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Registration No. 333-232260

PROSPECTUS



This is an initial public offering of common stock by Fulcrum Therapeutics, Inc. We are selling 4,500,000 shares of common stock. The initial public offering price is \$16.00 per share.

Prior to this offering, there has been no public market for our common stock. Our common stock has been approved for listing on the Nasdaq Global Market under the symbol "FULC."

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

	<u>Per Share</u>	<u>Total</u>
Initial public offering price	\$16.00	\$72,000,000
Underwriting discounts and commissions ⁽¹⁾	\$1.12	\$5,040,000
Proceeds to Fulcrum, before expenses	\$14.88	\$66,960,000

(1) See "Underwriters" on page 194 for additional information regarding compensation of underwriters.

We have granted the underwriters the right to purchase up to an additional 675,000 shares of common stock. The underwriters may exercise this right at any time within 30 days after the date of this prospectus.

Investing in our common stock involves risks. See "Risk Factors" beginning on page 10 of this prospectus.

Neither the Securities and Exchange Commission nor any state securities commission has approved or disapproved of these securities or passed upon the accuracy or adequacy of this prospectus. Any representation to the contrary is a criminal offense.

The underwriters expect to deliver the shares of common stock to purchasers on or about July 22, 2019.

MORGAN STANLEY

BofA MERRILL LYNCH

SVB LEERINK

July 17, 2019

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Neither we nor the underwriters have authorized anyone to provide you with any information other than that contained in this prospectus, any amendment or supplement to this prospectus or in any free writing prospectus we may authorize to be delivered or made available to you. We and the underwriters take no responsibility for, and can provide no assurance as to the reliability of, any other information that others may give you. We are offering to sell, and seeking offers to buy, shares of our common stock only in jurisdictions where offers and sales are permitted. The information contained in this prospectus is accurate only as of the date of this prospectus, regardless of the time of delivery of this prospectus or any sale of shares of our common stock. Our business, financial condition, results of operations and prospects may have changed since that date.

For investors outside 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 in the United States. Persons outside 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 the United States.

Trademarks, service marks and trade names appearing in this prospectus are the property of their respective owners. Solely for convenience, some of the trademarks, service marks and trade names referred to in this prospectus are listed without the ® and ™ symbols.

PROSPECTUS SUMMARY

This summary highlights information contained elsewhere 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 our consolidated financial statements and the related notes thereto and the information set forth in the sections titled "Risk Factors" and "Management's Discussion and Analysis of Financial Condition and Results of Operations." Unless the context otherwise requires, we use the terms "company," "we," "us" and "our" in this prospectus to refer to Fulcrum Therapeutics, Inc.

Overview

We are a clinical-stage biopharmaceutical company focused on improving the lives of patients with genetically defined diseases in areas of high unmet medical need, with an initial focus on rare diseases. We have developed a proprietary product engine that we employ to systematically identify and validate cellular drug targets that can potentially modulate gene expression to treat the known root cause of genetically defined diseases. We are using our product engine to identify targets that can be drugged by small molecules regardless of the particular underlying mechanism of gene mis-expression. We have identified drug targets to treat the root causes of facioscapulohumeral muscular dystrophy, or FSHD, and certain hemoglobinopathies, namely sickle cell disease, or SCD, and β -thalassemia. We expect to initiate a Phase 2b clinical trial of losmapimod, our product candidate for FSHD, in mid-2019. We commenced a Phase 1 clinical trial in February 2019 to obtain safety and tolerability data for losmapimod in patients with FSHD. We plan to submit an investigational new drug application, or IND, for FTX-HbF, our product candidate for certain hemoglobinopathies, in mid-2020.

We are using our proprietary product engine to identify and validate drug targets and develop product candidates to address diseases caused by the mis-expression of certain genes. Our product engine integrates patient-derived tissue-relevant cell models and drug target screens with our pharmacologically-diverse small molecule compound library and customized CRISPR libraries. We also employ computational biology and FulcrumSeek, our proprietary relational database, to guide target selection and to generate hypotheses on other targets that might be relevant along a gene regulatory pathway.

Our first product candidate, losmapimod, is a small molecule that we are developing for the treatment of FSHD, a rare, progressive and disabling muscle wasting disorder that leads to significant physical impairments and disability. Losmapimod selectively targets p38a/b mitogen activated protein kinase, or p38a/b. We utilized our product engine to discover that inhibition of p38a/b reduced expression of the *DUX4* gene in muscle cells derived from patients with FSHD. The mis-expression of the *DUX4* gene is the known root cause of FSHD. There are no approved therapies for FSHD, one of the most common forms of muscular dystrophy, with an estimated patient population of 16,000 to 38,000 in the United States.

Following our discovery of the role of p38a/b inhibitors in the reduction of *DUX4* expression, we performed an extensive review of known compounds. As a result of our evaluation, we identified losmapimod as the preferred developmental candidate based on the substantial and attractive preclinical and clinical data. We in-licensed losmapimod from affiliates of GlaxoSmithKline, or GSK, in February 2019 and received active pharmaceutical ingredient and losmapimod tablets that had been manufactured by GSK. GSK had previously treated nearly 3,500 subjects with losmapimod across multiple clinical trials, including one Phase 3 clinical trial. GSK did not conduct a clinical trial of losmapimod in patients with FSHD or any other muscle disorder. We have conducted extensive preclinical testing of losmapimod in patient-derived tissue-relevant cell models and have observed that losmapimod selectively reduced *DUX4*-driven gene expression and restored a healthy gene expression signature with minimal impact on healthy human muscle cells or other cell types.

