

Global Blood Therapeutics, Inc.

Form S-1/A

June 20, 2016

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As filed with the Securities and Exchange Commission on June 20, 2016

Registration No. 333-211976

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

AMENDMENT NO. 1
TO
FORM S-1
REGISTRATION STATEMENT
UNDER
THE SECURITIES ACT OF 1933

GLOBAL BLOOD THERAPEUTICS, INC.
(Exact name of Registrant as specified in its charter)

Delaware (State or other jurisdiction of incorporation or organization)	2834 (Primary Standard Industrial Classification Code Number) 400 East Jamie Court, Suite 101	27-4825712 (I.R.S. Employer Identification No.)
--	--	--

South San Francisco, California 94080

(650) 741-7700

(Address, including zip code and telephone number, including area code, of Registrant's principal executive offices)

Ted W. Love, M.D.

President and Chief Executive Officer

Global Blood Therapeutics, Inc.

400 East Jamie Court, Suite 101

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(Name, address, including zip code, and telephone number, including area code, of agent for service)

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Approximate date of commencement of proposed sale to public: As soon as practicable after this Registration Statement becomes effective.

If any of the securities being registered on this Form are to be offered on a delayed or continuous basis pursuant to Rule 415 under the Securities Act of 1933, check the following box:

If this Form is filed to register additional securities for an offering pursuant to Rule 462(b) under the Securities Act, please check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering:

If this Form is a post-effective amendment filed pursuant to Rule 462(c) under the Securities Act, check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering:

If this Form is a post-effective amendment filed pursuant to Rule 462(d) under the Securities Act, check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering:

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

Large Accelerated Filer	<input type="checkbox"/>	Accelerated Filer	<input type="checkbox"/>
Non-Accelerated Filer	<input checked="" type="checkbox"/> (Do not check if a smaller reporting company)	Smaller Reporting Company	<input type="checkbox"/>

The Registrant hereby amends this Registration Statement on such date or dates as may be necessary to delay its effective date until the Registrant shall file a further amendment which specifically states that this Registration Statement shall thereafter become effective in accordance with Section 8(a) of the Securities Act of 1933 or until the Registration Statement shall become effective on such date as the Securities and Exchange Commission, acting pursuant to said Section 8(a), may determine.

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The information in this preliminary prospectus is not complete and may be changed. We may not sell these securities until the registration statement filed with the Securities and Exchange Commission is effective. This preliminary prospectus is not an offer to sell these securities and it is not soliciting an offer to buy these securities in any jurisdiction where the offer or sale is not permitted.

PRELIMINARY PROSPECTUS (Subject to Completion)

Dated June 20, 2016

\$100,000,000

COMMON STOCK

Global Blood Therapeutics, Inc. is offering \$100,000,000 in shares of common stock. Our common stock is listed on The NASDAQ Global Select Market under the symbol GBT. At an assumed offering price of \$17.83 per share, the last reported sale price of our common stock on The NASDAQ Global Select Market on June 17, 2016, we would be offering 5,608,524 shares of our common stock.

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 \$ A SHARE

	Price to Public	Underwriting Discounts and Commissions ⁽¹⁾	Proceeds, before expenses, to Global Blood Therapeutics, Inc.
Per Share	\$	\$	\$
Total	\$	\$	\$

(1) The underwriters will receive compensation in addition to underwriting discounts and commissions. See Underwriting beginning on page 102 for additional information regarding underwriting compensation. We have granted the underwriters an option to purchase up to \$15,000,000 in 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 _____, 2016.

**J.P. Morgan
Cowen and Company**
_____, 2016

**Morgan Stanley
Wedbush PacGrow**

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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	\$100.0 million in shares of common stock
Common stock to be outstanding after this offering	35,144,973 shares based on an assumed offering price of \$17.83 per share, the closing price of our common stock on The NASDAQ Global Select Market on June 17, 2016.
Underwriters' option	We have granted the underwriters an option to purchase a maximum of \$15.0 million in 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 \$93.5 million, or \$107.6 million if the underwriters fully exercise their option to purchase additional shares, and after deducting estimated 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, assumes the sale of \$100.0 million in shares of common stock at an assumed offering price of \$17.83 per share, the last reported sale price of our common stock on The NASDAQ Global Select Market on June 17, 2016 and excludes:	

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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;

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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

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 \$15.0 million in shares of our common stock in this offering.

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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)(2)
	(unaudited)	
	(in thousands)	
Balance Sheet Data:		
Cash and cash equivalents	\$ 133,984	\$ 227,434
Working capital	125,043	218,493
Total assets	138,971	232,421
Additional paid-in capital	241,157	334,602
Accumulated deficit	(115,065)	(115,065)
Total stockholders' equity	126,122	219,572

- (1) The as adjusted column reflects the sale by us of \$100.0 million of shares of our common stock in this offering at an assumed public offering price of \$17.83 per share, which was the last reported sale price of our common stock on The NASDAQ Global Select Market on June 17, 2016 after deducting underwriting discounts and commissions and estimated offering expenses payable by us.
- (2) Each \$1.00 increase (decrease) in the assumed public offering price of \$17.83 per share, the last reported sale price of our common stock on The NASDAQ Global Select Market on June 17, 2016, would (decrease) increase the number of shares of common stock to be issued by us in this offering by (297,850) and 333,246, respectively, assuming the aggregate dollar amount of shares offered by us, as set forth on the cover page of this prospectus, remains the same and after deducting underwriting discounts and commissions and estimated offering expenses payable by us. We may also increase or decrease the aggregate dollar amount of shares we are offering. Each increase (decrease) of \$1.0 million of shares offered by us would increase (decrease) the as adjusted amount of cash and cash equivalents, working capital, total assets, additional paid-in capital and total stockholders' equity by approximately \$0.9 million, assuming that the assumed public offering price remains the same, and after deducting underwriting discounts and commissions and estimated offering expenses payable by us. The as adjusted information discussed above is illustrative only and will be adjusted based on the actual public offering price and other terms of this offering determined at pricing.

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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

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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,

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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

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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

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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

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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

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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

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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

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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,

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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 thr