectus Summary, Risk Factors, Use of Proceeds, Management s Discussion and Analysis of Financial Condition and Results of Operations and Business in this prospectus or the documents incorporated by reference. We have made these statements in reliance on the safe harbor provisions of the Private Securities Litigation Reform Act of 1995. Although we believe that the expectations reflected in these forward-looking statements are reasonable, these statements relate to our strategy, future operations, future financial position, future revenue, projected costs, prospects, plans, objectives of management and expected market growth, and involve known and unknown risks, uncertainties and other factors that may cause our actual results, levels of activity, performance or achievements to be materially different from any future results, levels of activity, performance or achievements expressed or implied by these forward-looking statements. Forward-looking statements in this prospectus include, but are not limited to, statements about:

- our expected uses of the net proceeds to us from this offering;
- the timing and the success of our ongoing Phase 1/2 clinical trial of GBT440 in healthy adult subjects and SCD patients;
- the timing and success of our planned additional clinical trials of GBT440 in both SCD and IPF or other chronic and acute hypoxemic pulmonary disorders and of any other product candidates we may develop in our target indications;
- our ability to enroll patients in 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 GBT440 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 GBT440 or any other product candidates we may develop;
- our ability to advance our other programs, including our development of GBT018713 as an orally administered kallikrein inhibitor for the prevention of angioedema attacks associated with HAE, through preclinical and clinical development, and the timing and scope of these development activities;
- our expectation that our existing capital resources and the net proceeds from this offering will be sufficient to enable us to fund our planned development of GBT440, GBT018713 and any other product candidates we may identify and pursue;

the benefits of the use of GBT440 or any other product candidates we may identify and develop;

our ability to successfully commercialize GBT440 or any other product candidates we may identify and pursue, if approved;

the rate and degree of market acceptance of GBT440 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 GBT440 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;

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

our ability to manufacture GBT440 in conformity with the FDA s requirements and to scale up manufacturing of GBT440 to commercial scale;

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

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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 GBT440 or any other product candidates we may identify and pursue;

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

our expectations regarding the time during which we will be an emerging growth company under the JOBS Act;

our financial performance; and

developments and projections relating to our competitors or our industry.

In some cases, you can identify forward-looking statements by terminology such as may, will, should, expects, intends, plans, anticipates, believes, estimates, predicts, potential, continue or the negative of these tern comparable terminology. These statements are only predictions. You should not place undue reliance on forward-looking statements because they involve known and unknown risks, uncertainties and other factors, which are, in some cases, beyond our control and which could materially affect results. Factors that may cause actual results to differ materially from current expectations include, among other things, those listed under Risk Factors and elsewhere in this prospectus and the documents incorporated by reference. If one or more of these risks or uncertainties occur, or if our underlying assumptions prove to be incorrect, actual events or results may vary significantly from those implied or projected by the forward-looking statements. No forward-looking statement is a guarantee of future performance. You should read this prospectus and the documents that we reference in this prospectus and have filed with the SEC as exhibits to the registration statement, of which this prospectus is a part, completely and with the understanding that our actual future results may be materially different from any future results expressed or implied by these forward-looking statements.

The forward-looking statements in this prospectus and the documents incorporated by reference represent our views as of their respective dates. We anticipate that subsequent events and developments will cause our views to change. However, while we may elect to update these forward-looking statements at some point in the future, we assume no obligation to update or revise any forward-looking statements except to the extent required by applicable law. You should, therefore, not rely on these forward-looking statements as representing our views as of any date subsequent to

the dates on which they were made.

This prospectus and the documents incorporated by reference also contain 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.

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USE OF PROCEEDS

We estimate that our net proceeds from the sale of 6,400,000 shares of our common stock in this offering will be approximately $112.3 million, or $129.2 million if the underwriters exercise in full their option to purchase additional shares, after deducting underwriting discounts and commissions and estimated offering expenses payable by us.

As of March 31, 2016, we had cash and cash equivalents of approximately $134.0 million. We intend to use the net proceeds from this offering and our cash and cash equivalents on hand as follows:

- approximately $90.0 million to fund our development of GBT440 for the treatment of SCD, including the completion of our ongoing Phase 1/2 clinical trial, planned clinical pharmacology studies and through the initiation of a pivotal clinical trial;
- approximately $30.0 million to conduct clinical trials of GBT440 for the treatment of hypoxemic pulmonary disorders, including IPF;
- approximately $20.0 million to complete and file an IND and begin clinical development of GBT018713 for the treatment of HAE; and
- the remaining proceeds, if any, to fund new and ongoing research and development activities, working capital and other general corporate purposes, which may include funding for the hiring of additional personnel, capital expenditures and the costs of operating as a public company.

Based on our current plans, we believe our cash and cash equivalents, together with the net proceeds to us from this offering, will be sufficient to fund our operations for at least the next 12 months.

We may also use a portion of the net proceeds to in-license, acquire or invest in new businesses, technology or assets. Although we have no specific agreements, commitments or understandings with respect to any in-license or acquisition, we evaluate such opportunities and engage in related discussions with other business entities from time to time.

This expected use of the net proceeds from this offering represents our intentions based upon our current plans and business conditions. As of the date of this prospectus, we cannot predict with certainty all of the particular uses for the net proceeds to be received upon the completion of this offering or the amounts that we will actually spend on the uses set forth above. The amounts and timing of our actual expenditures and the extent of our preclinical and clinical development activities may vary significantly depending on numerous factors, including the progress of our development efforts, the status of and results from nonclinical studies and our ongoing clinical trials or any clinical trials we may commence in the future, our ability to take advantage of expedited programs or to obtain regulatory approval for GBT440 and any other product candidates we may identify and pursue, the timing and costs associated with the manufacture and supply of GBT440 and any other product candidates we may identify and pursue for clinical development or commercialization, and any unforeseen cash needs. As a result, our management will retain broad discretion over the allocation of the net proceeds from this offering.

Pending our use of the net proceeds from this offering, we intend to invest the net proceeds in a variety of capital preservation investments, including short-term, investment-grade, interest-bearing instruments and U.S. government securities.

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PRICE RANGE OF COMMON STOCK

Our common stock began trading on The NASDAQ Global Select Market under the symbol GBT on August 12, 2015. Prior to that time, there was no public market for our common stock. The following table sets forth the high and low sale prices per share of our common stock, as reported on The NASDAQ Global Select Market, for the periods indicated.

	High	Low
Year Ended December 31, 2015		
Third quarter (from August 12, 2015)	$ 57.00	$ 33.01
Fourth quarter	$ 55.74	$ 28.73

	High	Low
Year Ending December 31, 2016		
First quarter	$ 31.97	$ 12.24
Second quarter (through June 20, 2016)	$ 27.99	$ 15.10

On June 20, 2016, the last reported sale price of our common stock as reported on The NASDAQ Global Select Market was $18.94 per share. As of June 17, 2016, we had approximately 23 holders of record of our common stock. The actual number of stockholders is greater than this number of record holders and includes stockholders who are beneficial owners but whose shares are held in street name by brokers and other nominees. This number of holders of record also does not include stockholders whose shares may be held in trust by other entities.

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DIVIDEND POLICY

We have never declared or paid dividends on our capital stock. We do not anticipate paying any dividends on our capital stock in the foreseeable future. We currently intend to retain all available funds and any future earnings to fund the development and growth of our business. Any future determination to declare dividends will be subject to the discretion of our board of directors and will depend on various factors, including applicable laws, our results of operations, financial condition, future prospects and any other factors deemed relevant by our board of directors. Investors should not purchase our common stock with the expectation of receiving cash dividends.

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CAPITALIZATION

The following table sets forth our cash and cash equivalents and capitalization as of March 31, 2016:

- on an actual basis; and
- on an as adjusted basis to give further effect to the sale of 6,400,000 shares of common stock in this offering at the public offering price of $18.75 per share, after deducting the underwriting discounts and commissions and estimated offering expenses payable by us.

You should read this information together with our audited financial statements and related notes appearing the sections entitled Management s Discussion and Analysis of Financial Condition and Results of Operations in our Annual Report on Form 10-K for the year ended December 31, 2015 and our Quarterly Report on Form 10-Q for the quarter ended March 31, 2016, and our financial statements and related notes therein, each of which is incorporated by reference herein.

	As of March 31, 2016	
	Actual	As Adjusted
	(unaudited)	
	(in thousands, except share and per share data)	
Cash and cash equivalents	$ 133,984	$ 246,234
Stockholders equity:		
Preferred stock, $0.001 par value; 5,000,000 shares authorized, no shares issued and outstanding, actual; no shares issued and outstanding, as adjusted		
Common stock, $0.001 par value per share; 150,000,000 shares authorized; 29,536,449 shares issued and outstanding, actual; 35,936,449 shares issued and outstanding, as adjusted	30	36
Additional paid-in capital	241,157	353,401
Accumulated deficit	(115,065)	(115,065)
Total stockholders equity	126,122	238,372
Total capitalization	$ 126,122	$ 238,372

The number of shares of common stock issued and outstanding actual and as adjusted in the table above excludes the following:

- 2,487,374 shares of our common stock issuable upon the exercise of stock options to purchase common stock that were outstanding as of March 31, 2016, with a weighted average exercise price of $9.67 per share;

992,176 shares of restricted common stock which were subject to our right of repurchase as of March 31, 2016;

115,900 shares of common stock issuable upon exercise of options granted subsequent to March 31, 2016 at a weighted-average exercise price of $19.38 per share;

2,379,284 shares of common stock reserved for future issuance under the 2015 Plan, as of March 31, 2016; and

112,100 shares of common stock reserved for future issuance under the 2015 ESPP as of March 31, 2016.

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DILUTION

If you invest in our common stock in this offering, your ownership interest will be diluted to the extent of the difference between the public offering price per share of our common stock and the as adjusted net tangible book value per share of our common stock immediately after this offering.

Net tangible book value per share is determined by dividing our total tangible assets less our total liabilities by the number of shares of common stock outstanding. Our historical net tangible book value as of March 31, 2016 was $126.1 million, or $4.27 per share.

Net tangible book value dilution per share to new investors represents the difference between the amount per share paid by purchasers of shares of common stock in this offering and the as adjusted net tangible book value per share of common stock immediately after completion of this offering. After giving effect to our sale of 6,400,000 shares of common stock in this offering at the public offering price of $18.75 per share, and after deducting underwriting discounts and commissions and estimated offering expenses payable by us, our as adjusted net tangible book value as of March 31, 2016 would have been $238.4 million, or $6.63 per share. This represents an immediate increase in as adjusted net tangible book value of $2.36 per share attributable to new investors and an immediate dilution in net tangible book value of $12.12 per share to purchasers of common stock in this offering at the public offering price, as illustrated in the following table:

Public offering price per share		$ 18.75
Historical net tangible book value per share as of March 31, 2016	$ 4.27	
Increase in net tangible book value per share attributable to new investors	2.36	
As adjusted net tangible book value per share after this offering		6.63
Dilution per share to investors participating in this offering		$ 12.12

If the underwriters option to purchase additional shares from us is exercised in full, the as adjusted net tangible book value per share after this offering would be $6.92 per share, the increase in as adjusted net tangible book value per share attributable to new investors would be $2.65 per share and the dilution to new investors purchasing shares in this offering would be $11.83 per share.

The following table summarizes, as of March 31, 2016, on an as adjusted basis described above, the number of shares of our common stock, the total consideration and the average price per share (i) paid to us by existing stockholders and (ii) to be paid by new investors purchasing shares of common stock in this offering at the public offering price of $18.75 per share, before deducting underwriting discounts and commissions and estimated offering expenses payable by us (in thousands, except shares, per share amounts and percentages):

	Shares Purchased		Total Consideration		Average Price per Share
	Number	Percent	Amount	Percent	
Existing stockholders	29,536,449	82%	$ 225,183	65%	$ 7.62
New investors	6,400,000	18	120,000	35	18.75

Totals	35,936,449	100%	$ 345,183	100%	$ 9.61

The foregoing calculations exclude the following shares as of March 31, 2016:

2,487,374 shares of our common stock issuable upon the exercise of stock options to purchase common stock that were outstanding as of March 31, 2016, with a weighted average exercise price of $9.67 per share;

992,176 shares of restricted common stock which are subject to our right of repurchase;

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115,900 shares of common stock issuable upon exercise of options granted subsequent to March 31, 2016 at a weighted-average exercise price of $19.38 per share;

2,379,284 shares of common stock reserved for issuance pursuant to future awards under the 2015 Plan; and

112,100 shares of common stock reserved for future issuance under the 2015 ESPP.

To the extent that any outstanding options are exercised, new options are issued under our stock-based compensation plans or we issue additional shares of common stock in the future, there will be further dilution to investors participating in this offering. To the extent that additional capital is raised through the sale of equity or convertible debt securities, the issuance of these securities may result in further dilution to our stockholders.

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BUSINESS

Overview

We are a clinical-stage biopharmaceutical company dedicated to discovering, developing and commercializing novel therapeutics to treat grievous blood-based disorders with significant unmet need. We are developing our initial product candidate, GBT440, as an oral, once-daily therapy for sickle cell disease, or SCD, and are currently evaluating GBT440 in SCD subjects in an ongoing Phase 1/2 clinical trial. SCD is a genetic disease 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. GBT440 inhibits abnormal hemoglobin polymerization, the underlying mechanism of RBC sickling. In our clinical trials of GBT440 in SCD subjects, we observed reduced markers of red blood cell destruction, improvements in anemia, improvements in markers of tissue oxygenation, reduced numbers of sickled RBCs, and reduced markers of inflammation. In addition to GBT440 for the treatment of SCD, we intend to evaluate GBT440 for the treatment of hypoxemic pulmonary disorders. In June 2016, we initiated clinical sites which began screening for a Phase 2a clinical trial of GBT440 in idiopathic pulmonary fibrosis, or IPF, and we expect to initiate a Phase 2b clinical trial of GBT440 in a hypoxemic pulmonary disorder in the second half of 2016. We are also engaged in other research and development activities targeted towards hereditary angioedema, or HAE. In 2015, we nominated GBT018713, a proprietary, small molecule kallikrein inhibitor, for development as an orally administered therapy intended for the prevention of HAE attacks. We plan to complete toxicology studies to enable the filing of an Investigational New Drug (IND) application, and subject to submission and effectiveness of the IND, we expect to initiate a Phase 1 clinical trial for GBT018713 in early 2017. We own or jointly own and have exclusively licensed rights to our portfolio of product candidates in the United States, Europe and other major markets. We own two issued U.S. patents that cover the composition of matter and method of use for GBT440, which are due to expire in 2032 and 2034 respectively, (absent any applicable patent term extensions), and we own or co-own additional pending patent applications in the United States and selected foreign countries.

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, the oxygen carrying protein inside red blood cells, releases oxygen at the tissues. In SCD, when oxygen is released at the tissues, HbS becomes sticky and aggregates into polymers, or long, rigid rods within an RBC, much like a sword within a balloon. The RBC assumes a sickled shape and becomes inflexible, which can cause blockage in small blood vessels. These polymers destroy RBCs and block blood flow, resulting in decreased oxygen delivery to tissues. 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. A 2014 publication noted that in the United States, SCD resulted in a shortened patient life expectancy by approximately 25 to 30 years even with available therapies.

Current treatment options for SCD are limited to hydroxyurea, or HU, blood transfusions and bone marrow transplantation. The utilization of these treatments is significantly limited due to their 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;

prevents or reduces the episodes or crises of severe pain associated with SCD;

modifies the long-term course of the disease;

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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.

GBT440 s therapeutic approach was inspired by the natural activity of fetal hemoglobin, or HbF. HbF, which is present during fetal development and in early infancy until it is replaced with adult hemoglobin, 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 polymerization, and thereby prevents hemoglobin polymers from forming.

GBT440 is a novel, investigational drug that increases hemoglobin s affinity for oxygen by binding to the alpha-chain of hemoglobin. GBT440 has been observed to keep a proportion of sickle hemoglobin in its oxygenated state, which cannot participate in polymerization. Similar to HbF, by diluting total HbS with a proportion of GBT440-bound hemoglobin, GBT440 prevents hemoglobin polymer formation.

In December 2014, we initiated our randomized, placebo-controlled, double-blind, single and multiple ascending dose Phase 1/2 clinical trial of GBT440 in healthy subjects and subjects with SCD. The study is being conducted in three parts: 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 SCD subjects), as illustrated in the figure below. We are evaluating the safety, tolerability, pharmacokinetics, or PK, and pharmacodynamics, or PD, of GBT440, as well as exploratory markers of SCD activity, including anti-hemolytic effects and SCD-related clinical effects.