We plan to conduct a randomized, double-blind placebo-controlled Phase 2b clinical trial to investigate whether treatment with losmapimod reduces *DUX4*-driven gene expression in affected skeletal

muscle. In this Phase 2b clinical trial, we will also evaluate the safety and tolerability of losmapimod. We plan to concurrently conduct an open label Phase 2 clinical trial to investigate the safety and tolerability of chronic treatment with losmapimod in patients with FSHD. In this open label trial, we will also evaluate the ability of losmapimod to reduce DUX4-driven gene expression in affected skeletal muscle over varying treatment durations. We expect to initiate the Phase 2b clinical trial at multiple sites in the United States and Europe and the open label Phase 2 clinical trial in Europe in mid-2019. We expect to complete a Phase 1 clinical trial in healthy volunteers and patients with FSHD in 2019. We utilized data from GSK's clinical trials of losmapimod and our preclinical data to submit in May 2019 an IND, and clinical trial applications, or CTAs, in Europe and Canada, that will enable us to advance our clinical development plan for losmapimod in FSHD, including initiating a Phase 2b clinical trial in mid-2019. The FDA accepted the IND in June 2019. The timing of the initiation of the Phase 2b clinical trial is not dependent on the completion of the Phase 1 clinical trial.

We are additionally conducting several preparatory studies to assess biomarker endpoints and clinical outcome assessments and are participating in a natural history study that will follow 150 subjects with FSHD in the United States and 70 subjects in Europe over 18 months. We expect to utilize the data generated from our preparatory studies and the natural history study to inform future clinical trial designs and discussions with regulatory agencies. We believe that these preparatory studies and the safety data from GSK's prior losmapimod clinical trials, together with safety and efficacy data generated from our Phase 1 and Phase 2 clinical trials, may enable us to apply for accelerated approval of losmapimod for the treatment of FSHD. If we observe positive results in our Phase 2b clinical trial based on our proposed biomarker efficacy endpoint of measuring DUX4-driven gene expression in muscle biopsies, we plan to discuss accelerated approval with regulatory agencies and may seek accelerated approval if such regulatory agencies agree that our biomarker endpoint is sufficiently predictive of clinical benefit. The FDA or other regulatory authorities may require us to conduct comparability assessments of GSK-manufactured tablets to tablets manufactured by us or another party.

Our second product candidate, FTX-HbF, is a small molecule designed to upregulate fetal hemoglobin in patients with SCD and b-thalassemia. SCD is a genetic blood disorder caused by a mutation in the b-subunit gene, or *HBB* gene. This mutation results in the formation of abnormal hemoglobin, which causes red blood cells, or RBCs, to change from a round shape into a sickle shape that significantly impairs their function. b-thalassemia is a rare blood disorder caused by various genetic mutations in the *HBB* gene that can significantly impair the production of RBCs.

We designed FTX-HbF to compensate for the root cause of these hemoglobinopathies by inducing the expression of the two g-globin genes, *HBG1/2*, whose expression is normally silenced shortly after birth. The *HBG1/2* genes encode for g-globin, a component of fetal hemoglobin, which is known to compensate for the presence of abnormal hemoglobin in SCD and b-thalassemia. We have observed *in vitro* and *in vivo* activation of the *HBG1/2* genes in preclinical studies with FTX-HbF. We have also observed that FTX-HbF demonstrated robust levels of fetal hemoglobin elevation with no adverse effect on important cellular health markers. We have initiated IND-enabling studies and plan to submit an IND for FTX-HbF in mid-2020.

According to the National Institutes of Health, or NIH, there are approximately 7,000 rare, genetically defined human diseases, many of which have inadequate or no approved treatments. We plan to utilize our product engine to complete four new drug target identification screens in 2019 in Duchenne muscular dystrophy, Friedreich ataxia, myotonic dystrophy 1 and a-synucleinopathies. We also expect to complete an additional six screens in 2020. Our current drug target identification and development efforts are focused on rare neuromuscular disorders, hemoglobinopathies and central nervous system, or CNS, diseases. We also anticipate utilizing our product engine to discover drug targets for genetically defined diseases in other therapeutic areas. In addition to drug targets that we prioritize for internal development, we may identify other drug targets that we would consider for development through partnerships.

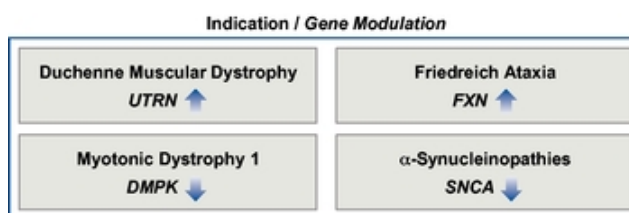
Our Pipeline

We designed our proprietary product engine with potential application across a broad array of genetically defined diseases with a known root cause. The following chart summarizes key information about our lead product candidates.

PROGRAM (PRODUCT CANDIDATE)	DIRECTION OF GENE MODULATION	DISCOVERY	PRECLINICAL	PHASE 1	PHASE 2	PHASE 3	NEXT MILESTONE
FSHD (losmapimod)	<i>DUX4</i> ↓	[Progress bar spanning Discovery, Preclinical, and Phase 1]					Initiate Phase 2b trial in mid-2019 Complete enrollment in Phase 1 trial in mid-2019
Sickle Cell Disease (FTX-HbF)	<i>HBG 1/2</i> ↑	[Progress bar spanning Discovery and Preclinical]					Submit IND in mid-2020
β-Thalassemia (FTX-HbF)	<i>HBG 1/2</i> ↑	[Progress bar spanning Discovery and Preclinical]					Submit IND in mid-2020

Our Discovery Screening Programs

We are leveraging the broad applicability of our product engine to discover drug targets for other rare, genetically defined neuromuscular and CNS diseases. We plan to complete four additional screens in 2019, seeking to identify and validate drug targets that can potentially modulate gene expression to address the root causes of Duchenne muscular dystrophy (*UTRN* gene), Friedreich ataxia (*FXN* gene), Myotonic dystrophy 1 (*DMPK* gene) and α-Synucleinopathies (*SNCA* gene).



Our Strategy

We are leveraging the broad applicability of our proprietary product engine to discover and develop small molecule therapies that modulate gene expression to address the known root cause of genetically defined diseases in areas of high unmet medical need, with an initial focus on rare diseases. We believe that our initial product candidates for the treatment of FSHD, SCD and β-thalassemia may have the potential to treat patients with these debilitating and, in some cases, life-threatening illnesses. The key components of our strategy include:

- Rapidly develop losmapimod for the treatment of FSHD.
- Advance FTX-HbF into clinical development.
- Continue to apply our proprietary product engine to grow our portfolio of product candidates for the treatment of genetically defined diseases.
- Further expand our product engine capabilities.
- Maximize the commercial potential of our product candidates.
- Selectively enter into strategic partnerships to maximize the value of our product engine and pipeline.

Risks Associated with Our Business

Our business is subject to a number of risks of which you should be aware before making an investment decision. These risks are discussed more fully in the "Risk Factors" section of this prospectus. These risks include, but are not limited to, the following:

- We have incurred significant losses since our inception. We expect to incur losses over the next several years and may never achieve or maintain profitability. As of March 31, 2019, we had an accumulated deficit of \$105.0 million.
- We will need substantial additional funding. If we are unable to raise capital when needed, we could be forced to delay, reduce or eliminate our product development programs or commercialization efforts.
- Our limited operating history may make it difficult for you to evaluate the success of our business to date and to assess our future viability.
- We have identified conditions and events, namely our need to raise additional capital, that raise substantial doubt about our ability to continue as a going concern, and our independent registered public accounting firm's report on our consolidated financial statements appearing at the end of this prospectus includes a going concern uncertainty paragraph.
- We are early in our development efforts, and we only have one product candidate in a clinical trial. Our other product candidate is in IND-enabling studies. If we are unable to commercialize our product candidates or experience significant delays in doing so, our business will be materially harmed.
- We may not be successful in our efforts to use our product engine to build a pipeline of product candidates.
- Clinical drug development involves a lengthy and expensive process, with an uncertain outcome. The results of preclinical studies and early clinical trials may not be predictive of future results. We may incur additional costs or experience delays in completing, or ultimately be unable to complete, the development and commercialization of our product candidates.
- Because we are developing some of our product candidates for the treatment of diseases in which there is little clinical experience and, in some cases, using new endpoints or methodologies, such as the measurement of DUX4-driven gene expression in muscle biopsies in our Phase 2b clinical trial of losmapimod for the treatment of FSHD, the FDA or other regulatory authorities may not consider the endpoints of our clinical trials to predict or provide clinically meaningful results.
- If serious adverse events or unacceptable side effects are identified during the development of our product candidates, we may need to abandon or limit our development of some of our product candidates.
- We face substantial competition, which may result in others discovering, developing or commercializing products before or more successfully than we do.
- We expect to rely on contract manufacturing organizations to manufacture our product candidates. If we are unable to enter into such arrangements as expected or if such organizations do not meet our supply requirements, development and/or commercialization of our product candidates may be delayed.
- We rely, and expect to continue to rely, on third parties to conduct our clinical trials, and those third parties may not perform satisfactorily, including failing to meet deadlines for the completion of such trials, which may harm our business.

- If we are unable to obtain, maintain, enforce and protect patent protection for our technology and product candidates or if the scope of the patent protection obtained is not sufficiently broad, our competitors could develop and commercialize technology and products similar or identical to ours, and our ability to successfully develop and commercialize our technology and product candidates may be adversely affected. The composition of matter patents for losmapimod licensed from GSK are expected to expire in 2023. Although we have filed patent applications directed to new methods of using losmapimod and other p38 inhibitors to treat FSHD that, if granted, would be expected to expire in 2038, we cannot be certain that any patents will be granted in respect of these patent applications. We do not own or in-license any patented intellectual property related to our product engine.
- If we fail to comply with our obligations in our intellectual property licenses and funding arrangements with third parties, or otherwise experience disruptions to our business relationships with our licensors, we could lose intellectual property rights that are important to our business.

Our Corporate Information

We were incorporated under the laws of the state of Delaware on August 18, 2015 under the name Fulcrum Therapeutics, Inc. Our principal executive offices are located at 26 Landsdowne Street, Cambridge, Massachusetts 02139, and our telephone number is (617) 651-8851. Our website address is <http://www.fulcrumtx.com>. The information contained on, or that can be accessed through, our website is not a part of this prospectus. We have included our website address in this prospectus solely as an inactive textual reference.

Implications of Being an Emerging Growth Company

As a company with less than \$1.07 billion in revenue during our last fiscal year, we qualify as an "emerging growth company" as defined in the Jumpstart Our Business Startups Act of 2012, or the JOBS Act, and we may remain an emerging growth company for up to five years or until such earlier time as we have more than \$1.07 billion in annual revenue, the market value of our stock held by non-affiliates is more than \$700 million or we issue more than \$1 billion of non-convertible debt over a three-year period. For so long as we remain an emerging growth company, we are permitted and intend to rely on exemptions from certain disclosure and other requirements that are applicable to public companies that are not emerging growth companies. In particular, in this prospectus, we have provided only two years of audited financial statements and have not included all of the executive compensation related information that would be required if we were not an emerging growth company. Accordingly, the information contained herein may be different than the information you receive from other public companies in which you hold stock.