Cohort = 8 subjects (6 active, 2 placebo)*

**** Except SCD subjects in Part B: 500mg cohort (10 active:4 placebo); 700mg cohort (12 active:4 placebo)***

We reported initial results from our Phase 1/2 clinical trial at the American Society of Hematology meeting in December 2015, and additional results from this clinical trial at the European Hematological Association

(EHA) meeting in June 2016. Among the 34 SCD subjects who received multiple doses of GBT440 (1000mg, 700mg or 500mg per day), a hematologic response to therapy was demonstrated in 100% of the subjects as evidenced by improvements in one or more markers of hemolysis and anemia (hemoglobin, unconjugated bilirubin and percentage reticulocyte counts). Furthermore, marked reductions in irreversibly sickled cells in the peripheral blood were observed in all cohorts from baseline (Day -1) to Day 28. Subjects treated for 90 days showed sustained improvement in bilirubin and percentage reticulocyte counts, continued reductions in sickled RBCs and a median 1.1 g/dL increase in hemoglobin. GBT440 s pharmacological mechanism of action and linear, dose-proportional pharmacokinetics were demonstrated in this study. Additionally, GBT440 was well tolerated through 90 days of dosing; the most common treatment-related adverse events were mild to moderate headaches and gastrointestinal disorders which were observed in numerically higher frequencies in the placebo arms in comparison to the GBT440 treated arms. We believe the initial observations from this trial demonstrate a favorable safety profile and pharmaceutical properties, and the potential for GBT440 to serve as a disease-modifying therapy for SCD. In the third quarter of 2016, we intend to engage in discussions with U.S. and European regulatory authorities to define the future development plan for GBT440. In 2015, the FDA granted Fast Track Designation and Orphan Drug Designation for GBT440 for the treatment of SCD.

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 90,000 to 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. The global incidence of SCD is estimated to be 250,000 to 300,000 births annually. One study estimated 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.

Beyond SCD, building on data from preclinical models of hypoxemia, we initiated clinical sites which began screening for a Phase 2a clinical trial in IPF in June 2016, and we expect to initiate a Phase 2b clinical trial of GBT440 in a hypoxemic pulmonary disorder in the second half of 2016. Results from these clinical trials will guide further clinical development in IPF, as well as other chronic and acute hypoxemic pulmonary disorders.

Additionally, in 2015 we nominated GBT018713, a proprietary, small molecule kallikrein inhibitor, for development as an orally administered therapy intended for the prevention of hereditary angioedema, or HAE, attacks. All currently marketed therapeutics for HAE must be administered intravenously or by subcutaneous injection. As a result, we believe that the availability of an oral agent targeting a validated mechanism that prevents HAE attacks would have the potential to transform the treatment paradigm for this disease. We plan to complete toxicology studies to enable the filing of an Investigational New Drug (IND) application, submit an IND, and expect to initiate a Phase 1 study for GBT018713 in early 2017.

To execute on this opportunity, 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 18 drug approvals, including Avastin, CellCept, Herceptin, INTEGRILIN, Kaletra, Kyprolis and Rituxan. We intend to leverage this expertise and experience to rapidly advance the development of GBT440 for SCD, determine the potential of GBT440 in hypoxemic pulmonary disorders initially in IPF, pursue an IND filing for GBT18713 in HAE, and advance other product candidates that we may identify and develop.

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Our Development Pipeline

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

GBT440 for the Treatment of Sickle Cell Disease

We are developing GBT440 as a once-daily, oral therapy for patients with SCD. We are investigating GBT440 s potential to inhibit the abnormal polymerization of hemoglobin, which is the underlying mechanism of red blood cell sickling and leads to the associated complications that characterize SCD. We have designed a clinical program for GBT440 targeted at the treatment of adults, adolescents, children and infants across all SCD genotypes. In December 2014, we initiated our first clinical trial of GBT440, in which we are evaluating GBT440 in both healthy subjects and SCD subjects. Because we have designed this trial to assess safety and tolerability, as well as PK, PD and other exploratory endpoints, including anti-hemolytic and anti-sickling effects, we characterize the trial as a Phase 1/2 clinical trial.

Sickle Cell Disease Overview

SCD is a grievous disease that can lead to hemolytic anemia (the destruction of RBCs within blood vessels), vaso-occlusion (blocked blood flow to tissues), 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 (a medical emergency due to refractory penile erection) and premature death. A 2014 publication noted that in the United States SCD results in a decrease of approximately 25 to 30 years in life expectancy.

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 sickle hemoglobin, or HbS. Hemoglobin is a protein in RBCs that carries oxygen from the lungs to the body s tissues and returns carbon dioxide from the tissues back to the lungs. Hemoglobin accomplishes this diametric function by binding and then releasing oxygen through allosterism, a process by which the hemoglobin molecule changes 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. Oxyhemoglobin, the high oxygen affinity form of hemoglobin, is formed in the lungs during respiration, when oxygen binds to the

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hemoglobin molecule, while 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 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 elongated 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; and

HbS/ßthal, where one gene is HbS, and the other is Beta thalassemia.

Market Opportunity in SCD

The CDC estimates the prevalence of SCD at 90,000 to 100,000 individuals in the United States. 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. The global incidence of SCD is estimated to be 250,000 to 300,000 births annually. SCD patient populations are primarily concentrated in sub-Saharan Africa, the Middle East, South Asia and Latin America.

SCD is a standard part of mandatory newborn screening in the United States. 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 mechanism, GBT440 may show activity across all SCD genotypes, although all of the subjects studied to date have involved the HbSS genotype.

SCD is associated with high treatment costs. One study estimated that in the United States, the average annual cost for the care of an adult HbSS SCD patient exceeds $200,000 and the cumulative lifetime cost exceeds $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 and effective 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. HU, 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. HU is the only therapeutic approved for SCD, and there is no approved therapeutic for SCD in pediatric patients in the United States. The use of HU is significantly limited by its side effect profile, variable patient responses and concerns of long-term toxicity. HU s side effects include impairment of fertility and the suppression of white blood cells (neutropenia) and platelets (thrombocytopenia), which place patients at risk for infection and bleeding.

In addition to HU treatment, another option for SCD patients is transfusions with normal blood. Blood transfusions, however, 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 HU, 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;
- 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.

Overview of Hemoglobin Biology and GBT440 s Mechanism of Action

As described above, hemoglobin accomplishes its diametric function of transporting oxygen from the lungs to the body s tissues and returning 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

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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 GBT440, bind to hemoglobin, resulting in increased oxygen affinity. The effect of these compounds on the measured OEC is a shift of the curve to the left on the horizontal axis, as shown in the graph below. 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 GBT440.

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, could potentially delay the polymerization of HbS and prevent the sickling of RBCs, which may be able to ameliorate many, if not all, of the clinical manifestations of this disease. 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 GBT440.

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, GBT440 would need to bind to only approximately 10-30% of the total hemoglobin in a patient s blood. One theoretical concern with increasing the affinity of hemoglobin for oxygen, however, is that excessive oxygen affinity could prevent hemoglobin from releasing oxygen into the tissues, thus causing hypoxia. Based on HbF data, our animal toxicology studies, and our ongoing clinical trial data, we believe our target modification of the total hemoglobin in a patient s blood would not adversely compromise oxygen delivery to the tissues.

Furthermore, earlier generation compounds provide proof of concept that hemoglobin modification results in clinical benefit. For example, oral cyanate was developed in the early 1970s for the treatment of SCD. Cyanate reacts in a carbamylation reaction with the amino-terminal valine of both the alpha and beta chains of hemoglobin. This inhibits polymerization of HbS by increasing hemoglobin oxygen affinity. In a study of 31 patients, a dose that resulted in greater than 0.3 mole of carbamyl group per mole of Hb tetramer resulted in a mean increase in Hb of 1.1 g/dL over a mean observation period of 11 months. One subject who achieved high

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carbamylation levels (>0.9 moles per Hb tetramer) experienced a p50 decrease from 32.5 to 24 mmHg, >3 g/dL rise in hemoglobin with a marked decrease in serum bilirubin (2.6 to 1.0 mg/dL) and reticulocyte counts (16% to 2%) over a 10-week period. A retrospective analysis of the frequency of crisis revealed a decrease from 3.6 to 2.1 crises per year between the two groups of patients with low (<0.3 mole of carbamyl group per mole of Hb tetramer) and high (³0.3 mole) carbamylation. Due to the toxicity of this compound, however, which resulted in anorexia, weight loss and neuropathy, this treatment strategy was abandoned. In 1976, an attempt to ameliorate SCD in 8 subjects over two years was investigated using weekly extracorporeal carbamylation with sodium cyanate. Over a three-month period, a stable level of 35-50% of circulating RBCs was carbamylated. The mean whole blood P50 declined from 33 to 26 mmHg, and the mean hemoglobin level increased from 6.4 to 9.1 g/dL. Absolute decreases in reticulocytes and ISCs of 58% and 65%, respectively, were observed. The mean red cell life span increased to 21.6 days compared to pretreatment life span of 13.2 days. Importantly, the improvement in hematologic parameters translated into clinical benefit with an 80% drop in severe sickle pain crises. Additionally, three subjects with chronic leg ulcers and one with frequent priapism experienced complete resolution. While extracorporeal RBC carbamylation with sodium cyanate is too arduous for routine clinical practice, we believe these data provide additional proof of concept for a hemoglobin modifier that prevents deoxyHbS polymerization in SCD.

Ongoing Phase 1/2 Clinical Trial of GBT440

In December 2014, we initiated our first clinical trial of GBT440, a randomized, placebo-controlled, double-blind, single and multiple ascending dose study in which we are evaluating the safety, tolerability, PK and PD of GBT440 in both healthy subjects and subjects with SCD. We refer to this trial as study GBT440-001. The trial is currently being conducted at Guy s Hospital in London, United Kingdom, and is designed to enroll between 96 and 128 subjects, randomized 6: 2 (GBT440:placebo) in approximately 16 cohorts. The study is being conducted in three parts: 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 SCD subjects). We also intend to evaluate exploratory markers of SCD activity, including anti-hemolytic effects, and SCD-related clinical effects. We are evaluating GBT440 s ability to prevent the hemolysis or destruction of RBCs in SCD subjects by measuring the blood levels of bilirubin and LDH, as well as reticulocyte counts. Hemoglobin and LDH are released when RBCs undergo hemolysis, with hemoglobin being metabolized to bilirubin; reticulocytes are young RBCs that are released by the bone marrow in response to the ongoing hemolysis. Since LDH is generally more variable because it is released from tissues other than RBCs and measures only intravascular hemolysis whereas SCD hemolysis is primarily extravascular, we believe that lower levels of bilirubin and reduced reticulocyte counts represent potential markers for decreased hemolysis. We believe that findings of anti-sickling activity may translate into an improvement in anemia and may indicate a decrease in RBC damage and an improvement in RBC function which could lead to a reduction in or prevention of the downstream effects such as pain episodes, leg ulcers and organ damage associated with RBC sickling in SCD patients. We anticipate that some of the data generated in this Phase 1/2 clinical trial could be used to support early proof-of-concept regarding the anti-sickling and clinical benefit of GBT440 in SCD patients.

We reported initial results from our Phase 1/2 clinical trial at the American Society of Hematology meeting in December 2015 and additional data at the European Hematology Association (EHA) meeting in June 2016, both of which are detailed below. As of the most recent data cut on June 2, 2016 in preparation for EHA, we have dosed 48 subjects in the Part A single dose administration cohorts: 40 healthy volunteers (30 of whom received GBT440 and ten of whom received placebo) and eight SCD subjects (six of whom received GBT440 and two of whom received placebo). Additionally, in the Part B multiple dose administration cohorts, we have dosed 62 subjects, comprised of 24 healthy volunteers (18 of whom received GBT440 and six of whom received placebo) and 38 SCD subjects (28 of whom received GBT440 and 10 of whom received placebo). All 24 healthy volunteers (in three dose cohorts) have completed 15-day dosing (18 of whom received GBT440 and six of whom received placebo). In 38 SCD subjects, three GBT440 dose levels have been administered for 28 days: 16 subjects have received 700 mg (12 of whom

received GBT440 and four of whom received placebo); 14 subjects have received 500 mg (10 of whom received GBT440 and four of whom received placebo) and eight subjects

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have received 1000 mg (six of whom received GBT440 and two of whom received placebo). We initiated the first cohort in the Part C 90-day dose administration in SCD subjects in December 2015 and presented these data at EHA. In this 90 day cohort, six subjects received 700 mg of GBT440 and two subjects received placebo. A second 90 day cohort is currently ongoing, in which six of eight subjects have received 900 mg of GBT440 or placebo. Additionally, one subject with SCD has been enrolled in an ongoing cohort of subjects with HbSC or HbS/ß+thalassemia. Subjects in this cohort will receive 600 mg of GBT or placebo for 28 days.

Overall, a total of 177 subjects, including 137 healthy subjects and 40 SCD subjects, have been administered single or multiple doses of GBT440 across six clinical studies. A total of 88 subjects (48 healthy subjects and 40 SCD subjects) have received GBT440 in the Phase 1/2 clinical trial, GBT440-001. In addition to the ongoing Phase 1/2 clinical trial, there are five clinical pharmacology studies ongoing, in which a total of 89 healthy subjects have received GBT440. Overall, the most commonly reported adverse events (AEs) regardless of treatment causality, across SCD subjects included headache, back pain, pain, cough, diarrhea, rhinitis, fatigue, rash and sickle cell crisis. For subjects treated with GBT440, none of the sickle cell crises occurred while subjects were being treated with GBT440. Of these AEs, the most common treatment related AEs include headache and gastrointestinal disorders. Headaches have occurred with similar incidence in both GBT440 (41%) and placebo-treated (67%) subjects. To date, no drug-related serious adverse events, or SAEs, have been reported. No SAEs were reported in the single dose cohorts or in healthy subjects who received multiple doses of GBT440. A total of nine SAEs were reported in SCD subjects in the multiple dose cohorts. Seven of the reported SAEs were sickle cell crises which occurred after completion of the treatment period (during follow-up) and one event of infection with hemolysis occurred during treatment; all of these were considered by the investigator to be unrelated or unlikely to be related to the study drug, and all were consistent with SCD (sickle cell anemia with crisis or infection with hemolysis). One of these SAEs involving a sickle cell crisis requiring hospitalization was reported in a placebo subject. Additionally, one event of an ovarian cyst occurred after completion of the treatment period (during follow-up) and was considered by the investigator to be unrelated to the study drug.

No subjects in the single dose cohorts discontinued study drug due to an AE. Two healthy subjects who received multiple doses of GBT440 experienced adverse events leading to dose discontinuation; one subject discontinued the study drug on Day 12 due to a Grade 1/mild generalized rash and one subject discontinued study drug on Day 7 due to a Grade 2/moderate headache; the events in both subjects resolved without treatment. Two SCD subjects had dose reductions. One subject in the 28-day 700 mg GBT440 cohort had a dose reduction on Day 11 to 400 mg (due to the events of Grade 1 disturbance in attention, abdominal pain and nausea). One subject in the 28-day 500 mg GBT440 cohort had a dose reduction to 300 mg on Day 10 (after one day of dose interruption) and then from 300 to 200 mg on Day 17; this was due to a rapid rise in Hb (Hb increase of approximately 2 g/dL over approximately 7 days) that met the protocol-defined criteria for dose reduction. The subject was clinically well with no signs or symptoms of blood hyperviscosity and had decreasing reticulocytes and erythropoietin, consistent with improved oxygen delivery to tissues. Additionally, one SCD subject in the 28-day 1000 mg GBT440 cohort developed a Grade 2 rash on Day 14 which led to study drug discontinuation. This event appeared as a maculopapular rash on upper and lower extremities, face, neck, and trunk with no lymphadenopathy nor fever. The event was treated with an oral antihistamine and resolved within four days.

The pharmacokinetic data from SCD subjects shows a dose proportional increase in GBT440 exposure following single and multiple dosing. The half-life was observed to be approximately 2.8 days in healthy subjects and 1.6 days in SCD subjects. We believe the shorter half-life in SCD subjects may be due to higher RBC turnover and/or anemia in SCD patients.

Among the 28 SCD subjects who received multiple doses of GBT440 (1000mg, 700mg or 500mg per day), a hematologic response to therapy was demonstrated in 100% of the subjects as evidenced by significant improvements in one or more clinical markers of hemolysis and anemia (hemoglobin, unconjugated bilirubin, reticulocyte count).

Furthermore marked reductions in sickled RBCs in the peripheral blood were observed in all cohorts from baseline (Day -1) to Day 28. There was no evidence of tissue hypoxia; trends to erythropoietin reduction in 500 mg and 700 mg cohorts and the reduction in reticulocyte counts in all cohorts are consistent

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with an improvement in tissue oxygen delivery. The erythropoietin levels were transiently elevated in the 1000 mg (500 mg administered twice a day) cohort. The cause is unclear but the cardiopulmonary exercise testing in these subjects did not suggest impairment in oxygen consumption based on VO2 max measurements.

The change in the hematologic parameters from baseline to Day 28 are shown in the table below. Due to the high variability in the LDH levels, the maximum change during the 28-day treatment period is shown.

Change from baseline to Day 28 **(median, 25th and 75th percentile)**	**500mg qd** **n=10**	**700mg qd** **n=12**	**lOOOmg** **(500mg bid)** **n=5**	**Placebo** **(pooled)** **n=12**
Unconjugated bilirubin (%)	-30.6 (-48.9, -15.4)	-42.6 (-44.3, -23.8)	-56.3 (-57.8, -47.1)	2.0 (-24.6, 9.9)
Lactate dehydrogenase (%)	-19.8 (-39.0, 6.2)	-11.9 (-30.1, -5.7)	-12.4 (-20.2, -12.2)	-4.8 (-13.1, -2.3)
% Reticulocytes (%)	-31.2 (-48.9, -20.8)	-37.0 (-52.6, -4.5)	-49.9 (-64.3, -34.4)	9.0 (1.7, 13.8)
Hemoglobin (g/dL)	0.4 (0.1, 0.7)	0.7 (0.5, 1.0)	0.0 (-0.4, 0.3)	-0.1 (-0.3, 0.4)
Irreversibly sickled cells (%)	-56.4 (-70.2, -26.2)	-45.9 (-93.0, -6.0)	-45.7 (-57.9, 5.9)	8.4 (-11.9, 16.8)

Subjects treated for 90 days showed sustained improvement in bilirubin, reticulocyte and ISC counts, and a greater increase in hemoglobin than at day 28 as shown in the table below.

Change from baseline to Day 90 **(median, 25th and 75th percentile)**	**700mg qd** **n=6**	**Placebo** **n=2**
Unconjugated bilirubin (%)	-37.2 (-43.4, -23.7)	18.5 (16.2, 20.8)
Lactate dehydrogenase (%)	0.8 (-14.7. 1.1)	7.2 (1.2, 13.2)
% Reticulocytes	-21.0 (-32.9, -18.1)	22.3 (5.7, 38.8)
Hemoglobin (g/dL)	1.1	-0.2

	(0.6, 1.3)	(-0.3, 0)
Irreversibly sickled cells (%)	-67.4*	13.2
	(-76.6, -58.6)	(9.9, 16.5)

* n=5 at Day 90

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A representative image of the peripheral blood in a patient treated with GBT440 at baseline and Day 90 and a graph of sickle cell counts over 90 days are shown in the figure below.

We believe the expanding clinical evidence demonstrating that GBT440 was well tolerated over 90 days of dosing and that GBT440 inhibits irreversibly sickled cells, improves hemolytic anemia, and reduces RBC damage continues to support the potential for GBT440 to serve as a disease-modifying therapy for SCD. We are currently enrolling SCD subjects in the final cohort, 900 mg for 90 days, to corroborate our clinical findings. We expect to receive data from these additional subjects in the second half of 2016. In addition, we anticipate initiating a PK study in pediatric subjects with SCD in the first half of 2016.

Subsequent Clinical and Regulatory Path for GBT440

Based upon the data from the multiple cohorts of our Phase 1/2 clinical trial in SCD subjects we intend to engage in discussions with U.S. and European regulatory authorities to define the future development plan for GBT440. The objectives of these regulatory interactions will include discussion of study design for additional clinical trials, trial endpoints and the development of GBT440 in other patient populations, including pediatrics.

We believe GBT440 may hold significant potential for SCD patients and could become the first mechanism-based and disease-modifying therapeutic for this grievous disease. In 2015, the FDA granted Fast Track Designation status and Orphan Drug Designation status for GBT440 for the treatment of SCD.

Evaluation of GBT440 and Analogs in Hypoxemic Pulmonary Disorders

In hypoxemic pulmonary disorders, where the lungs cannot supply adequate oxygen to the blood, we believe that hemoglobin modifiers that left-shift the OEC have the potential to enable increased oxygen uptake in the lungs, resulting in improved oxygen delivery to tissues. The primary goal in treating patients affected by these disorders is to increase hemoglobin oxygen affinity in order to transfer more oxygen into the blood to compensate for the reduced oxygen absorption associated with the underlying lung disease. Supplemental oxygen therapy is a well-established lifesaving treatment in acute and chronic hypoxemic conditions, but is associated with a number of risks, including local and systemic side effects and places a significant burden on the patients quality of life due to the demand of the delivery equipment and ultimately psycho-social decline. Accordingly, we believe a drug that improves oxygen uptake and delivery, thereby providing benefits similar to oxygen therapy without the associated risks and burden to patients, could fill a significant unmet medical need.

We are evaluating our proprietary compounds in a variety of disorders in which hypoxemia is believed to play a key role in disease progression and adverse patient outcomes, including idiopathic pulmonary fibrosis, or IPF, and other chronic and acute lung disorders. Since GBT440 is intended to address the hypoxemic aspects of IPF, we believe that GBT440 could be administered potentially in combination with other therapeutics focused on slowing the rate of disease progression, such as pirfenidone and nintedanib.

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IPF is a fatal disease characterized by irreversible, progressive scarring of the lungs, which leads to their deterioration. IPF causes shortness of breath and destruction of healthy lung tissue, resulting in hypoxemia, tissue hypoxia, and ultimately organ failure. The prognosis is poor for patients with IPF, which occurs primarily in people over 50 years old, with a median survival time from diagnosis of two to three years. A 2012 publication estimated that there are approximately 90,000 patients with IPF in the United States.

We have observed in a mouse model of hypoxia (Study 1) that oral dosing with a hemoglobin-modifying analog of GBT440 may potentially provide protection against extreme hypoxia (5% oxygen, far lower than 21% atmospheric oxygen), as shown by improvements in survival (as measured by heart rate < 60 mmHg) and hypoxemia in treated animals compared to control. We believe this is based upon the compound s effect on increased hemoglobin oxygen affinity. The results of this study are summarized in the graph below:

Study 1: Tolerance of animals to 5% O2 hypoxia

Based on the results of Study 1, we initiated two additional animal studies in disease models of acute (Study 2) and chronic (Study 3) lung injury, where we also observed improvements in hypoxemia and survival in animals treated with a hemoglobin-modifying analog of GBT440 compared to controls.

In the acute lung injury model (Study 2), lipopolysaccharide, or LPS (a potent pro-inflammatory bacterial endotoxin), was used to induce lung injury. Additionally, animals were exposed to 5% O2 producing hypoxemia. In the chronic lung injury model (Study 3), bleomycin was used to induce lung injury for 14 days, resulting in increased fibrosis and hypoxemia over a period of two weeks. The animals were then treated, starting at day 8, with a GBT440 analog or control. The results of these studies are shown in the graphs below, which suggest that a hemoglobin-modifying agent such as GBT440 may improve oxygen uptake in a lung with diffuse injury characterized by acute inflammation or fibrosis.

Study 2: Tolerance of LPS-treated animals to 5% O2 hypoxia

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Study 3: Effect of a GBT440 analog on arterial oxygen saturation levels in bleomycin-injured mice

Based on these results, we initiated clinical sites which began screening for a Phase 2a clinical trial of GBT440 in IPF in June 2016, and we expect to initiate a Phase 2b clinical trial of GBT440 in a hypoxemic pulmonary disorder in the second half of 2016.

Oral Kallikrein Inhibitor in Hereditary Angioedema

We are also engaged in the discovery of small molecules to produce an oral prophylactic therapy for HAE. HAE is a rare, genetic disorder characterized by severe and potentially life-threatening systemic inflammation that is estimated to affect approximately 6,500 people in the United States and approximately one in 50,000 people globally. HAE is caused by a deficiency in a protein called C1-INH, whose role is to prevent the uncontrolled production of kallikrein in blood plasma. Kallikrein is an enzyme in blood that generates bradykinin, which in turn directly stimulates blood vessel swelling, leakage and tissue inflammation. This can lead to excruciating pain, tissue deformation, and in some cases, airway obstruction and death. Plasma kallikrein is a clinically validated target and serves as a key component in the regulation of inflammation and contact activation pathways. Kallikrein s role in HAE is well established, and previous studies have demonstrated that kallikrein inhibition can reverse and/or prevent angioedema attacks.

All currently marketed therapeutics for HAE must be administered intravenously or by subcutaneous injection. As a result, we believe that the availability of an oral prophylactic agent would have the potential to transform the treatment paradigm for this disease. We are currently conducting preclinical research to develop an orally available therapeutic that could potently and selectively inhibit plasma kallikrein for the treatment of HAE. In 2015, we nominated GBT018713, a proprietary, small molecule kallikrein inhibitor, for development as an orally administered therapy intended for the prevention of HAE attacks. We plan to complete toxicology studies to enable the submission of an IND in the second half of 2016, and subject to the submission and effectiveness of our IND, expect to initiate a Phase 1 clinical trial for GBT018713 in early 2017.

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 trial of GBT440. We have not entered into long-term agreements with our current CMOs. We intend to continue to rely on CMOs for later-stage development and commercialization of GBT440, as well as the development and commercialization of any other product candidates that we may identify. Although we rely on CMOs, we have personnel and third-party consultants with extensive manufacturing experience to oversee the relationships with our contract manufacturers.

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We believe the synthesis of the drug substance for GBT440 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 GBT440 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 commercial demands.

Drug product formulation development work for GBT440 is in progress to support both adult and pediatric patient populations. We have contracted with third-party manufacturers capable of both formulation development and drug product manufacturing. We plan to identify a second drug product manufacturer in the future to add further capacity and redundancy to our supply chain to support late-stage development and commercialization.

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 by filing patent applications directed to compositions and methods of treatment created or identified from our ongoing development of our product candidates. Our success will depend 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. We seek to obtain domestic and international patent protection, and endeavor to promptly file patent applications for new commercially valuable inventions.

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 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.

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 priority of invention.

Patents

Our patent portfolio includes four issued U.S. patents, one allowed U.S. patent applications, and several U.S. and foreign patent applications in various stages of prosecution. We have sole ownership of the issued U.S. patents (U.S.

Patent Nos. 9,018,210 and 9,248,199) covering GBT440. U.S. Patent No. 9,018,210, issued on April 28, 2015, covers the composition of matter for GBT440 and U.S. Patent No. 9,248,199, issued on February 2, 2016, covers the methods of use of GBT440 and will expire in 2032 and 2034, respectively, absent any applicable patent term extensions. The issued U.S. patents (U.S. Patent Nos. 8,952,171 and 9,012,450),

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covering the composition of matter for GBT440 analogs, were granted on February 10, 2015 and April 21, 2015, respectively, and are currently expected to expire in 2033 and 2032, respectively, absent any applicable patent term extensions. We also own jointly with, and have exclusively licensed from, the Regents worldwide patent rights to U.S. Patent No. 9,012,450 and U.S. patent applications 13/730,674 and 13/730,730 covering GBT440 and GBT440 analogs. In exchange for the exclusive license, we have agreed to pay a royalty to the Regents of less than 1% on future net sales and 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. The foreign patent applications covering the composition of matter for GBT440 and analogs, if issued, would in each case be expected to expire between 2032 and 2035, absent any applicable patent term extensions. Our patent applications fall into three major categories: (i) GBT440; (ii) GBT440 analogs and (iii) kallikrein modulators.

GBT440 patent portfolio. Our patent portfolio relating to GBT440 is comprised of ten patent families and includes patent applications covering certain compositions of matter, methods of use, method of manufacture, and certain polymorphs related to GBT440 pending in a variety of jurisdictions, including the United States, jurisdictions under the Patent Cooperation Treaty, or PCT, Argentina, and Taiwan. The issued U.S. patent (U.S. Patent No. 9,018,210 and 9,248,199) covering the composition of matter and methods of use for GBT440, respectively, were granted on April 28, 2015 and February 2, 2016, respectively, and are currently expected to expire in 2032 and 2034, respectively, absent any applicable patent term extensions. Any patents that may issue from our other patent applications relating to GBT440 in the United States, if issued, would be expected to expire between 2032 and 2037, absent any applicable patent term extensions. Any patents that may issue from corresponding PCT and foreign patent applications, if issued, would also be 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 the Regents.

GBT440 analogs patent portfolio. Our patent portfolio relating to GBT440 analogs is comprised of eight patent families and includes patent applications covering certain compositions of matter and methods of use for GBT440 analogs pending in a variety of jurisdictions, including the United States, jurisdictions under the PCT, Argentina and Taiwan. The two issued U.S. patents (U.S. Patent No. 8,952,171 and U.S. Patent No. 9,012,450, respectively) covering the composition of matter for GBT440 analogs are currently expected to expire in 2033 and 2032, respectively, absent any applicable patent term extensions. Any patents that may issue from the other patent applications relating to GBT440 analogs in the United States, if issued, would be expected to expire between 2032 and 2035, absent any applicable patent term extensions. Any patents that may issue from corresponding PCT and foreign patent applications, if issued, would be expected to expire between 2032 and 2035, absent any applicable patent term extensions. Some of these pending patent applications are jointly owned by us and the Regents.

Kallikrein modulators patent portfolio. Our patent portfolio relating to kallikrein modulators is comprised of three patent families covering certain compositions of matter for kallikrein modulators pending in the United States, with potential foreign rights under the Paris Convention. Any patents that may issue from these applications, if issued, would be expected to expire between 2035 and 2036 absent any applicable patent term extensions.

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-

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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 product candidates receive FDA approval, we expect to apply for patent term extension on patents, if issued, covering those products, their methods of use and/or methods of manufacture.

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 and to consider building additional capabilities that may be necessary to effectively support the commercialization of GBT440 when we believe a regulatory approval in a particular geography is likely. Because SCD is a rare disease in these geographic markets, with a concentrated prescribing audience and a small number of key opinion leaders who significantly influence the treatments prescribed for the relevant patient population, we believe that we can effectively address the market using our own targeted, specialty sales and marketing organization supported by internal sales personnel, an internal marketing group and distribution support. Additional capabilities important to the SCD and hematology marketplace include the management of key accounts such as managed care organizations, specialty pharmacies and government accounts.

Outside of the United States and core European markets, where appropriate, we may utilize strategic partners, distributors or contract sales forces to expand the commercial availability of GBT440. In addition, we believe the other indications that we may pursue with our product candidates can also be addressed with a small, dedicated sales force. 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 or indications or 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.

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In the area of SCD, we expect to face competition from HU (marketed as DROXIA or Hydrea by Bristol-Myers Squibb Company as well as in generic form), which is currently the only approved therapeutic for the treatment of SCD. Several companies are also developing product candidates for chronic treatment in SCD, including Selexys Pharmaceuticals Corporation (in collaboration with Novartis AG), which is engaged in the clinical development of SelG1, an anti-P-selectin monoclonal antibody, and Baxter International Inc./Shire plc, which has completed a Phase 2 clinical trial of Bax-555, an orally available small molecule compound that is also intended to work by increasing hemoglobin oxygen affinity. 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 SCD, including hematopoietic stem cell transplantation, gene therapy and gene editing. In particular, Bellicum Pharmaceuticals, Inc. is conducting a Phase 1/2 clinical trial of BPX-501 as an adjunct T-cell therapy administered after allogeneic hematopoietic stem cell transplant in pediatric patients with orphan inherited blood disorders, and 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 HSCs into the patient s bloodstream. While not directly competitive with preventative agents like GBT440, several agents are also in development for the acute treatment of SCD crises including rivipansel (under development by Pfizer Inc.) and vepoloxamer (under development by Mast Therapeutics, Inc.).

In IPF, we expect to face competition from the approved therapeutics, including pirfenidone (marketed by Genentech, a member of the Roche Group, as Esbriet in the U.S., Canada, EU and other markets, by Shionogi as Pirespa in Japan, and in generic form in certain markets) and nintedanib, marketed by Boehringer Ingelheim GmbH in the U.S. and EU as Ofev. In addition, several new anti-fibrotic agents are being investigated in Phase 1 and Phase 2 clinical trials, including FibroGen Inc. s FG-3019, a connective tissue growth factor monoclonal antibody. Since GBT440 s approach is to address the hypoxemic aspects of IPF, we believe that GBT440 could be administered potentially in combination with pirfenidone and nintedanib or other agents in development.