THE OFFERING

Common stock offered	4,500,000 shares
Common stock to be outstanding immediately following this offering	23,340,014 shares
Option to purchase additional shares	We have granted the underwriters an option for a period of 30 days to purchase up to 675,000 additional shares of our common stock.
Use of proceeds	<p>We estimate that the net proceeds from this offering will be approximately \$63.9 million (or approximately \$73.9 million if the underwriters exercise their option to purchase additional shares in full), based on the initial public offering price of \$16.00 per share, after deducting underwriting discounts and commissions and estimated offering expenses payable by us.</p> <p>We intend to use the net proceeds from this offering, together with our existing cash and cash equivalents, to advance losmapimod for FSHD, to advance our hemoglobinopathies program, to fund our ongoing product engine and discovery efforts and for working capital and other general corporate purposes. See "Use of Proceeds."</p>
Risk factors	You should read the "Risk Factors" section of this prospectus for a discussion of factors to consider carefully before deciding to invest in shares of our common stock.
Nasdaq Global Market symbol	"FULC"

The number of shares of our common stock to be outstanding after this offering is based on 2,768,596 shares of our common stock outstanding as of June 30, 2019, including 898,310 shares of unvested restricted stock subject to repurchase by us, and 16,071,418 shares of our common stock issuable upon the automatic conversion of all outstanding shares of our preferred stock upon the closing of this offering.

The number of shares of our common stock to be outstanding after this offering excludes:

- 1,592,753 shares of common stock issuable upon exercise of stock options outstanding as of June 30, 2019 at a weighted average exercise price of \$7.81 per share;
- 281,503 shares of common stock reserved for future issuance under our 2016 Stock Incentive Plan, as amended, or the 2016 Plan, as of June 30, 2019; and
- 2,017,142 and 252,142 additional shares of our common stock available for future issuance under our 2019 Stock Incentive Plan, of which our board of directors has granted options to purchase an aggregate of 308,486 shares of common stock to certain of our employees and non-employee directors effective upon the commencement of trading of our common stock on the Nasdaq Global Market, and our 2019 Employee Stock Purchase Plan, respectively, as well as any automatic increases in the number of shares of common stock reserved for future issuance under these plans.

Unless otherwise indicated, all information in this prospectus assumes:

- no exercise of the outstanding options described above;
- no exercise by the underwriters of their option to purchase additional shares of our common stock;

- the automatic conversion of all outstanding shares of our preferred stock into an aggregate of 16,071,418 shares of our common stock upon the closing of this offering; and
- the filing and effectiveness of our restated certificate of incorporation and the adoption of our amended and restated bylaws upon the closing of this offering.

In addition, unless otherwise indicated, all information in this prospectus gives effect to a one-for-seven reverse stock split of our common stock that became effective on July 5, 2019.

SUMMARY CONSOLIDATED FINANCIAL DATA

You should read the following summary consolidated financial data together with our consolidated financial statements and the related notes appearing at the end of this prospectus and the "Selected Consolidated Financial Data" and "Management's Discussion and Analysis of Financial Condition and Results of Operations" sections of this prospectus. We have derived the consolidated statement of operations data for the years ended December 31, 2017 and 2018 from our annual consolidated financial statements appearing at the end of this prospectus. The consolidated statement of operations data for the three months ended March 31, 2018 and 2019 and the consolidated balance sheet data as of March 31, 2019 have been derived from our interim consolidated financial statements appearing at the end of this prospectus and have been prepared on the same basis as the annual consolidated financial statements. In the opinion of management, the interim data reflect all normal recurring adjustments necessary for the fair presentation of the financial information in those statements. Our historical results are not necessarily indicative of the results that may be expected in the future, and our results for any interim period are not necessarily indicative of the results that should be expected for any full year or any other period.

	Year Ended December 31,		Three Months Ended March 31,	
	2017	2018	2018	2019
(in thousands, except per share data)				
Consolidated Statement of Operations Data:				
Operating expenses:				
Research and development	\$ 18,494	\$ 25,184	\$ 5,573	\$ 34,629
General and administrative	4,499	8,314	1,737	2,598
Total operating expenses	22,993	33,498	7,310	37,227
Loss from operations	(22,993)	(33,498)	(7,310)	(37,227)
Other income, net:				
Interest income, net	1	518	—	377
Other income	28	392	370	7
Net loss and comprehensive loss	\$ (22,964)	\$ (32,588)	\$ (6,940)	\$ (36,843)
Cumulative convertible preferred stock dividends	\$ (2,407)	\$ (6,559)	(828)	(3,041)
Net loss attributable to common stockholders	\$ (25,371)	\$ (39,147)	\$ (7,768)	\$ (39,884)
Net loss per share attributable to common stockholders, basic and diluted ⁽¹⁾	\$ (35.68)	\$ (31.14)	\$ (7.62)	\$ (24.29)
Weighted average number of common shares used in net loss per share attributable to common stockholders, basic and diluted ⁽¹⁾	711	1,257	1,019	1,642
Pro forma net loss per share attributable to common stockholders, basic and diluted ⁽¹⁾		\$ (2.98)		\$ (2.17)
Pro forma weighted average number of common shares used in net loss per share attributable to common stockholders, basic and diluted ⁽¹⁾		10,951		16,940

- (1) See Note 12 to our annual and interim consolidated financial statements appearing at the end of this prospectus for details on the calculation of basic and diluted net loss per share attributable to common stockholders and basic and diluted pro forma net loss per share attributable to common stockholders.

	As of March 31, 2019		
	Actual	Pro Forma ⁽²⁾	Pro Forma As Adjusted ⁽³⁾
	(in thousands)		
Consolidated Balance Sheet Data:			
Cash and cash equivalents	\$ 62,452	\$ 62,452	\$ 126,312
Working capital ⁽¹⁾	59,306	59,306	123,166
Total assets	75,588	75,588	139,448
Convertible preferred stock	165,136	—	—
Total stockholders' (deficit) equity	(99,687)	65,449	129,309

- (1) We define working capital as current assets less current liabilities.
- (2) The pro forma balance sheet data give effect to the automatic conversion of all outstanding shares of our preferred stock into an aggregate of 16,071,418 shares of common stock upon the closing of this offering.
- (3) The pro forma as adjusted balance sheet data give further effect to our issuance and sale of 4,500,000 shares of our common stock in this offering at the initial public offering price of \$16.00 per share, after deducting underwriting discounts and commissions and estimated offering expenses payable by us.