In HAE, we expect to face competition from several FDA-approved therapeutics, including Cinryze, marketed by Shire plc in the United States and Europe for the prevention of angioedema attacks in adults and adolescents; Firazyr, marketed by Shire plc in the United States, Europe and certain other geographic territories for the treatment of acute angioedema attacks in adult patients; KALBITOR, marketed by Dyax Corp. for the resolution of acute attacks in adolescent and adult HAE patients; Berinert, marketed by CSL Behring for the treatment of acute abdominal, facial or laryngeal attacks of HAE in adults and adolescents; and Ruconest, marketed by Pharming Group NV in Europe and Salix Pharmaceuticals, Ltd. in the United States for the treatment of acute angioedema attacks in adult patients. We are also aware of companies, including Dyax Corp./Shire plc and Biocryst Pharmaceuticals, Inc., that are engaged in the clinical development of other product candidates, including a kallikrein monoclonal antibody and oral kallkrein inhibitors, respectively, for the chronic treatment of HAE patients.

Many 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,

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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, voluntary 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 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;
- 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 to accept it for filing;

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 our product candidates will be granted on a timely basis, or at all. The data required to support an NDA is 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

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testing in humans. The sponsor 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.

A sponsor who wishes to conduct a clinical trial outside the United States may, but need not, obtain FDA authorization to conduct the clinical trial under an IND. If a foreign clinical trial is not conducted under an IND, the sponsor may submit data from the clinical trial to the FDA in support of an NDA. The FDA will accept a well-designed and well-conducted foreign clinical study not conducted under an IND if the study was conducted in accordance with good clinical practice, and the FDA is able to validate the data through an onsite inspection if the agency deems necessary.

Clinical trials

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

Phase 2 clinical trials typically involve studies in disease-affected patients to determine the dose required to produce the desired benefits. At the same time, safety and further 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 for its intended use, its safety in use, and to establish the overall benefit/risk relationship of the product 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. These trials are used 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.

Progress reports detailing the results of the clinical trials, among other information, must be submitted at least annually to the FDA and written IND safety reports must be submitted to the FDA and the investigators within 15 calendar days for serious and unexpected suspected adverse events, findings from other studies

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suggesting a significant risk to humans exposed to the drug, findings from animal or in vitro testing that suggests a significant risk for human subjects, and any clinically important increase in the rate of a serious suspected adverse reaction over that listed in the protocol or investigator brochure. Additionally, a sponsor must notify FDA of any unexpected fatal or life-threatening suspected adverse reaction no later than 7 calendar days after the sponsor s 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 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 must be accompanied by a user fee. The FDA adjusts the PDUFA user fees on an annual basis. According to the FDA s fee schedule, effective through September 30, 2016, the user fee for an application requiring clinical data, such as an NDA, is approximately $2.4 million. PDUFA also imposes an annual product fee for human drugs (approximately $0.1 million) and an annual establishment fee (approximately $0.6 million) on facilities used to manufacture prescription drugs. Fee waivers or reductions are available in certain circumstances, including a waiver of the application fee for the first application filed by a small business. 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 Federal Food, Drug, and Cosmetic Act is not subject to an application fee unless the application includes an indication for other than a rare disease or condition. GBT440 for the treatment of sickle cell disease has been granted orphan drug designation and qualifies for an orphan user fee exemption.

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 must make a decision on accepting an NDA for filing within 60 days of receipt. Once the submission 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 has 10 months from the 60-day filing date in which to complete its initial review of a standard NDA and respond to the applicant, and six months from the 60-day filing date for an NDA designated for priority review. 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.

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Before approving an NDA, the FDA will conduct a pre-approval inspection of the manufacturing facilities for the new product to determine whether they comply with cGMPs. 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. The FDA will likely re-analyze the clinical trial data, which could result in extensive discussions between the FDA and the applicant during the review process. The review and evaluation of an NDA by the FDA is extensive and time consuming and may take longer than originally planned to complete, and we may not receive a timely approval, if at all.

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. A Complete Response Letter 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 an additional registrational Phase 3 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 resubmit the NDA, addressing all of the deficiencies identified in the letter, withdraw the application or request an opportunity for a hearing. Even if such data and information are submitted, the FDA may ultimately decide that the NDA does not satisfy the criteria for approval. Data obtained from clinical trials are not always conclusive and the FDA may interpret data differently than we interpret the same data.

Orphan drug designation

Under the Orphan Drug Act, 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 and for which there is no reasonable expectation that the cost of developing and making a drug product available in the United States for this type of disease or condition will be recovered from sales of the product. Orphan product designation must be requested before submitting an NDA. After the FDA grants orphan product designation, the identity of the therapeutic agent and its potential orphan use are disclosed publicly by the FDA. Orphan product designation does not convey any advantage in or shorten the duration of the regulatory review and approval process.

If a product that has orphan designation subsequently receives the first FDA approval for the disease or condition for which it has such designation, the product is entitled to orphan product exclusivity, which means that the FDA may not approve any other applications to market the same drug 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 or obtain approval for the same product but for a different indication than that for which the orphan product has exclusivity. Orphan product exclusivity also could block the approval of one of our products for seven years if a competitor obtains approval of the same product as defined by the FDA for the same indication we are seeking, or if our product candidate is determined to be contained within the competitor s product for the same indication or disease. 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.

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Expedited development and review programs

The FDA has a Fast Track program that is intended to expedite or facilitate the process for reviewing new drugs that meet certain criteria. Specifically, new drugs are eligible for Fast Track designation if they are intended to treat a serious or life threatening condition and 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. The sponsor of a new drug may request the FDA to designate the drug as a Fast Track product at any time during the clinical development of the product prior to receiving NDA approval.

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. 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 in an effort to facilitate the review. A product may also be eligible for accelerated approval.

An investigational drug may obtain accelerated approval if it treats a serious or life-threatening condition and generally provides a meaningful advantage over available therapies and demonstrates an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, or IMM, that is reasonably likely to predict an effect on IMM or other clinical benefit. As a condition of approval, the FDA may require that a sponsor of a drug receiving accelerated approval perform adequate and well-controlled post-marketing clinical trials. If the FDA concludes that a drug shown to be effective can be safely used only if distribution or use is restricted, it will require such post-marketing restrictions, as it deems necessary to assure safe use of the drug.

Additionally, a drug may be eligible for designation 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. The benefits of breakthrough therapy designation include the same benefits as fast track designation, plus 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, 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 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. The Food and Drug Administration Safety and Innovation Act, which was signed into law on July 9, 2012, amended the FDCA to require that 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 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.

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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 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. 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. Further, if there are any modifications to the drug, including changes in indications, labeling, or manufacturing processes or facilities, the applicant may be required to submit and obtain FDA approval of a new NDA or NDA supplement, which may require the applicant to develop additional data or conduct additional nonclinical studies and clinical trials.

The FDA regulations require that products be manufactured in specific approved facilities and in accordance with cGMP. 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 regulations. These manufacturers must comply with cGMP regulations 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 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, 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 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 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 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

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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 of between $5,500 and $11,000 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 subjects 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 modifications to product labeling; (iii) the recall or discontinuation of our products; or (iv) additional record-keeping requirements. If any such changes were to be imposed, they could adversely affect the operation of our business.

U.S. patent term restoration and marketing exclusivity

Depending upon the timing, duration and specifics of the FDA approval 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 extension and the application for the extension must be submitted prior to the expiration of the patent. The USPTO, in consultation with the FDA, reviews and approves the application for any patent term extension or restoration. In the future, we intend to apply for restoration of patent term for one of our currently owned or licensed patents to add patent life beyond its current expiration

date, depending on the expected length of the clinical trials and other factors involved in the filing of the relevant NDA. The request for patent term extension must be filed within a very short time frame after approval of the drug by the FDA. Failure to meet this time frame negates any patent term extension available.

Marketing exclusivity provisions under the FDCA can also delay the submission or the approval of certain marketing applications. The FDCA provides 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. 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 NDA holder. 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 or condition of use. Five-year and three-year exclusivity will not delay the submission or approval of a full NDA. However, an applicant submitting a full NDA would be required to conduct or obtain a right of reference to all of the nonclinical studies and adequate and well-controlled clinical trials necessary to demonstrate safety and efficacy. Orphan drug exclusivity, as described above, may offer a seven-year period of marketing exclusivity, except in certain circumstances. Pediatric exclusivity is another type of regulatory market exclusivity in the United States. Pediatric exclusivity, if granted, adds six months to existing exclusivity periods and patent terms. This six-month exclusivity, which runs from the end of other exclusivity protection or patent term, may be granted based on the voluntary completion of a pediatric trial in accordance with an FDA-issued Written Request for such a trial. The FDA issues a written request for pediatric clinical trials prior to approval of a NDA only where it determines that information relating to the use of a drug in a pediatric population, or part of the pediatric population, may produce health benefits in that population.

European Union drug development

In the EU, our future products 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 agencies 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.

The EU clinical trials legislation is currently undergoing a revision process mainly aimed at harmonizing and streamlining the clinical trials authorization process, simplifying adverse event reporting procedures, improving the supervision of clinical trials, and increasing their transparency.

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European Union drug review and approval

In the European Economic Area, or EEA, (which is comprised of the 27 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 European Medicines Agency, or 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. 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.

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.

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.

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. In the United States, no uniform policy of coverage and reimbursement for drug products exists. 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. As a result, the coverage determination process is often a time-consuming and costly process that will require us to provide scientific and clinical support for the use of our product candidates to each payor separately, 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 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, 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 average manufacturer price, or 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, 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

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on Medicaid managed care utilization as of 2010 and by expanding the population potentially eligible for Medicaid drug benefits. The CMS expanded Medicaid rebate liability to the territories of the United States as well, effective April 1, 2017.

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 Part A and B, Part D coverage is not standardized. 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 products for which we receive marketing approval. However, any negotiated prices for 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, with the exception of children s hospitals, these newly eligible entities will not be eligible to receive discounted 340B pricing on orphan drugs. In addition, 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.

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. An increasing emphasis on cost containment measures in the United States has increased and we expect will continue to increase the pressure on pharmaceutical pricing. Coverage policies and third-party reimbursement rates may change at any time. Even if favorable coverage and reimbursement status is attained for one or more products for which we receive regulatory approval, less favorable coverage policies and reimbursement rates may be implemented in the future.

In addition, in most 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. 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. Historically, products launched in the EU do not follow price structures of the United States and generally prices tend to be significantly lower.

Employees

As of March 31, 2016, we employed 76 full-time employees, including 54 in research and development and 22 general and administrative and no part-time employees, 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.

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Research and Development

Research and development expense recognized were $36.7 million, $16.3 million and $12.9 million for the years ended December 31, 2015, 2014 and 2013, respectively. Research and development expense recognized were $12.4 million and $6.1 million for the three months ended March 31, 2016 and 2015, respectively.

Corporate Information

We were incorporated in Delaware in February 2011 and commenced operations in May 2012. Our principal executive offices are located at 400 East Jamie Court, Suite 100, South San Francisco, California 94080. Our telephone number is (650) 741-7700 and our e-mail address is investor@globalbloodtx.com. Our Internet website address is globalbloodtx.com. No portion of our website is incorporated by reference into this prospectus.

We completed our initial public offering, or IPO, in August 2015, in which we sold 6,900,000 shares of common stock, at a public offering price of $20.00 per share, the net proceeds of which totaled $126.2 million, after deducting underwriting discounts and commissions and offering expenses incurred by us. We qualify as an emerging growth company as defined in the Jumpstart Our Business Startups Act of 2012, as amended, or the JOBS Act. As an emerging growth company, we may take advantage of specified reduced disclosure and other requirements that are otherwise applicable generally to public companies. We would cease to be an emerging growth company on the date that is the earliest of: (i) the last day of the fiscal year in which we have total annual gross revenues of $1 billion or more; (ii) December 31, 2020; (iii) the date on which we have issued more than $1 billion in nonconvertible debt during the previous three years; or (iv) the date on which we are deemed to be a large accelerated filer under the rules of the SEC.

You are advised to read this prospectus 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 final prospectus filed with the SEC on August 12, 2015 under Rule 424(b) of the Securities Act of 1933, as amended, our Annual Report on Form 10-K, 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 at the SEC s Public Reference Room at 100 F Street, N.E. Washington, D.C. 20549. In addition, the SEC maintains information for electronic filers (including Global Blood Therapeutics, Inc.) at its website at www.sec.gov. The public may obtain information regarding the operation of the Public Reference Room by calling the SEC at 1-800-SEC-0330. 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.

Facilities

Our headquarters, where we have office and research and development laboratory space, is located in South San Francisco, California, where we lease 28,000 square feet of space pursuant to two separate noncancelable operating leases. In 2012 we entered into a noncancelable operating lease for approximately 16,000 square feet that expires in April 2018; and in 2014 we assumed a second noncancelable operating lease from a neighboring tenant for approximately 12,000 square feet that expires in April 2018. We believe that our existing facilities are sufficient for our current needs.

Legal Proceedings

As of the date of this prospectus, we were not party to any material legal matters or claims. In the future, we may become party to legal matters and claims arising in the ordinary course of business, the resolution of which we do not

anticipate would have a material adverse impact on our financial position, results of operations or cash flows.

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CERTAIN RELATIONSHIPS AND RELATED PARTY TRANSACTIONS

Other than compensation arrangements, we describe below the transactions, and series of similar transactions, since January 1, 2013, to which we were a party or will be a party, in which:

- the amounts involved exceeded or will exceed $120,000; and
- any of our directors, executive officers or holders of more than 5% of our capital stock, or any member of the immediate family of the foregoing persons, had or will have a direct or indirect material interest.

In connection with the completion of our IPO in August 2015, we adopted a written related party policy that requires all future transactions between us and any director, executive officer, holder of 5% or more of any class of our capital stock or any member of the immediate family of, or entities affiliated with, any of them, or any other related persons (as defined in Item 404 of Regulation S-K) or their affiliates, in which the amount involved is equal to or greater than $120,000, be approved in advance by our audit committee. Any request for such a transaction must first be presented to our audit committee for review, consideration and approval. In approving or rejecting any such proposal, our audit committee is to consider the relevant facts and circumstances available and deemed relevant to the audit committee, including, but not limited to, the extent of the related party s interest in the transaction, and whether the transaction is on terms no less favorable to us than terms we could have generally obtained from an unaffiliated third party under the same or similar circumstances.

Private Placements of Securities

Series A Preferred Stock Financing

In May 2012, we entered into a securities purchase agreement with Third Rock Ventures II, L.P., or TRV II, pursuant to which we issued, in a series of closings, an aggregate of 40,663,168 shares of our Series A redeemable convertible preferred stock at a purchase price of $1.00 per share. In April 2014, we entered into a joinder agreement and an amendment to the securities purchase agreement, pursuant to which Third Rock Ventures III, L.P., or TRV III, was added as a purchaser under the securities purchase agreement and we increased the aggregate number of shares of Series A redeemable convertible preferred stock issuable under such agreement to 50,163,168.

The following table summarizes the participation in the Series A redeemable convertible preferred stock financing by any of our directors, executive officers, holders of more than 5% of our voting securities, or any member of the immediate family of the foregoing persons:

Name	Shares of Series A Preferred	Aggregate Purchase Price Paid	Date Purchased
Third Rock Ventures II, L.P.	13,663,168	$ 13,663,168[1]	5/31/2012
Third Rock Ventures II, L.P.	5,000,000	$ 5,000,000	2/28/2013
Third Rock Ventures II, L.P.	5,000,000	$ 5,000,000	7/12/2013

Third Rock Ventures II, L.P.	5,000,000	$	5,000,000	10/31/2013
Third Rock Ventures II, L.P.	5,000,000	$	5,000,000	1/31/2014
Third Rock Ventures II, L.P.	5,000,000	$	5,000,000	4/29/2014
Third Rock Ventures III, L.P.	5,000,000	$	5,000,000	4/29/2014
Third Rock Ventures II, L.P.	3,000,000	$	3,000,000	10/1/2014
Third Rock Ventures III, L.P.	3,000,000	$	3,000,000	10/1/2014

(1) Includes 3,663,168 shares of Series A redeemable convertible preferred stock issued at a price of $1.00 per share upon the conversion of principal and accrued interest under convertible promissory notes previously issued by us to TRV II.

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Series B Preferred Stock Financing

In December 2014, we entered into a securities purchase agreement with various investors, pursuant to which we agreed to issue, in a single closing, an aggregate of 19,200,000 shares of our Series B redeemable convertible preferred stock at a price of $2.50 per share.

The following table summarizes the participation in the Series B redeemable convertible preferred stock financing by any of our directors, executive officers, holders of more than 5% of our voting securities, or any member of the immediate family of the foregoing persons:

Name	Shares of Series B Preferred	Aggregate Purchase Price Paid	Date Purchased
Fidelity Select Portfolios: Biotechnology Portfolio	8,985,915	$ 22,464,787.50	12/22/2014
Fidelity Advisors Series VII: Fidelity Advisor Biotechnology Fund	1,814,085	$ 4,535,212.50	12/22/2014

Agreements with Stockholders

In connection with the Series B redeemable convertible preferred stock financing, we entered into the Amended and Restated Investors Rights Agreement, dated as of December 22, 2014, with certain of our stockholders, including our principal stockholders and their affiliates and the Amended and Restated Stockholders Agreement, dated as of December 22, 2014, with certain of our stockholders, including our principal stockholders and their affiliates. All of the material provisions of these agreements terminated immediately prior to the completion of our IPO, other than the provisions relating to registration rights, which entitle the holders of such rights to have us register their shares of our common stock for sale in the United States. See Description of Capital Stock Registration Rights.

Since our inception in 2011, we have received consulting and management services from TRV, pursuant to an unwritten agreement with TRV, or the TRV Agreement, which through its affiliates, has a controlling interest in us. During the year ended December 31, 2015, we incurred expenses from TRV of an aggregate of $44,400 for these services, which included, among other things, $33,600 in consulting services provided by Dr. Homcy, a member of our Board of Directors. We did not incur additional expenses under the TRV Agreement during the three months ended March 31, 2016.

We have incurred expenses from TRV of an aggregate of approximately $2,557,000 for these services from our inception through March 31, 2016 pursuant to the TRV Agreement. Our director, Dr. Homcy, currently provides us with consulting services pursuant to the TRV Agreement. Dr. Homcy and Mr. Starr, another member of our board of directors during 2015, are affiliated with TRV. Dr. Homcy did not receive any cash compensation from us, as his consulting services were provided to us through TRV.

Participation in Initial Public Offering

In August 2015, certain of our officers purchased an aggregate of 57,500 shares of our common stock in our IPO at the initial public offering price of $20.00 per share as follows:

Beneficial Owner	Shares Purchased in Offering	Aggregate Purchase Price
Ted W. Love, M.D. [1]	10,000	$ 200,000
Eleanor L. Ramos, M.D.	10,000	$ 200,000
Jung E. Choi	25,000	$ 500,000
Peter Radovich	12,500	$ 250,000

(1) Includes 5,000 shares purchased directly by Dr. Love and 5,000 shares purchased by Dr. Love s immediate family members in the IPO.

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Executive Officer and Director Compensation

See Proposal 1 Election of Directors Director Compensation and Compensation of Executive Officers in our Definitive Proxy Statement for our 2016 annual meeting of stockholders filed with the SEC on April 28, 2016 for information regarding compensation of directors and executive officers.

Indemnification Agreements

We have entered into or plan to enter into indemnification agreements with each of our directors and executive officers, the form of which is incorporated by reference as an exhibit to the registration statement of which this prospectus is a part. The indemnification agreements and our amended and restated certificate of incorporation and amended and restated bylaws require us to indemnify our directors and officers to the fullest extent permitted by Delaware law.

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PRINCIPAL STOCKHOLDERS

The following table presents information concerning the beneficial ownership of the shares of our common stock as of May 31, 2016, by:

- each person we know to be the beneficial owner of 5% or more of our outstanding shares of our capital stock;
- each of our directors;
- each of our named executive officers; and
- all of our executive officers and directors as a group.

We have determined beneficial ownership in accordance with SEC rules. The information does not necessarily indicate beneficial ownership for any other purpose. Under these rules, a person is deemed to be a beneficial owner of our common stock if that person has a right to acquire ownership within 60 days by the exercise of options. A person is also deemed to be a beneficial owner of our common stock if that person has or shares voting power, which includes the power to vote or direct the voting of our common stock, or investment power, which includes the power to dispose of or to direct the disposition of such capital stock. Except in cases where community property laws apply or as indicated in the footnotes to this table, we believe that each stockholder identified in the table possesses sole voting and investment power over all shares of common stock shown as beneficially owned by the stockholder.

Percentage of beneficial ownership in the table below is based on 30,532,523 shares of common stock deemed to be outstanding as of May 31, 2016, and 36,932,523 shares of common stock outstanding after the completion of this offering, assuming no exercise of outstanding options and no exercise of the underwriters option to purchase additional shares of our common stock. If the underwriters exercise their option to purchase additional shares in full, we will sell an aggregate of 960,000 additional shares of common stock. Shares of common stock subject to options that are currently exercisable or exercisable within 60 days of May 31, 2016 are considered outstanding and beneficially owned by the person holding the options for the purpose of computing the percentage ownership of that person but are not treated as outstanding for the purpose of computing the percentage ownership of any other person. Unless otherwise indicated below, the address of each beneficial owner listed below is c/o Global Blood Therapeutics, Inc., 400 East Jamie Court, Suite 101, South San Francisco, CA 94080.

Name and Address of Beneficial Owner [1]	Number of Shares Beneficially Owned before Offering	Number of Shares Beneficially Owned after Offering	Percentage of Shares Beneficially Owned before Offering	Percentage of Shares Beneficially Owned after Offering
5% or Greater Stockholders:				
Entities affiliated with Third Rock Ventures [2]	14,760,904	14,760,904	48.3%	40.0%

Entities affiliated with Fidelity [3]	4,568,562	4,568,562	15.0%	12.4%
Executive Officers and Directors:				
Ted W. Love, M.D. [4]	1,147,636	1,147,636	3.8%	3.1%
Jeffrey Farrow			*%	*%
Eleanor L. Ramos, M.D. [5]	118,291	118,291	*%	*%
Hing L. Sham, Ph.D. [6]	82,311	82,311	*%	*%
Uma Sinha, Ph.D. [7]	111,248	111,248	*%	*%
Michael W. Bonney [8]	4,166	4,166	*%	*%
Willie L. Brown, Jr. [9]	38,044	38,044	*%	*%
Charles Homcy, M.D. [10]	228,035	228,035	*%	*%
Scott W. Morrison [11]	5,000	5,000	*%	*%
Mark Perry [12]	43,044	43,044	*%	*%
Deval Patrick [13]	25,812	25,812	*%	*%
Glenn F. Pierce, M.D., Ph.D. [14]	4,166	4,166	*%	*%
Philip A. Pizzo, M.D. [15]	8,333	8,333	*%	*%
All executive officers and directors as a group (15 persons) [16]	2,038,246	2,038,246	6.6%	5.5%

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* Represents beneficial ownership of less than 1% of the shares of common stock.

(1) Unless otherwise indicated, the address for each beneficial owner is c/o Global Blood Therapeutics, Inc., 400 East Jamie Court, Suite 101, South San Francisco, CA 94080.

(2) Based solely on a report on Schedule 13G filed with the SEC on February 10, 2016, which indicates that (i) Third Rock Ventures II, L.P. (TRV II) directly owned, and had shared voting power and dispositive power over, 12,475,190 shares of common stock and (ii) Third Rock Ventures III, L.P. (TRV III) directly owned, and had shared voting power and dispositive power over 2,285,714 shares of common stock. Each of Third Rock Ventures GP II, L.P. (TRV GP II), the sole general partner of TRV II, and TRV GP II, LLC (TRV GP II LLC), the sole general partner of TRV GP II, and Mark Levin, Kevin P. Starr and Robert I. Tepper, the managing members of TRV GP II LLC, may be deemed to have voting and investment power over the shares held of record by TRV II, and each of Third Rock Ventures GP III, LP (TRV GP III), the sole general partner of TRV III, and TRV GP III, LLC (TRV GP III LLC), the sole general partner of TRV GP III, and Mark Levin, Kevin P. Starr and Robert I. Tepper, the managing managers of TRV GP III LLC, may be deemed to have voting and investment power over the shares held of record by TRV III. The address for each of TRV II and TRV III is 29 Newbury Street, 3rd Floor, Boston, MA 02116.

(3) Based solely on a report on Schedule 13G/A filed with the SEC on February 12, 2016, which indicates that FMR LLC had sole voting power with respect to 226,576 shares of common stock and had sole dispositive power over 4,568,562 shares of common stock. Abigail P. Johnson is a Director, the Vice Chairman, the Chief Executive Officer and the President of FMR LLC. Members of the Johnson family including Abigail P. Johnson, are the predominant owners, directly or through trusts, of Series B voting common shares of FMR LLC, representing 49% of the voting power of FMR LLC. The Johnson family group and all other Series B shareholders have entered into a shareholders voting agreement under which all Series B voting common shares will be voted in accordance with the majority vote of Series B voting common shares. Accordingly, through their ownership of voting common shares and the execution of the shareholders voting agreement, members of the Johnson family may be deemed, under the Investment Company Act of 1940, to form a controlling group with respect to FMR LLC. Neither FMR LLC nor Abigail P. Johnson has the sole power to vote or direct the voting of the shares owned directly by the various investment companies registered under the Investment Company Act (Fidelity Funds) advised by Fidelity Management & Research Company (FMR Co), a wholly owned subsidiary of FMR LLC, which power resides with the Fidelity Funds Boards of Trustees. Fidelity Management & Research Company carries out the voting of the shares under written guidelines established by the Fidelity Funds Boards of Trustees. The address for Fidelity Select Portfolios: Biotechnology Portfolio is Brown Brothers Harriman & Co., 525 Washington Blvd., Jersey City, NJ 07310, Attn: Michael Lerman, 15th Floor, Corporate Actions, and the address for Fidelity Advisor Series VII: Fidelity Advisor Biotechnology Fund is State Street Bank & Trust, PO Box 5756, Boston, MA 02206, Attn: Bangle & Co fbo Fidelity Advisor Series VII: Fidelity Advisor Biotechnology Fund.

(4) Includes (i) 1,142,636 shares of common stock held by Dr. Love, 560,891 shares of which would be subject to our right of repurchase; and (ii) 5,000 shares of common stock held by Dr. Love s two daughters, as to which Dr. Love disclaims beneficial ownership.

(5) Includes (i) 12,470 shares of common stock held by Dr. Ramos; (ii) 1,000 shares of common stock held by Dr. Ramos step-daughter; and (ii) 104,821 shares of common stock that Dr. Ramos has the right to acquire from us within 60 days of May 31, 2016 pursuant to the exercise of stock options.

(6) Includes (i) 36,775 shares of common stock held by Dr. Sham, 6,964 of which would be subject to our right of repurchase; and (ii) 45,536 shares of common stock that Dr. Sham has the right to acquire from us within 60 days of May 31, 2016 pursuant to the exercise of stock options.

(7) Includes 111,248 shares of common stock held by Dr. Sinha. Dr. Sinha s employment with us ended on July 14, 2015.

(8) Includes 4,166 shares of common stock that Mr. Bonney has the right to acquire from us within 60 days of May 31, 2016 pursuant to the exercise of stock options.

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(9) Includes (i) 21,428 shares of common stock held by Mr. Brown, 14,732 shares of which would be subject to our right of repurchase; and (ii) 16,616 shares of common stock that Mr. Brown has the right to acquire from us within 60 days of May 31, 2016 pursuant to the exercise of stock options.

(10) Includes (i) 212,685 shares of common stock held by Dr. Homcy; (ii) 1,600 shares of common stock held by The Charles J. Homcy Irrevocable Trust UA 2/18/99; and (iii) 13,750 shares of common stock that Dr. Homcy has the right to acquire from us within 60 days of May 31, 2016 pursuant to the exercise of stock options.

(11) Includes 5,000 shares of common stock that Mr. Morrison has the right to acquire from us within 60 days of May 31, 2016 pursuant to the exercise of stock options.

(12) Includes (i) 26,428 shares of common stock held by Mr. Perry, 16,071 shares of which would be subject to our right of repurchase; and (ii) 16,616 shares of common stock that Mr. Perry has the right to acquire from us within 60 days of May 31, 2016 pursuant to the exercise of stock options.

(13) Includes (i) 2,500 shares of common stock held by Mr. Patrick; and (ii) 23,312 shares of common stock that Mr. Patrick has the right to acquire from us within 60 days of May 31, 2016 pursuant to the exercise of stock options.

(14) Includes 4,166 shares of common stock that Dr. Pierce has the right to acquire from us within 60 days of May 31, 2016 pursuant to the exercise of stock options.

(15) Includes 8,333 shares of common stock that Dr. Pizzo has the right to acquire from us within 60 days of May 31, 2016 pursuant to the exercise of stock options.

(16) Includes the number of shares beneficially owned by the named executive officers and directors listed in the table above, excluding 111,248 shares of common stock held by Dr. Sinha in footnote no. 7 above, as well as (i) 143,606 shares of common stock held by Jung Choi, 107,142 shares of which would be subject to our right of repurchase, 25,000 shares of common stock held by The 2005 William Park and Jung Choi Family Trust and 33,393 shares of common stock that Ms. Choi has the right to acquire from us within 60 days of May 31, 2016 pursuant to the exercise of stock options; (ii) 13,725 shares of common stock held by Peter Radovich and 49,107 shares of common stock that Mr. Radovich has the right to acquire from us within 60 days of May 31, 2016 pursuant to the exercise of stock options; and (iii) 2,594 shares of common stock held by John Schembri and 65,983 shares of common stock that Mr. Schembri has the right to acquire from us within 60 days of May 31, 2016 pursuant to the exercise of stock options.

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DESCRIPTION OF CAPITAL STOCK

Upon the completion of this offering, and assuming the same capitalization as of May 31, 2016, our authorized capital stock will consist of 150,000,000 shares of common stock, par value $0.001 per share, and 5,000,000 shares of preferred stock, par value $0.001 per share, all of which will be undesignated, and there will be 36,932,523 shares of common stock outstanding and no shares of preferred stock outstanding. As of June 17, 2016, we had approximately 23 record holders of our capital stock. The actual number of stockholders is greater than this number of record holders and includes stockholders who are beneficial owners but whose shares are held in street name by brokers and other nominees. This number of holders of record also does not include stockholders whose shares may be held in trust by other entities.

In addition, upon the completion of this offering, and assuming the same capitalization as of March 31, 2016, options to purchase 2,487,374 shares of our common stock will be outstanding and 2,379,284 shares of our common stock will be reserved for future grants under our equity incentive plans.

The following description of our capital stock and provisions of our restated certificate of incorporation and amended and restated bylaws are summaries of material terms and provisions and are qualified by reference to our restated certificate of incorporation and amended and restated bylaws, copies of which have been filed with the SEC and are incorporated by reference as exhibits to the registration statement of which this prospectus is a part.

Common Stock

We are authorized to issue one class of common stock. Holders of our common stock are entitled to one vote for each share of common stock held of record for the election of directors and on all matters submitted to a vote of stockholders. Holders of our common stock are entitled to receive dividends ratably, if any, as may be declared by our board of directors out of legally available funds, subject to any preferential dividend rights of any preferred stock then outstanding. Upon our dissolution, liquidation or winding up, holders of our common stock are entitled to share ratably in our net assets legally available after the payment of all our debts and other liabilities, subject to the preferential rights of any preferred stock then outstanding. Holders of our common stock have no preemptive, subscription, redemption or conversion rights and no sinking fund provisions are applicable to our common stock. The rights, preferences and privileges of holders of common stock are subject to, and may be adversely affected by, the rights of the holders of shares of any series of preferred stock that we may designate and issue in the future. Except as described under Antitakeover Effects of Delaware Law and Provisions of our Restated Certificate of Incorporation and Amended and Restated Bylaws below, a majority vote of the holders of common stock is generally required to take action under our restated certificate of incorporation and amended and restated bylaws.