RISK FACTORS

Investing in our common stock involves a high degree of risk. You should carefully consider the risks and uncertainties described below together with all of the other information contained in this prospectus, including our consolidated financial statements and the related notes appearing at the end of this prospectus, before deciding to invest in our common stock. If any of the following risks actually occur, our business, prospects, operating results and financial condition could suffer materially. In such event, the trading price of our common stock could decline and you might lose all or part of your investment.

Risks Related to our Financial Position and Need for Additional Capital

We have incurred significant losses since our inception. We expect to incur losses over the next several years and may never achieve or maintain profitability.

Since inception, we have incurred significant operating losses. Our net loss was \$23.0 million for the year ended December 31, 2017, \$32.6 million for the year ended December 31, 2018 and \$36.8 million for the three months ended March 31, 2019. As of March 31, 2019, we had an accumulated deficit of \$105.0 million. To date, we have financed our operations primarily through the issuance of convertible notes and convertible preferred stock. We have devoted substantially all of our financial resources and efforts to research and development, including clinical trials and preclinical studies. We are still in the early stages of development of our product candidates, and we have not completed development of any product candidates. We expect to continue to incur significant expenses and operating losses over the next several years. Our net losses may fluctuate significantly from quarter to quarter and year to year. We anticipate that our expenses will increase substantially as we:

- continue our clinical development of losmapimod, including our ongoing Phase 1 clinical trial and planned Phase 2b clinical trial and Phase 2 open label clinical trial;
- continue investigational new drug application, or IND, enabling studies and prepare for a planned Phase 1 clinical trial of FTX-HbF;
- advance clinical-stage product candidates into later stage trials;
- pursue the discovery of drug targets for other rare diseases and the subsequent development of any resulting product candidates;
- seek regulatory approvals for any product candidates that successfully complete clinical trials;
- scale up our manufacturing processes and capabilities, or arrange for a third party to do so on our behalf, to support our clinical trials of our product candidates and commercialization of any of our product candidates for which we may obtain marketing approval;
- establish a sales, marketing and distribution infrastructure to commercialize any products for which we may obtain regulatory approval;
- acquire or in-license products, product candidates, technologies and/or data referencing rights;
- make any milestone payments to affiliates of GlaxoSmithKline plc, or GSK, under our right of reference and license agreement with GSK upon the achievement of specified clinical or regulatory milestones;
- maintain, expand, enforce, defend and protect our intellectual property;
- hire additional clinical, quality control and scientific personnel; and
- add operational, financial and management information systems and personnel, including personnel to support our product development and planned future commercialization efforts and our operations as a public company.

To become and remain profitable, we must succeed in developing, and eventually commercializing, a product or products that generate significant revenue. The ability to achieve this success will require us to be effective in a range of challenging activities, including completing preclinical testing and clinical trials of our product candidates, discovering additional product candidates, obtaining regulatory approval for these product candidates and manufacturing, marketing and selling any products for which we may obtain regulatory approval. We are only in the preliminary stages of most of these activities. We may never succeed in these activities and, even if we do, may never generate revenues that are significant enough to achieve profitability. Because of the numerous risks and uncertainties associated with pharmaceutical product development, we are unable to accurately predict the timing or amount of increased expenses or when, or if, we will be able to achieve profitability. Our expenses will increase if, among other things:

- we are required by the U.S. Food and Drug Administration, or the FDA, the European Medicines Agency, or the EMA, or other regulatory authorities to perform trials or studies in addition to, or different than, those expected;
- there are any delays in completing our clinical trials or the development of any of our product candidates; or
- there are any third-party challenges to our intellectual property or we need to defend against any intellectual property-related claim.

Even if we do achieve profitability, we may not be able to sustain or increase profitability on a quarterly or annual basis. Our failure to become and remain profitable would depress the value of our company and could impair our ability to raise capital, expand our business, maintain our research and development efforts, diversify our pipeline of product candidates or even continue our operations. A decline in the value of our company could also cause you to lose all or part of your investment.

We will need substantial additional funding. If we are unable to raise capital when needed, we could be forced to delay, reduce or eliminate our product development programs or commercialization efforts.

We expect to devote substantial financial resources to our ongoing and planned activities, particularly as we continue our Phase 1 clinical trial of losmapimod and prepare for a planned Phase 2b clinical trial and Phase 2 open label clinical trial of losmapimod and planned Phase 1 clinical trial of FTX-HbF; and continue research and development and initiate additional clinical trials of, and seek regulatory approval for, these and other product candidates. We expect our expenses to increase substantially in connection with our ongoing activities, particularly as we advance our preclinical activities and clinical trials. In addition, if we obtain regulatory approval for any of our product candidates, we expect to incur significant commercialization expenses related to product manufacturing, sales, marketing and distribution. Furthermore, upon the closing of this offering, we expect to incur additional costs associated with operating as a public company. Accordingly, we will need to obtain substantial additional funding in connection with our continuing operations. If we are unable to raise capital when needed or on acceptable terms, we could be forced to delay, reduce or eliminate our research and development programs or any future commercialization efforts.

Our future capital requirements will depend on many factors, including:

- the progress, costs and results of our ongoing Phase 1 clinical trial of losmapimod;
- the scope, progress, results and costs of discovery research, preclinical development, laboratory testing and clinical trials for our product candidates, including our planned Phase 2b clinical trial and planned Phase 2 open label clinical trial of losmapimod and our planned Phase 1 clinical trial of FTX-HbF;
- the number of and development requirements for other product candidates that we pursue;
- the costs, timing and outcome of regulatory review of our product candidates;

- our ability to enter into contract manufacturing arrangements for supply of active pharmaceutical ingredient, or API, and manufacture of our product candidates and the terms of such arrangements;
- our ability to establish and maintain strategic collaborations, licensing or other arrangements and the financial terms of such arrangements;
- the payment or receipt of milestones and receipt of other collaboration-based revenues, if any;
- the costs and timing of future commercialization activities, including product manufacturing, sales, marketing and distribution, for any of our product candidates for which we may receive marketing approval;
- the amount and timing of revenue, if any, received from commercial sales of our product candidates for which we receive marketing approval;
- the costs and timing of preparing, filing and prosecuting patent applications, maintaining and enforcing our intellectual property and proprietary rights and defending any intellectual property-related claims; and
- the extent to which we acquire or in-license other products, product candidates, technologies or data referencing rights.

As of March 31, 2019, we had cash and cash equivalents of approximately \$62.5 million. We believe that the net proceeds from this offering, together with our existing cash and cash equivalents as of March 31, 2019, will enable us to fund our operating expenses and capital expenditure requirements into the third quarter of 2021. However, we have based this estimate on assumptions that may prove to be wrong, and our operating plan may change as a result of many factors currently unknown to us. As a result, we could deplete our capital resources sooner than we currently expect.

Identifying potential product candidates and conducting preclinical testing and clinical trials is a time-consuming, expensive and uncertain process that takes years to complete, and we may never generate the necessary data or results required to obtain regulatory approval and achieve product sales. In addition, our product candidates, if approved, may not achieve commercial success. Commercial revenues, if any, will not be derived unless and until we can achieve sales of products, which we do not anticipate for many years, if at all. Accordingly, we will need to continue to rely on additional financing to achieve our business objectives. Adequate additional financing may not be available to us on acceptable terms, or at all. 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. If adequate funds are not available to us on a timely basis, we may be required to delay, limit, reduce or terminate preclinical studies, clinical trials or other development activities for one or more of our product candidates or discovery stage programs or delay, limit, reduce or terminate our establishment of sales and marketing capabilities or other activities that may be necessary to commercialize our product candidates.

Raising additional capital may cause dilution to our stockholders, including purchasers of our common stock in this offering, restrict our operations or require us to relinquish rights to our technologies or product candidates.

Until such time, if ever, as we can generate substantial product revenues, we expect to finance our cash needs through a combination of equity offerings, debt financings, collaborations, strategic alliances and marketing, distribution or licensing arrangements. We do not have any committed external source of funds. To the extent that we raise additional capital through the sale of equity or convertible debt securities, your ownership interest will be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect your rights as a common stockholder. Debt financing and preferred equity financing, if available, may involve agreements that include covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, selling or licensing our assets, making capital expenditures or declaring dividends.

If we raise additional funds through collaborations, strategic alliances or marketing, distribution or licensing arrangements with third parties, we may have to relinquish valuable rights to our technologies, future revenue streams, research programs or product candidates or grant licenses on terms that may not be favorable to us. If we are unable to raise additional funds through equity or debt financings when needed, we may be required to delay, limit, reduce or terminate our product development or future commercialization efforts or grant rights to develop and market product candidates that we would otherwise prefer to develop and market ourselves.

Our limited operating history may make it difficult for you to evaluate the success of our business to date and to assess our future viability.

We commenced activities in 2015 and are an early-stage company. Our operations to date have been limited to organizing and staffing our company, business planning, raising capital, developing our technology, identifying drug targets and potential product candidates, undertaking preclinical studies and conducting one early-stage clinical trial. We have not yet demonstrated our ability to successfully develop any product candidate, obtain regulatory approvals, manufacture a commercial scale product or arrange for a third party to do so on our behalf, or conduct sales and marketing activities necessary for successful product commercialization. Consequently, any predictions you make about our future success or viability may not be as accurate as they could be if we had a longer operating history or a history of successfully developing and commercializing products.

In addition, as our business grows, we may encounter unforeseen expenses, difficulties, complications, delays and other known and unknown factors. We will need to transition at some point from a company with a research and development focus to a company capable of supporting commercial activities. We may not be successful in such a transition.

We expect our financial condition and operating results to fluctuate significantly from quarter-to-quarter and year-to-year due to a variety of factors, many of which are beyond our control. Accordingly, you should not rely upon the results of any quarterly or annual periods as indications of future operating performance.

We have identified conditions and events that raise substantial doubt about our ability to continue as a going concern.

We may be forced to delay or reduce the scope of our development programs and/or limit or cease our operations if we are unable to obtain additional funding to support our current operating plan. We have identified conditions and events that raise substantial doubt about our ability to continue as a going concern. As of March 31, 2019, we had approximately \$62.5 million in cash and cash equivalents. Based on our available cash resources, we believe we do not have sufficient cash on hand to support current operations for at least one year from the date that the consolidated financial statements for the year ended December 31, 2018 and the consolidated financial statements for the three months ended March 31, 2019 appearing at the end of this prospectus were issued. This condition raises substantial doubt about our ability to continue as a going concern for at least one year from the date of issuance of the financial statements appearing at the end of this prospectus, and our independent registered public accounting firm's report on our consolidated financial statements appearing at the end of this prospectus includes a going concern uncertainty paragraph. We will need to raise additional capital in this offering and/or otherwise to fund our future operations and remain as a going concern. However, we cannot guarantee that we will be able to obtain sufficient additional funding in this offering or otherwise or that such funding, if available, will be obtainable on terms satisfactory to us. In the event that we are unable to obtain sufficient additional funding, there can be no assurance that we will be able to continue as a going concern.

Comprehensive tax reform legislation passed in 2017 could adversely affect our business and financial condition.