Preferred Stock

Our board of directors is authorized, without action by the stockholders, to designate and issue up to an aggregate of 5,000,000 shares of preferred stock in one or more series. Our board of directors can designate the rights, preferences and privileges of the shares of each series and any of its qualifications, limitations or restrictions. Our board of directors may authorize the issuance of preferred stock with voting or conversion rights that could adversely affect the voting power or other rights of the holders of common stock. The issuance of preferred stock, while providing flexibility in connection with possible future financings and acquisitions and other corporate purposes could, under certain circumstances, have the effect of restricting dividends on our common stock, diluting the voting power of our common stock, impairing the liquidation rights of our common stock, or delaying, deferring or preventing a change in control of our company, which might harm the market price of our common stock. See also Antitakeover Effects of Delaware Law and Provisions of our Restated Certificate of Incorporation and Amended and Restated

Bylaws Provisions of our Restated Certificate of Incorporation and Amended and Restated Bylaws Undesignated preferred stock below.

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Our board of directors will make any determination to issue such shares based on its judgment as to our company s best interests and the best interests of our stockholders. We have no shares of preferred stock outstanding and we have no current plans to issue any shares of preferred stock following completion of this offering.

Registration Rights

The holders of 14,760,904 shares of our common stock, or their permitted transferees, which we refer to as our registrable securities, are entitled to rights with respect to the registration of these securities under the Securities Act. These rights are provided under the terms of the investor rights agreement. The investor rights agreement includes demand registration rights, short-form registration rights and piggyback registration rights. All fees, costs and expenses incurred in connection with registrations under the investor rights agreement will be borne by us, and all selling expenses, including underwriting discounts and selling commissions, will be borne by the holders of the shares being registered.

Demand Registration Rights

The holders of our registrable securities are entitled to demand registration rights. Under the terms of the investor rights agreement, we will be required, upon the request of holders of at least 25% of our outstanding registrable securities, to file a registration statement with an anticipated offering amount of at least $3.0 million and use commercially reasonable efforts to effect the registration of these shares for public resale. We are required to effect up to two registrations pursuant to this provision of the investor rights agreement.

Short Form Registration Rights

The holders of our registrable securities are also entitled to short form registration rights. Pursuant to the investor rights agreement, if we are eligible to file a registration statement on Form S-3, upon the request of holders of at least 25% of our outstanding registrable securities to sell registrable securities with an anticipated aggregate offering amount of at least $1.0 million, we will be required to use our commercially reasonable efforts to effect a registration of such shares. We are required to effect up to two registrations in any twelve month period pursuant to this provision of the investor rights agreement.

Piggyback Registration Rights

The holders of our registrable securities are entitled to piggyback registration rights. If we register any of our securities either for our own account or for the account of other security holders, the holders of our outstanding registrable securities are entitled to include their shares in the registration. Subject to certain exceptions contained in the investor rights agreement, we and the underwriters may limit the number of shares included in the underwritten offering if the underwriters determine that marketing factors require a limitation of the number of shares to be underwritten.

Indemnification

Our investor rights agreement contains customary cross-indemnification provisions, under which we are obligated to indemnify holders of registrable securities in the event of material misstatements or omissions in the registration statement attributable to us, and they are obligated to indemnify us for material misstatements or omissions attributable to them.

Expiration of Registration Rights

The registration rights granted under the investor rights agreement will terminate upon the earlier of (i) certain events constituting a sale of the company, (ii) at such time when all registrable securities could be sold under Rule 144 of the Securities Act or a similar exemption without limitation during a three-month period without registration or (iii) the third anniversary of our IPO.

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Antitakeover Effects of Delaware Law and Provisions of our Restated Certificate of Incorporation and Amended and Restated Bylaws

Certain provisions of the Delaware General Corporation Law and of our restated certificate of incorporation and amended and restated bylaws could have the effect of delaying, deferring or discouraging another party from acquiring control of us. These provisions, which are summarized below, are expected to discourage certain types of coercive takeover practices and inadequate takeover bids and, as a consequence, they might also inhibit temporary fluctuations in the market price of our common stock that often result from actual or rumored hostile takeover attempts. These provisions are also designed in part to encourage anyone seeking to acquire control of us to first negotiate with our board of directors. These provisions might also have the effect of preventing changes in our management. It is possible that these provisions could make it more difficult to accomplish transactions that stockholders might otherwise deem to be in their best interests. However, we believe that the advantages gained by protecting our ability to negotiate with any unsolicited and potentially unfriendly acquirer outweigh the disadvantages of discouraging such proposals, including those priced above the then-current market value of our common stock, because, among other reasons, the negotiation of such proposals could improve their terms.

Delaware Takeover Statute

We are subject to the provisions of Section 203 of the Delaware General Corporation Law. In general, Section 203 prohibits a publicly held Delaware corporation from engaging in a business combination with an interested stockholder for a three-year period following the time that this stockholder becomes an interested stockholder, unless the business combination is approved in a prescribed manner. Under Section 203, a business combination between a corporation and an interested stockholder is prohibited unless it satisfies one of the following conditions:

- before the stockholder became interested, our board of directors approved either the business combination or the transaction which resulted in the stockholder becoming an interested stockholder;
- upon consummation of the transaction which resulted in the stockholder becoming an interested stockholder, the interested stockholder owned at least 85% of the voting stock of the corporation outstanding at the time the transaction commenced, excluding for purposes of determining the voting stock outstanding, shares owned by persons who are directors and also officers, and employee stock plans, in some instances, but not the outstanding voting stock owned by the interested stockholder; or
- at or after the time the stockholder became interested, the business combination was approved by our board of directors and authorized at an annual or special meeting of the stockholders by the affirmative vote of at least two-thirds of the outstanding voting stock which is not owned by the interested stockholder.

Section 203 defines a business combination to include:

- any merger or consolidation involving the corporation and the interested stockholder;

any sale, transfer, lease, pledge, exchange, mortgage or other disposition involving the interested stockholder of 10% or more of the assets of the corporation;

subject to exceptions, any transaction that results in the issuance or transfer by the corporation of any stock of the corporation to the interested stockholder;

subject to exceptions, any transaction involving the corporation that has the effect of increasing the proportionate share of the stock of any class or series of the corporation beneficially owned by the interested stockholder; or

the receipt by the interested stockholder of the benefit of any loans, advances, guarantees, pledges or other financial benefits provided by or through the corporation.

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In general, Section 203 defines an interested stockholder as any entity or person beneficially owning 15% or more of the outstanding voting stock of the corporation and any entity or person affiliated with or controlling or controlled by the entity or person.

Provisions of our Restated Certificate of Incorporation and Amended and Restated Bylaws

Our restated certificate of incorporation and amended and restated bylaws include a number of provisions that may have the effect of delaying, deferring or discouraging another party from acquiring control of us and encouraging persons considering unsolicited tender offers or other unilateral takeover proposals to negotiate with our board of directors rather than pursue non-negotiated takeover attempts. These provisions include the items described below.

Board composition and filling vacancies. In accordance with our restated certificate of incorporation, our board is divided into three classes serving staggered three-year terms, with one class being elected each year. Our restated certificate of incorporation also provides that directors may be removed only for cause and then only by the affirmative vote of the holders of 75% or more of the shares then entitled to vote at an election of directors. Furthermore, any vacancy on our board of directors, however occurring, including a vacancy resulting from an increase in the size of our board, may only be filled by the affirmative vote of a majority of our directors then in office even if less than a quorum.

No written consent of stockholders. Our restated certificate of incorporation provides that all stockholder actions are required to be taken by a vote of the stockholders at an annual or special meeting, and that stockholders may not take any action by written consent in lieu of a meeting. This limit may lengthen the amount of time required to take stockholder actions and would prevent the amendment of our bylaws or removal of directors by our stockholder without holding a meeting of stockholders.

Meetings of stockholders. Our bylaws provide that only a majority of the members of our board of directors then in office may call special meetings of stockholders and only those matters set forth in the notice of the special meeting may be considered or acted upon at a special meeting of stockholders. Our bylaws limit the business that may be conducted at an annual meeting of stockholders to those matters properly brought before the meeting.

Advance notice requirements. Our bylaws establish advance notice procedures with regard to stockholder proposals relating to the nomination of candidates for election as directors or new business to be brought before meetings of our stockholders. These procedures provide that notice of stockholder proposals must be timely given in writing to our corporate secretary prior to the meeting at which the action is to be taken. Generally, to be timely, notice must be received at our principal executive offices not less than 90 days or more than 120 days prior to the first anniversary date of the annual meeting for the preceding year. The notice must contain certain information specified in our bylaws.

Amendment to certificate of incorporation and bylaws. As required by the Delaware General Corporation Law, any amendment of our restated certificate of incorporation must first be approved by a majority of our board of directors, and if required by law or our restated certificate of incorporation, must thereafter be approved by a majority of the outstanding shares entitled to vote on the amendment, and a majority of the outstanding shares of each class entitled to vote thereon as a class, except that the amendment of the provisions relating to stockholder action, directors, limitation of liability and the amendment of our restated certificate of incorporation must be approved by not less than 75% of the outstanding shares entitled to vote on the amendment, and not less than 75% of the outstanding shares of each class entitled to vote thereon as a class. Our bylaws may be amended by the affirmative vote of a majority vote of the directors then in office, subject to any limitations set forth in the bylaws; and may also be amended by the affirmative vote of at least 75% of the outstanding shares entitled to vote on the amendment, or, if the board of directors

recommends that the stockholders approve the amendment, by the affirmative vote of the majority of the outstanding shares entitled to vote on the amendment, in each case voting together as a single class.

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Undesignated preferred stock. Our restated certificate of incorporation provides for authorized shares of preferred stock. The existence of authorized but unissued shares of preferred stock may enable our board of directors to render more difficult or to discourage an attempt to obtain control of us by means of a merger, tender offer, proxy contest or otherwise. For example, if in the due exercise of its fiduciary obligations, our board of directors were to determine that a takeover proposal is not in the best interests of us or our stockholders, our board of directors could cause shares of preferred stock to be issued without stockholder approval in one or more private offerings or other transactions that might dilute the voting or other rights of the proposed acquirer or insurgent stockholder or stockholder group. In this regard, our restated certificate of incorporation grants our board of directors broad power to establish the rights and preferences of authorized and unissued shares of preferred stock. The issuance of shares of preferred stock could decrease the amount of earnings and assets available for distribution to holders of shares of common stock. The issuance may also adversely affect the rights and powers, including voting rights, of these holders and may have the effect of delaying, deterring or preventing a change in control of us.

Transfer Agent and Registrar

The transfer agent and registrar for our common stock is American Stock Transfer & Trust Company, LLC. The transfer agent and registrar s address is 6201 15th Avenue, Brooklyn, NY 11219.

Listing

Our common stock is listed on The NASDAQ Global Select Market under the symbol GBT.

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SHARES ELIGIBLE FOR FUTURE SALE

Future sales of our common stock in the public market, or the availability of such shares for sale in the public market, could adversely affect market prices prevailing from time to time. As described below, only a limited number of shares will be available for sale shortly after this offering due to contractual and legal restrictions on resale. Nevertheless, sales of our common stock in the public market after such restrictions lapse, or the perception those sales may occur, could adversely affect the prevailing market price at such time and our ability to raise equity capital in the future.

Based on the number of shares of common stock outstanding as of May 31, 2016, upon completion of this offering, 36,932,523 shares of common stock will be outstanding, assuming no exercise by the underwriters of their option to purchase additional shares and no exercise of options. All of the shares sold in this offering will be freely tradable. The remaining shares of common stock outstanding after this offering will be restricted as a result of securities laws or lock-up agreements as described below. Following the expiration of the lock-up period, all shares will be eligible for resale in compliance with Rule 144 or Rule 701 under the Securities Act. Restricted securities as defined under Rule 144 of the Securities Act were issued and sold by us in reliance on exemptions from the registration requirements of the Securities Act. These shares may be sold in the public market only if registered or qualified for an exemption from registration, such as under Rule 144 or Rule 701 under the Securities Act.

Rule 144

In general, a person who has beneficially owned restricted stock for at least six months would be entitled to sell their securities provided that (i) such person is not deemed to have been one of our affiliates at the time of, or at any time during the 90 days preceding, a sale and (ii) we are subject to the Exchange Act periodic reporting requirements for at least 90 days before the sale. Persons who have beneficially owned restricted shares for at least six months but who are our affiliates at the time of, or any time during the 90 days preceding, a sale, would be subject to additional restrictions, by which such person would be entitled to sell within any three-month period only a number of securities that does not exceed the greater of either of the following:

- 1% of the number of shares then outstanding, which will equal approximately 369,325 shares immediately after this offering assuming no exercise of the underwriters option to purchase additional shares, based on the number of shares outstanding as of May 31, 2016; or
- the average weekly trading volume of our common stock on The NASDAQ Global Select Market during the four calendar weeks preceding the filing of a notice on Form 144 with respect to the sale.

Such sales both by affiliates and by non-affiliates must also comply with the manner of sale, current public information and notice provisions of Rule 144.

Rule 701

Rule 701 under the Securities Act, or Rule 701, as in effect on the date of this prospectus, permits resales of shares in reliance upon Rule 144 but without compliance with certain restrictions of Rule 144, including the holding period requirement. Most of our employees, executive officers or directors who purchased shares under a written compensatory plan or contract may be entitled to rely on the resale provisions of Rule 701. However, substantially all Rule 701 shares are subject to lock-up agreements as described below and under Underwriting included elsewhere in

this prospectus and will become eligible for sale upon the expiration of the restrictions set forth in those agreements.

Lock-up Agreements

In connection with this offering, we and our executive officers and directors have agreed with the underwriters that for a period of 90 days after the date of this prospectus, and holders of 14,760,904 shares of our

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outstanding common stock have agreed with the underwriters that for a period of 45 days after the date of this prospectus, subject to certain exceptions, we and they will not offer, sell, assign, transfer, pledge, contract to sell or otherwise dispose of or hedge any shares of our common stock or any securities convertible into or exchangeable for shares of our common stock. J.P. Morgan Securities LLC and Morgan Stanley & Co. LLC may, in their sole discretion, at any time, release all or any portion of the shares from the restrictions in this agreement.

Rule 10b5-1 Trading Plans

Certain of our officers and directors may adopt written plans, known as Rule 10b5-1 trading plans, in which they will contract with a broker to buy or sell shares of our common stock on a periodic basis to diversify their assets and investments. Under these 10b5-1 trading plans, a broker may execute trades pursuant to parameters established by the officer or director when entering into the plan, without further direction from such officer or director. Such sales would not commence until the expiration of the applicable lock-up agreements entered into by such officer or director in connection with this offering.

Registration Rights

We are party to an investor rights agreement pursuant to which the holders of 14,760,904 shares of our common stock have the right to demand that we file a registration statement or request that their shares of our common stock be covered by a registration statement that we are otherwise filing. See Description of Capital Stock Registration Rights in this prospectus. Except for shares purchased by affiliates, registration of their shares under the Securities Act would result in these shares becoming freely tradable without restriction under the Securities Act immediately upon effectiveness of the registration, subject to the expiration of the lock-up period described above and under Underwriting in this prospectus, and to the extent such shares have been released from any repurchase option that we may hold.

Equity Incentive Plans

We have filed Form S-8 registration statements under the Securities Act to register shares of our common stock subject to options outstanding or reserved for issuance under our equity incentive plans. Shares covered by these registration statements are eligible for sale in the public markets, subject to Rule 144 limitations applicable to affiliates and any lock-up agreements. For a more complete discussion of our equity incentive plans, see our Definitive Proxy Statement for our 2016 annual meeting of stockholders, as filed with the SEC on April 28, 2016.

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MATERIAL U.S. FEDERAL INCOME AND ESTATE TAX CONSIDERATIONS FOR NON-U.S. HOLDERS

The following is a general discussion of certain material U.S. federal income and estate tax considerations relating to ownership and disposition of our common stock by a non-U.S. holder. For purposes of this discussion, the term non-U.S. holder means a beneficial owner of our common stock that is not, for U.S. federal income tax purposes a partnership or:

- an individual who is a citizen or resident of the United States;
- a corporation, or other entity treated as a corporation for U.S. federal income tax purposes, created or organized in or under the laws of the United States or of any political subdivision of the United States;
- an estate the income of which is subject to U.S. federal income taxation regardless of its source; or
- a trust, if a U.S. court is able to exercise primary supervision over the administration of the trust and one or more U.S. persons (as defined in the Code) have authority to control all substantial decisions of the trust or if the trust has a valid election in effect to be treated as a U.S. person under applicable U.S. Treasury Regulations.

A modified definition of non-U.S. holder applies for U.S. federal estate tax purposes (as discussed below).

This discussion is based on current provisions of the Code, existing and proposed U.S. Treasury Regulations promulgated thereunder, current administrative rulings and judicial decisions, all as in effect as of the date of this prospectus and all of which are subject to change or to differing interpretation, possibly with retroactive effect. Any change could alter the tax consequences to non-U.S. holders described in this prospectus. In addition, the Internal Revenue Service, or the IRS, could challenge one or more of the tax consequences described in this prospectus.