On December 22, 2017, the U.S. government enacted legislation commonly referred to as the Tax Cuts and Jobs Act, or the TCJA, which significantly reformed the Internal Revenue Code of 1986, as amended, or the Code. The TCJA, among other things, contains significant changes to corporate taxation, including reduction of the corporate tax rate from a top marginal rate of 35% to a flat rate of 21%, limitation of the tax deduction for net interest expense to 30% of adjusted earnings (except for certain small businesses), limitation of the deduction for net operating losses, or NOLs, to 80% of current year taxable income and elimination of NOL carrybacks, in each case, for losses arising in taxable years beginning after December 31, 2017 (though any such NOLs may be carried forward indefinitely), one-time taxation of offshore earnings at reduced rates regardless of whether they are repatriated, elimination of U.S. tax on foreign earnings (subject to certain important exceptions), immediate deductions for certain new investments instead of deductions for depreciation expense over time, and modifying or repealing many business deductions and credits. Notwithstanding the reduction in the corporate income tax rate, the overall impact of the TCJA remains uncertain and our business and financial condition could be adversely affected. In addition, how various states will respond to the TCJA continues to be uncertain. The impact of this tax reform on holders of our common stock is also uncertain and could be adverse. We urge prospective investors in our common stock to consult with their legal and tax advisors with respect to TCJA and the potential tax consequences of investing in or holding our common stock.

Our ability to use our NOLs and research and development tax credit carryforwards to offset future taxable income may be subject to certain limitations.

As of December 31, 2018, we had federal and state net operating loss carryforwards of \$60.7 million and \$60.5 million, respectively, which begin to expire in 2035. Approximately \$29.7 million of the federal net operating losses can be carried forward indefinitely. As of December 31, 2018, we also had federal and state research and development tax credit carryforwards of \$1.5 million and \$1.3 million, respectively, which begin to expire in 2035. These net operating loss and tax credit carryforwards could expire unused and be unavailable to offset future income tax liabilities.

We have a history of cumulative losses and anticipate that we will continue to incur significant losses in the foreseeable future; thus, we do not know whether or when we will generate taxable income necessary to utilize our NOLs or research and development tax credit carryforwards.

In general, under Section 382 of the Code and corresponding provisions of state law, a corporation that undergoes an "ownership change" is subject to limitations on its ability to utilize its pre-change NOLs and research and development tax credit carryforwards to offset future taxable income. We have not conducted a study to assess whether any such ownership changes have occurred. We may have experienced such ownership changes in the past and may experience such ownership changes in the future as a result of this offering and/or subsequent changes in our stock ownership (which may be outside our control). As a result, if, and to the extent that, we earn net taxable income, our ability to use our pre-change NOLs and research and development tax credit carryforwards to offset such taxable income may be subject to limitations. Our NOLs or credits may also be impaired under state law.

In addition, as described above in "Comprehensive tax reform legislation passed in 2017 could adversely affect our business and financial condition," the TCJA includes changes to U.S. federal tax rates and the rules governing NOL carryforwards that may significantly impact our ability to utilize our NOLs to offset taxable income in the future.

Risks Related to the Discovery and Development of our Product Candidates

We are early in our development efforts, and we only have one product candidate in a clinical trial. Our other product candidate is in IND-enabling studies. If we are unable to commercialize our product candidates or experience significant delays in doing so, our business will be materially harmed.

We are early in our development efforts, and we have advanced only one candidate into clinical trials, losmapimod for the treatment of facioscapulohumeral muscular dystrophy, or FSHD. FTX-HbF, our other product candidate, is in IND-enabling studies. We have invested substantially all of our efforts and financial resources in our proprietary product engine to identify and validate cellular drug targets that can potentially modulate gene expression to address the root cause of rare diseases. Our ability to generate product revenues, which we do not expect will occur for many years, if ever, will depend heavily on the successful development, regulatory approval and eventual commercialization of our product candidates. The success of our product candidates will depend on several factors, including the following:

- successfully completing preclinical studies and clinical trials;
- acceptance by the FDA or other regulatory agencies of the INDs, clinical trial applications, or CTAs, or other regulatory filings for losmapimod, FTX-HbF and future product candidates;
- expanding and maintaining a workforce of experienced scientists and others to continue to develop our product candidates;
- successfully applying for and receiving marketing approvals from applicable regulatory authorities;
- obtaining and maintaining intellectual property protection and regulatory exclusivity for our product candidates;
- making arrangements with third-party manufacturers for, or establishing, commercial manufacturing capabilities;
- establishing sales, marketing and distribution capabilities and successfully launching commercial sales of the products, if and when approved, whether alone or in collaboration with others;
- acceptance of the products, if and when approved, by patients, the medical community and third-party payors;
- effectively competing with other therapies;
- obtaining and maintaining coverage, adequate pricing and adequate reimbursement from third-party payors, including government payors;
- maintaining, enforcing, defending and protecting our rights in our intellectual property portfolio;
- not infringing, misappropriating or otherwise violating others' intellectual property or proprietary rights; and
- maintaining a continued acceptable safety profile of the products following receipt of any regulatory approvals.

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 develop and commercialize our product candidates, which would materially harm our business.

We may not be successful in our efforts to use our product engine to build a pipeline of product candidates.

A key element of our strategy is to use our proprietary product engine to identify and validate cellular drug targets that can potentially modulate gene expression to address the root cause of rare diseases, with an initial focus on identifying small molecules specific to the identified cellular target. Even if we are

successful in identifying drug targets and potential product candidates, such candidates that we identify may not be suitable for clinical development, including as a result of being shown to have harmful side effects or other characteristics that indicate that they are unlikely to receive marketing approval and achieve market acceptance. Identifying, developing, obtaining regulatory approval for and commercializing additional product candidates will require substantial additional funding and is prone to the risks of failure inherent in product development. We cannot provide you any assurance that we will be able to successfully identify additional product candidates with our product engine, advance any of these additional product candidates through the development process or successfully commercialize any such additional product candidates. Regulatory authorities have substantial discretion in the approval process and may cause delays in the approval or rejection of an application. As a result of these factors, it is difficult for us to predict the time and cost of product candidate development. There can be no assurance that any development problems we experience in the future related to our proprietary product engine or any of our research or development programs will not cause significant delays or unanticipated costs, or that such development problems can be solved. If we do not successfully identify, develop, obtain regulatory approval for and commercialize product candidates based upon our technological approach, we will not be able to generate product revenues.