We assume in this discussion that each non-U.S. holder holds shares of our common stock as a capital asset (generally, property held for investment) within the meaning of Section 1221 of the Code. This discussion does not address all aspects of U.S. federal income and estate taxation that may be relevant to a particular non-U.S. holder in light of that non-U.S. holder s individual circumstances nor does it address any aspects of state, local or non-U.S. taxes, alternative minimum tax, or U.S. federal taxes other than income and estate taxes. This discussion also does not consider any specific facts or circumstances that may apply to a non-U.S. holder and does not address the special tax rules that may apply to particular non-U.S. holders, such as:

- insurance companies;
- tax-exempt organizations;

financial institutions;

brokers or dealers in securities;

pension plans;

controlled foreign corporations;

passive foreign investment companies;

owners that hold our common stock as part of a straddle, hedge, conversion transaction, synthetic security or other integrated investment;

certain U.S. expatriates;

persons who have elected to mark securities to market;

persons subject to the unearned income Medicare contribution tax; or

persons that acquire our common stock as compensation for services.

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In addition, this discussion does not address the tax treatment of partnerships (including any entity or arrangement treated as a partnership for U.S. federal income tax purposes) or other entities that are transparent for U.S. federal income tax purposes or persons who hold their common stock through such entities. In the case of a holder that is classified as a partnership for U.S. federal income tax purposes, the tax treatment of a person treated as a partner in such partnership for U.S. federal income tax purposes generally will depend on the status of the partner and the activities of the partner and the partnership. A person treated as a partner in a partnership or who holds their stock through another transparent entity should consult his, her or its own tax advisor regarding the tax consequences of the ownership and disposition of our common stock through a partnership or other transparent entity, as applicable.

Prospective investors should consult their own tax advisors regarding the U.S. federal, state, local and non-U.S. income and other tax considerations of acquiring, holding and disposing of our common stock.

Distributions on our Common Stock

We do not currently expect to pay dividends. See Dividend Policy above in this prospectus. However, in the event that we do pay distributions of cash or property on our common stock, those distributions will constitute dividends for U.S. federal income tax purposes to the extent paid from our current or accumulated earnings and profits, as determined under U.S. federal income tax principles. If a distribution exceeds our current and accumulated earnings and profits, the excess will be treated as a tax-free return of the non-U.S. holder s investment, up to such holder s tax basis in our common stock. Any remaining excess will be treated as capital gain, subject to the tax treatment described below under the heading Gain on Sale, Exchange or Other Taxable Disposition of Common Stock.

Subject also to the discussions below under the headings Information Reporting and Backup Withholding Tax and Foreign Account Tax Compliance Act, dividends paid to a non-U.S. holder generally will be subject to withholding of U.S. federal income tax at a 30% rate or such lower rate as may be specified by an applicable income tax treaty between the United States and such holder s country of residence. If we are unable to determine, at a time reasonably close to the date of payment of a distribution on our common stock, what portion, if any, of the distribution will constitute a dividend, then we may withhold U.S. federal income tax on the basis of assuming that the full amount of the distribution will be a dividend. If we or another withholding agent apply over-withholding, a non-U.S. holder may be entitled to a refund or credit of any excess tax withheld by timely filing an appropriate claim with the IRS.

Dividends that are treated as effectively connected with a trade or business conducted by a non-U.S. holder within the United States, and, if an applicable income tax treaty so provides, that are attributable to a permanent establishment or a fixed base maintained by the non-U.S. holder within the United States, are generally exempt from the 30% withholding tax if the non-U.S. holder satisfies applicable certification and disclosure requirements. To obtain this exemption, a non-U.S. holder must generally provide us with a properly executed original IRS Form W-8ECI properly certifying such exemption. However, such U.S. effectively connected income, net of specified deductions and credits, will be taxed at the same graduated U.S. federal income tax rates applicable to U.S. persons (as defined in the Code). Any U.S. effectively connected income received by a non-U.S. holder that is a corporation may also, under certain circumstances, be subject to an additional branch profits tax at a 30% rate or such lower rate as may be specified by an applicable income tax treaty between the United States and such holder s country of residence.

A non-U.S. holder of our common stock who claims the benefit of an applicable income tax treaty between the United States and such holder s country of residence generally will be required to provide a properly executed IRS Form W-8BEN or W-8BEN-E (or applicable successor form) and satisfy applicable certification and other requirements. Non-U.S. holders are urged to consult their own tax advisors regarding their entitlement to benefits under a relevant income tax treaty.

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A non-U.S. holder that is eligible for a reduced rate of U.S. withholding tax under an income tax treaty may obtain a refund or credit of any excess amounts withheld by timely filing an appropriate claim with the IRS.

Any documentation provided to an applicable withholding agent may need to be updated in certain circumstances. The certification requirements described above also may require a non-U.S. holder to provide its U.S. taxpayer identification number.

Gain on Sale, Exchange or Other Taxable Disposition of Common Stock

Subject to the discussions below under the headings Information Reporting and Backup Withholding Tax and Foreign Account Tax Compliance Act, a non-U.S. holder generally will not be subject to U.S. federal income tax or withholding tax on gain recognized on a sale, exchange or other taxable disposition of our common stock unless:

- the gain is effectively connected with the non-U.S. holder s conduct of a trade or business in the United States, and, if an applicable income tax treaty so provides, the gain is attributable to a permanent establishment or fixed base maintained by the non-U.S. holder in the United States; in these cases, the non-U.S. holder will be taxed on a net income basis at the regular graduated rates and in the manner applicable to U.S. persons, and, if the non-U.S. holder is a foreign corporation, an additional branch profits tax at a rate of 30%, or a lower rate as may be specified by an applicable income tax treaty, may also apply;

- the non-U.S. holder is an individual present in the United States for 183 days or more in the taxable year of the disposition and certain other conditions are met, in which case the non-U.S. holder will be subject to a 30% tax (or such lower rate as may be specified by an applicable income tax treaty) on the amount by which the non-U.S. holder s capital gains allocable to U.S. sources exceed capital losses allocable to U.S. sources during the taxable year of the disposition; or

- we are or were a U.S. real property holding corporation during a certain look-back period, unless our common stock is regularly traded on an established securities market and the non-U.S. holder held no more than five percent of our outstanding common stock, directly or indirectly, during the shorter of the five-year period ending on the date of the disposition or the period that the non-U.S. holder held our common stock. Generally, a corporation is a U.S. real property holding corporation if the fair market value of its U.S. real property interests equals or exceeds 50% of the sum of the fair market value of its worldwide real property interests plus its other assets used or held for use in a trade or business. Although there can be no assurance, we believe that we have not been and are not currently, and we do not anticipate becoming, a U.S. real property holding corporation for U.S. federal income tax purposes.

Information Reporting and Backup Withholding Tax

We (or the applicable paying agent) must report annually to the IRS and to each non-U.S. holder the gross amount of the distributions on our common stock paid to such holder and the tax withheld, if any, with respect to such distributions. Non-U.S. holders may have to comply with specific certification procedures to establish that the holder is not a U.S. person (as defined in the Code) in order to avoid backup withholding at the applicable rate with respect to dividends on our common stock. Generally, a holder will comply with such procedures if it provides a properly executed IRS Form W-8BEN or W-8BEN-E or otherwise meets documentary evidence requirements for establishing that it is a non-U.S. holder, or otherwise establishes an exemption.

Information reporting and backup withholding generally will apply to the proceeds of a disposition of our common stock by a non-U.S. holder effected by or through the U.S. office of any broker, U.S. or foreign, unless the holder certifies its status as a non-U.S. holder and satisfies certain other requirements, or otherwise establishes an exemption. Generally, information reporting and backup withholding will not apply to a payment

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of disposition proceeds to a non-U.S. holder where the transaction is effected outside the United States through a non-U.S. office of a broker. However, for information reporting purposes, dispositions effected through a non-U.S. office of a broker with substantial U.S. ownership or operations generally will be treated in a manner similar to dispositions effected through a U.S. office of a broker. Non-U.S. holders should consult their own tax advisors regarding the application of the information reporting and backup withholding rules to them.

Copies of information returns may be made available to the tax authorities of the country in which the non-U.S. holder resides or is incorporated under the provisions of a specific treaty or agreement. Any documentation provided to an applicable withholding agent may need to be updated in certain circumstances.

Backup withholding is not an additional tax. Any amounts withheld under the backup withholding rules from a payment to a non-U.S. holder may be refunded or credited against the non-U.S. holder s U.S. federal income tax liability, if any, provided that an appropriate claim is timely filed with the IRS.

Foreign Account Tax Compliance Act

Legislation commonly referred to as the Foreign Account Tax Compliance Act and associated guidance, or collectively, FATCA, will generally impose a 30% withholding tax on any withholdable payment (as defined below) to a foreign financial institution, unless such institution enters into an agreement with the U.S. government to collect and provide to the U.S. tax authorities substantial information regarding U.S. account holders of such institution (which would include certain equity and debt holders of such institution, as well as certain account holders that are foreign entities with U.S. owners) or another applicable exception applies or such institution is compliant with applicable foreign law enacted in connection with an applicable intergovernmental agreement between the United States and a foreign jurisdiction. FATCA will also generally impose a 30% withholding tax on any withholdable payment (as defined below) to a foreign entity that is not a financial institution, unless such entity provides the withholding agent with a certification identifying the substantial U.S. owners of the entity (which generally includes any U.S. person who directly or indirectly owns more than 10% of the entity), if any, or another applicable exception applies or such entity is compliant with applicable foreign law enacted in connection with an applicable intergovernmental agreement between the United States and a foreign jurisdiction. Under certain circumstances, a non-U.S. holder might be eligible for refunds or credits of such taxes.

Withholdable payments generally include dividends on our common stock, and beginning on January 1, 2019, will also include the gross proceeds of a disposition of our common stock. The FATCA withholding tax will apply regardless of whether a payment would otherwise be exempt from or not subject to U.S. nonresident withholding tax (e.g., as capital gain).

Federal Estate Tax

Common stock owned or treated as owned by an individual who is a non-U.S. holder (as specially defined for U.S. federal estate tax purposes) at the time of death will be included in the individual s gross estate for U.S. federal estate tax purposes and, therefore, may be subject to U.S. federal estate tax, unless an applicable estate tax or other treaty provides otherwise.

The preceding discussion of material U.S. federal tax considerations is for general information only. It is not tax advice. Prospective investors should consult their own tax advisors regarding the particular U.S. federal, state, local and non-U.S. tax consequences of purchasing, holding and disposing of our common stock, including the consequences of any proposed changes in applicable laws.

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UNDERWRITING

We are offering the shares of common stock described in this prospectus through a number of underwriters. J.P. Morgan Securities LLC and Morgan Stanley & Co. LLC are acting as joint book-running managers of the offering and as representatives of the underwriters. We have entered into an underwriting agreement with the underwriters. Subject to the terms and conditions of the underwriting agreement, we have agreed to sell to the underwriters, and each underwriter has severally agreed to purchase, at the public offering price less the underwriting discounts and commissions set forth on the cover page of this prospectus, the number of shares of common stock listed next to its name in the following table:

Name	Number of Shares
J.P. Morgan Securities LLC	2,560,000
Morgan Stanley & Co. LLC	2,176,000
Cowen and Company, LLC	1,152,000
Wedbush Securities Inc.	512,000
Total	6,400,000

The underwriters are committed to purchase all the common shares offered by us if they purchase any shares. The underwriting agreement also provides that if an underwriter defaults, the purchase commitments of non-defaulting underwriters may also be increased or the offering may be terminated.

The underwriters propose to offer the common shares directly to the public at the public offering price set forth on the cover page of this prospectus and to certain dealers at that price less a concession not in excess of $0.6750 per share. After the initial offering of the shares to the public, the offering price and other selling terms may be changed by the underwriters.

The underwriters have an option to buy up to 960,000 additional shares of common stock from us. The underwriters have 30 days from the date of this prospectus to exercise this option to purchase additional shares. If any shares are purchased with this option to purchase additional shares, the underwriters will purchase shares in approximately the same proportion as shown in the table above. If any additional shares of common stock are purchased, the underwriters will offer the additional shares on the same terms as those on which the shares are being offered.

The underwriting fee is equal to the public offering price per share of common stock less the amount paid by the underwriters to us per share of common stock. The underwriting fee is $1.1250 per share. The following table shows the per share and total underwriting discounts and commissions to be paid to the underwriters assuming both no exercise and full exercise of the underwriters option to purchase additional shares.

	Without option to purchase additional shares exercise	With full option to purchase additional shares exercise
Per Share	$ 1.1250	$ 1.1250

Total	$ 7,200,000	$ 8,280,000

We estimate that the total expenses of this offering, including registration, filing and listing fees, printing fees and legal and accounting expenses, but excluding the underwriting discounts and commissions, will be approximately $550,000. We have agreed to reimburse the underwriters up to $25,000 for expenses relating to the clearance of this offering with the Financial Industry Regulatory Authority, Inc. A prospectus in electronic format may be made available on the web sites maintained by one or more underwriters, or selling group

members, if any, participating in the offering. The underwriters may agree to allocate a number of shares to underwriters and selling group members for sale to their online brokerage account holders. Internet distributions will be allocated by the representatives to underwriters and selling group members that may make Internet distributions on the same basis as other allocations.

We and our executive officers and directors have agreed that for a period of 90 days after the date of this prospectus, and certain of our principal stockholders have agreed that for a period of 45 days after the date of this prospectus (as applicable, the restricted period), without the prior written consent of J.P. Morgan Securities LLC and Morgan Stanley & Co. LLC on behalf of the underwriters, we and they will not:

- offer, pledge, sell, contract to sell, sell any option or contract to purchase, purchase any option or contract to sell, grant any option, right or warrant to purchase, lend or otherwise transfer or dispose of, directly or indirectly, any shares of common stock or any securities convertible into or exercisable or exchangeable for shares of common stock;

- file any registration statement with the Securities and Exchange Commission relating to the offering of any shares of common stock or any securities convertible into or exercisable or exchangeable for common stock; or

- enter into any swap or other arrangement that transfers to another, in whole or in part, any of the economic consequences of ownership of our common stock;

whether any such transaction described above is to be settled by delivery of common stock or such other securities, in cash or otherwise. In addition, we and each such person agrees that, without the prior written consent of J.P. Morgan Securities LLC and Morgan Stanley & Co. LLC on behalf of the underwriters, we or such other person will not, during the restricted period, make any demand for, or exercise any right with respect to, the registration of any shares of common stock or any security convertible into or exercisable or exchangeable for common stock.

The restrictions described in the immediately preceding paragraph do not apply to:

- the sale of shares to the underwriters;

- our issuance of common stock upon the exercise of an option or a warrant or the conversion of a security outstanding on the date of, and described in, this prospectus;

- the transfer of common stock to us pursuant to the exercise of our right to repurchase certain shares in connection with the termination of employment or board service under agreements entered into pursuant to our equity incentive plans;

transactions by any person other than us relating to shares of common stock or other securities acquired in open market transactions after the completion of the offering of the shares; provided that no filing under Section 16(a) of the Securities Exchange Act of 1934, as amended (the Exchange Act), is required or voluntarily made in connection with subsequent sales of the common stock or other securities acquired in such open market transactions;

our sale or issuance of or entry into an agreement to sell or issue shares of common stock in connection with our acquisition of one or more businesses, products, assets or technologies or in connection with certain strategic transactions; provided, that, the aggregate number of shares of common stock that we may sell or issue or agree to sell or issue pursuant to this provision cannot exceed 5% of the total number of shares of common stock issued and outstanding immediately following the completion of this offering and provided further that each recipient of such shares pursuant to this provision must execute and deliver to the representatives, on or prior to such issuance, a lock-up agreement; or

the establishment of a trading plan pursuant to Rule 10b5-1 under the Exchange Act for the transfer of shares of common stock, provided that (i) such plan does not provide for the transfer of common stock during the restricted period and (ii) to the extent a public announcement or filing under the Exchange

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Act, if any, is required or voluntarily made regarding the establishment of such plan, such announcement or filing shall include a statement to the effect that no transfer of common stock may be made under such plan during the restricted period.

J.P. Morgan Securities LLC and Morgan Stanley & Co. LLC, in their sole discretion, may release our common stock and other securities subject to the lock-up agreements described above in whole or in part at any time with or without notice.

We have agreed to indemnify the underwriters against certain liabilities, including liabilities under the Securities Act of 1933.

Our common stock is listed on The NASDAQ Global Select Market under the symbol GBT .

In connection with this offering, the underwriters may engage in stabilizing transactions, which involves making bids for, purchasing and selling shares of common stock in the open market for the purpose of preventing or retarding a decline in the market price of the common stock while this offering is in progress. These stabilizing transactions may include making short sales of the common stock, which involves the sale by the underwriters of a greater number of shares of common stock than they are required to purchase in this offering, and purchasing shares of common stock on the open market to cover positions created by short sales. Short sales may be covered shorts, which are short positions in an amount not greater than the underwriters option to purchase additional shares referred to above, or may be naked shorts, which are short positions in excess of that amount. The underwriters may close out any covered short position either by exercising their option to purchase additional shares, in whole or in part, or by purchasing shares in the open market. In making this determination, the underwriters will consider, among other things, the price of shares available for purchase in the open market compared to the price at which the underwriters may purchase shares through the option to purchase additional shares. A naked short position is more likely to be created if the underwriters are concerned that there may be downward pressure on the price of the common stock in the open market that could adversely affect investors who purchase in this offering. To the extent that the underwriters create a naked short position, they will purchase shares in the open market to cover the position.

The underwriters have advised us that, pursuant to Regulation M of the Securities Act of 1933, they may also engage in other activities that stabilize, maintain or otherwise affect the price of the common stock, including the imposition of penalty bids. This means that if the representatives of the underwriters purchase common stock in the open market in stabilizing transactions or to cover short sales, the representatives can require the underwriters that sold those shares as part of this offering to repay the underwriting discount received by them.

These activities may have the effect of raising or maintaining the market price of the common stock or preventing or retarding a decline in the market price of the common stock, and, as a result, the price of the common stock may be higher than the price that otherwise might exist in the open market. If the underwriters commence these activities, they may discontinue them at any time. The underwriters may carry out these transactions on the The NASDAQ Global Select Market, in the over-the-counter market or otherwise.

In addition, in connection with this offering certain of the underwriters (and selling group members) may engage in passive market making transactions in our common stock on The NASDAQ Global Select Market prior to the pricing and completion of this offering. Passive market making consists of displaying bids on The NASDAQ Global Select Market no higher than the bid prices of independent market makers and making purchases at prices no higher than these independent bids and effected in response to order flow. Net purchases by a passive market maker on each day are generally limited to a specified percentage of the passive market maker s average daily trading volume in the common stock during a specified period and must be discontinued when such limit is reached. Passive market making may cause the price of our common stock to be higher than the price that otherwise would exist in the open market in

the absence of these transactions. If passive market making is commenced, it may be discontinued at any time.

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Certain of the underwriters and their affiliates have provided in the past to us and our affiliates and may provide from time to time in the future certain commercial banking, financial advisory, investment banking and other services for us and such affiliates in the ordinary course of their business, for which they have received and may continue to receive customary fees and commissions. In addition, from time to time, certain of the underwriters and their affiliates may effect transactions for their own account or the account of customers, and hold on behalf of themselves or their customers, long or short positions in our debt or equity securities or loans, and may do so in the future.

Selling Restrictions

Other than in the United States, no action has been taken by us or the underwriters that would permit a public offering of the securities offered by this prospectus in any jurisdiction where action for that purpose is required. The securities offered by this prospectus may not be offered or sold, directly or indirectly, nor may this prospectus or any other offering material or advertisements in connection with the offer and sale of any such securities be distributed or published in any jurisdiction, except under circumstances that will result in compliance with the applicable rules and regulations of that jurisdiction. Persons into whose possession this prospectus comes are advised to inform themselves about and to observe any restrictions relating to the offering and the distribution of this prospectus. This prospectus does not constitute an offer to sell or a solicitation of an offer to buy any securities offered by this prospectus in any jurisdiction in which such an offer or a solicitation is unlawful.

Notice to Prospective Investors in European Economic Area

In relation to each Member State of the European Economic Area (each, a Relevant Member State), no offer of shares may be made to the public in that Relevant Member State other than:

A. to any legal entity which is a qualified investor as defined in the Prospectus Directive;

B. to fewer than 100 or, if the Relevant Member State has implemented the relevant provision of the 2010 PD Amending Directive, 150, natural or legal persons (other than qualified investors as defined in the Prospectus Directive), as permitted under the Prospectus Directive, subject to obtaining the prior consent of the representatives; or

C. in any other circumstances falling within Article 3(2) of the Prospectus Directive,

provided that no such offer of shares shall require the Company or the representatives to publish a prospectus pursuant to Article 3 of the Prospectus Directive or supplement a prospectus pursuant to Article 16 of the Prospectus Directive.

Each person in a Relevant Member State who initially acquires any shares or to whom any offer is made will be deemed to have represented, acknowledged and agreed that it is a qualified investor within the meaning of the law in that Relevant Member State implementing Article 2(1)(e) of the Prospectus Directive. In the case of any shares being offered to a financial intermediary as that term is used in Article 3(2) of the Prospectus Directive, each such financial intermediary will be deemed to have represented, acknowledged and agreed that the shares acquired by it in the offer have not been acquired on a non-discretionary basis on behalf of, nor have they been acquired with a view to their offer or resale to, persons in circumstances which may give rise to an offer of any shares to the public other than their

offer or resale in a Relevant Member State to qualified investors as so defined or in circumstances in which the prior consent of the representatives has been obtained to each such proposed offer or resale.

The Company, the representatives and their affiliates will rely upon the truth and accuracy of the foregoing representations, acknowledgements and agreements.

This prospectus has been prepared on the basis that any offer of shares in any Relevant Member State will be made pursuant to an exemption under the Prospectus Directive from the requirement to publish a prospectus for offers of shares. Accordingly any person making or intending to make an offer in that Relevant Member State

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of shares which are the subject of the offering contemplated in this prospectus may only do so in circumstances in which no obligation arises for the Company or any of the underwriters to publish a prospectus pursuant to Article 3 of the Prospectus Directive in relation to such offer. Neither the Company nor the underwriters have authorized, nor do they authorize, the making of any offer of shares in circumstances in which an obligation arises for the Company or the underwriters to publish a prospectus for such offer.

For the purpose of the above provisions, the expression an offer to the public in relation to any shares in any Relevant Member State means the communication in any form and by any means of sufficient information on the terms of the offer and the shares to be offered so as to enable an investor to decide to purchase or subscribe the shares, as the same may be varied in the Relevant Member State by any measure implementing the Prospectus Directive in the Relevant Member State and the expression Prospectus Directive means Directive 2003/71/EC (including the 2010 PD Amending Directive, to the extent implemented in the Relevant Member States) and includes any relevant implementing measure in the Relevant Member State and the expression 2010 PD Amending Directive means Directive 2010/73/EU.

Notice to Prospective Investors in United Kingdom

In addition, in the United Kingdom, this document is being distributed only to, and is directed only at, and any offer subsequently made may only be directed at persons who are qualified investors (as defined in the Prospectus Directive) (i) who have professional experience in matters relating to investments falling within Article 19 (5) of the Financial Services and Markets Act 2000 (Financial Promotion) Order 2005, as amended (the Order) and/or (ii) who are high net worth companies (or persons to whom it may otherwise be lawfully communicated) falling within Article 49(2)(a) to (d) of the Order (all such persons together being referred to as relevant persons).

Any person in the United Kingdom that is not a relevant person should not act or rely on the information included in this document or use it as basis for taking any action. In the United Kingdom, any investment or investment activity that this document relates to may be made or taken exclusively by relevant persons. Any person in the United Kingdom that is not a relevant person should not act or rely on this document or any of its contents.

Notice to Prospective Investors in Japan

The shares have not been and will not be registered under the Financial Instruments and Exchange Act. Accordingly, the shares may not be offered or sold, directly or indirectly, in Japan or to, or for the benefit of, any resident of Japan (which term as used herein means any person resident in Japan, including any corporation or other entity organized under the laws of Japan), or to others for re-offering or resale, directly or indirectly, in Japan or to or for the benefit of a resident of Japan, except pursuant to an exemption from the registration requirements of, and otherwise in compliance with, the Financial Instruments and Exchange Act and any other applicable laws, regulations and ministerial guidelines of Japan.

Notice to Prospective Investors in Hong Kong

The shares have not been offered or sold and will not be offered or sold in Hong Kong, by means of any document, other than (a) to professional investors as defined in the Securities and Futures Ordinance (Cap. 571) of Hong Kong and any rules made under that Ordinance; or (b) in other circumstances which do not result in the document being a prospectus as defined in the Companies Ordinance (Cap. 32) of Hong Kong or which do not constitute an offer to the public within the meaning of that Ordinance. No advertisement, invitation or document relating to the shares has been or may be issued or has been or may be in the possession of any person for the purposes of issue, whether in Hong Kong or elsewhere, which is directed at, or the contents of which are likely to be accessed or read by, the public of

Hong Kong (except if permitted to do so under the securities laws of Hong Kong) other than with respect to shares which are or are intended to be disposed of only to persons outside Hong Kong or only to professional investors as defined in the Securities and Futures Ordinance and any rules made under that Ordinance.

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Notice to Prospective Investors in Singapore

This prospectus has not been registered as a prospectus with the Monetary Authority of Singapore. Accordingly, this prospectus and any other document or material in connection with the offer or sale, or invitation for subscription or purchase, of shares may not be circulated or distributed, nor may the shares be offered or sold, or be made the subject of an invitation for subscription or purchase, whether directly or indirectly, to persons in Singapore other than (i) to an institutional investor under Section 274 of the Securities and Futures Act, Chapter 289 of Singapore (the SFA), (ii) to a relevant person pursuant to Section 275(1), or any person pursuant to Section 275(1A), and in accordance with the conditions specified in Section 275, of the SFA, or (iii) otherwise pursuant to, and in accordance with the conditions of, any other applicable provision of the SFA.

Where the shares are subscribed or purchased under Section 275 of the SFA by a relevant person which is:

(a) a corporation (which is not an accredited investor (as defined in Section 4A of the SFA)) the sole business of which is to hold investments and the entire share capital of which is owned by one or more individuals, each of whom is an accredited investor; or

(b) a trust (where the trustee is not an accredited investor) whose sole purpose is to hold investments and each beneficiary of the trust is an individual who is an accredited investor,

securities (as defined in Section 239(1) of the SFA) of that corporation or the beneficiaries rights and interest (howsoever described) in that trust shall not be transferred within six months after that corporation or that trust has acquired the shares pursuant to an offer made under Section 275 of the SFA except:

(a) to an institutional investor or to a relevant person defined in Section 275(2) of the SFA, or to any person arising from an offer referred to in Section 275(1A) or Section 276(4)(i)(B) of the SFA;

(b) where no consideration is or will be given for the transfer;

(c) where the transfer is by operation of law;

(d) as specified in Section 276(7) of the SFA; or

(e) as specified in Regulation 32 of the Securities and Futures (Offers of Investments) (Shares and Debentures) Regulations 2005 of Singapore

Notice to Prospective Investors in Canada

The securities may be sold only to purchasers purchasing, or deemed to be purchasing, as principal that are accredited investors, as defined in National Instrument 45-106 *Prospectus Exemptions* or subsection 73.3(1) of the *Securities Act* (Ontario), and are permitted clients, as defined in National Instrument 31-103 *Registration Requirements, Exemptions*

and Ongoing Registrant Obligations. Any resale of the securities must be made in accordance with an exemption from, or in a transaction not subject to, the prospectus requirements of applicable securities laws.

Securities legislation in certain provinces or territories of Canada may provide a purchaser with remedies for rescission or damages if this prospectus (including any amendment thereto) contains a misrepresentation, provided that the remedies for rescission or damages are exercised by the purchaser within the time limit prescribed by the securities legislation of the purchaser s province or territory. The purchaser should refer to any applicable provisions of the securities legislation of the purchaser s province or territory for particulars of these rights or consult with a legal advisor.

Pursuant to section 3A.3 of National Instrument 33-105 *Underwriting Conflicts* (NI 33-105), the underwriters are not required to comply with the disclosure requirements of NI 33-105 regarding underwriter conflicts of interest in connection with this offering.

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LEGAL MATTERS

The validity of the common stock offered hereby will be passed upon for us by Goodwin Procter LLP, San Francisco, California and for the underwriters by Davis Polk & Wardwell LLP, Menlo Park, California.

EXPERTS

The financial statements of Global Blood Therapeutics, Inc. as of December 31, 2015 and 2014, and for each of the years in the three-year period ended December 31, 2015, are incorporated by reference herein and in reliance upon the report of KPMG LLP, independent registered public accounting firm, incorporated by reference herein, and upon the authority of said firm as experts in accounting and auditing.

WHERE YOU CAN FIND MORE INFORMATION

We have filed with the SEC a registration statement on Form S-1 under the Securities Act that registers the shares of our common stock to be sold in this offering. This prospectus does not contain all of the information set forth in the registration statement and the exhibits and schedules filed as part of the registration statement. For further information with respect to us and our common stock, we refer you to the registration statement and the exhibits and schedules filed as a part of the registration statement. Statements contained in this prospectus concerning the contents of any contract or any other document are not necessarily complete. If a contract or document has been filed as an exhibit to the registration statement, we refer you to the copy of the contract or document that has been filed. Each statement in this prospectus relating to a contract or document filed as an exhibit is qualified in all respects by the filed exhibit. The reports and other information we file with the SEC can be read and copied at the SEC s Public Reference Room at 100 F Street, NE, Washington D.C. 20549. Copies of these materials can be obtained at prescribed rates from the Public Reference Section of the SEC at the principal offices of the SEC, 100 F Street, NE, Washington D.C. 20549. You may obtain information regarding the operation of the public reference room by calling 1(800) SEC-0330. The SEC also maintains a web site (http://www.sec.gov) that contains reports, proxy and information statements and other information regarding issuers like us that file electronically with the SEC.

We are subject to the reporting and information requirements of the Exchange Act and, as a result, we file periodic reports, proxy statements and other information with the SEC. These periodic reports, proxy statements and other information will be available for inspection and copying at the SEC s public reference room and the web site of the SEC referred to above.

INCORPORATION OF CERTAIN INFORMATION BY REFERENCE

The SEC allows us to incorporate by reference information from other documents that we file with it, which means that we can disclose important information to you by referring you to those documents. The information incorporated by reference is considered to be part of this prospectus. Information in this prospectus supersedes information incorporated by reference that we filed with the SEC prior to the date of this prospectus. We incorporate by reference into this prospectus and the registration statement of which this prospectus is a part the information or documents listed below that we have filed with the SEC (SEC File No. 001-37539):

- our Annual Report on Form 10-K for the year ended December 31, 2015, filed with the SEC on March 29, 2016;

the information specifically incorporated by reference into our Annual Report on Form 10-K for the year ended December 31, 2015 from our Definitive Proxy Statement on Schedule 14A, filed with the SEC on April 28, 2016;

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our Quarterly Report on Form 10-Q for the quarter ended March 31, 2016, filed with the SEC on May 12, 2016;

our Current Reports on Form 8-K filed with the SEC on January 5, 2016 (as to Item 5.02 only), January 12, 2016, February 8, 2016 (as to Item 5.02 only), April 4, 2016 (as to Item 5.02 and Exhibit 10.1 only), June 10, 2016 and June 17, 2016; and

the description of our common stock contained in our registration statement on Form 8-A filed with the SEC on August 11, 2015, including any amendments or reports filed for the purposes of updating this description.

We will furnish without charge to you, on written or oral request, a copy of any or all of the documents incorporated by reference in this prospectus, including exhibits to these documents. You should direct any requests for documents to Investor Relations, Global Blood Therapeutics, Inc., 400 East Jamie Court, Suite 101, South San Francisco, CA 94080; telephone: (650) 741-7700.

You also may access these filings on our website at www.globalbloodtx.com. We do not incorporate the information on our website into this prospectus or any supplement to this prospectus and you should not consider any information on, or that can be accessed through, our website as part of this prospectus or any supplement to this prospectus (other than those filings with the SEC that we specifically incorporate by reference into this prospectus or any supplement to this prospectus).

Any statement contained in a document incorporated or deemed to be incorporated by reference in this prospectus will be deemed modified, superseded or replaced for purposes of this prospectus to the extent that a statement contained in this prospectus modifies, supersedes or replaces such statement.

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6,400,000 Shares

Common Stock

Prospectus

J.P. Morgan **Morgan Stanley**

Cowen and Company **Wedbush PacGrow**

June 20, 2016