Clinical drug development involves a lengthy and expensive process, with an uncertain outcome. The results of preclinical studies and early clinical trials may not be predictive of future results. We may incur additional costs or experience delays in completing, or ultimately be unable to complete, the development and commercialization of our product candidates.

We have one product candidate in clinical development and one product candidate in IND-enabling studies. The risk of failure for each of our product candidates is high. It is impossible to predict when or if any of our product candidates will prove effective or safe in humans or will receive regulatory approval. Before obtaining marketing approval from regulatory authorities for the sale of any product candidate, we must complete preclinical development and then conduct extensive clinical trials to demonstrate the safety and efficacy of our product candidates in humans. We have not yet begun or completed a pivotal clinical trial of any product candidate. Clinical trials may fail to demonstrate that our product candidates are safe for humans and effective for indicated uses. Even if the clinical trials are successful, changes in marketing approval policies during the development period, changes in or the enactment or promulgation of additional statutes, regulations or guidance or changes in regulatory review for each submitted product application may cause delays in the approval or rejection of an application.

Before we can commence clinical trials for a product candidate, we must complete extensive preclinical testing and studies that support our planned INDs and other regulatory filings in the United States and abroad. We cannot be certain of the timely completion or outcome of our preclinical testing and studies and cannot predict if the FDA or other regulatory agencies will accept our proposed clinical programs or if the outcome of our preclinical testing and studies will ultimately support the further development of our current or future product candidates. As a result, we cannot be sure that we will be able to submit INDs or similar applications for our preclinical programs on the timelines we expect, if at all, and we cannot be sure that submission of INDs or similar applications will result in the FDA or other regulatory authorities allowing clinical trials to begin. Furthermore, product candidates are subject to continued preclinical safety studies, which may be conducted concurrent with our clinical testing. The outcomes of these safety studies may delay the launch of or enrollment in future clinical trials and could impact our ability to continue to conduct our clinical trials.

Clinical testing is expensive, difficult to design and implement, can take many years to complete and is uncertain as to outcome. We cannot guarantee that any clinical trials will be conducted as planned or completed on schedule, or at all. A failure of one or more clinical trials can occur at any stage of testing, which may result from a multitude of factors, including, but not limited to, flaws in study design, dose selection issues, placebo effects, patient enrollment criteria and failure to demonstrate favorable safety or

efficacy traits. The outcome of preclinical testing and early clinical trials may not be predictive of the success of later clinical trials, and preliminary or interim results of a clinical trial do not necessarily predict final results. For example, our product candidates may fail to show the desired safety and efficacy in clinical development despite positive results in preclinical studies or having successfully advanced through initial clinical trials. Losmapimod may not be effective at reducing DUX4-driven gene expression or, even if losmapimod successfully reduces expression of DUX4-driven genes, such reduction may not result in overall clinical benefit. A lack of clinical benefit may be due to insufficient dosing or for other reasons. Many companies in the pharmaceutical and biotechnology industries have suffered significant setbacks in late-stage clinical trials even after achieving promising results in preclinical testing and earlier-stage clinical trials, and we cannot be certain that we will not face similar setbacks. Moreover, preclinical and clinical data are often susceptible to varying 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 of their products. Furthermore, the failure of any of our product candidates to demonstrate safety and efficacy in any clinical trial could negatively impact the perception of our other product candidates and/or cause the FDA or other regulatory authorities to require additional testing before approving any of our product candidates.

In February 2019, we entered into a right of reference and license agreement, or the GSK Agreement, with affiliates of GSK pursuant to which, among other things, GSK granted us a right of reference to certain INDs filed with the FDA and controlled by GSK or its affiliates relating to losmapimod and an exclusive worldwide license to certain of GSK's preclinical and clinical data with respect to losmapimod. Although losmapimod was originally evaluated by GSK in nearly 3,500 subjects, GSK did not evaluate losmapimod in FSHD or in any other muscular dystrophy, and most of the subjects in these trials were given a dose that was lower than our planned dosage of 15 mg of losmapimod twice per day, so the safety data generated from GSK's clinical trials of losmapimod may not be predictive or indicative of the results of our clinical trials. Similarly, while we believe the safety data from GSK's clinical trials may, in part, enable us to apply for accelerated approval, there can be no assurance that this will happen. Regulatory authorities may also raise questions regarding the transition in the future from GSK-manufactured tablets to tablets manufactured by us or another party, and we may be required to conduct comparability assessments, which could result in delays in development and additional costs.

We may experience numerous unforeseen events during, or as a result of, clinical trials that could delay or prevent our ability to receive marketing approval or commercialize our product candidates, including:

- regulators or institutional review boards, or IRBs, may not authorize us or our investigators to commence a clinical trial or conduct a clinical trial at a prospective trial site;
- we may experience delays in reaching, or fail to reach, agreement on acceptable clinical trial contracts or clinical trial protocols with prospective trial sites;
- regulators may decide the design of our clinical trials is flawed, for example if our trial protocol does not evaluate treatment effects in trial subjects for a sufficient length of time;
- clinical trials of our product candidates may produce negative or inconclusive results, and we may decide, or regulators may require us, to conduct additional clinical trials or abandon product development programs;
- we may be unable to establish clinical endpoints that applicable regulatory authorities would consider clinically meaningful, or, if we seek accelerated approval, biomarker efficacy endpoints that applicable regulatory authorities would consider likely to predict clinical benefit;
- preclinical testing may produce results based on which we may decide, or regulators may require us, to conduct additional preclinical studies before we proceed with certain clinical trials, limit the scope of our clinical trials, halt ongoing clinical trials or abandon product development programs;

- the number of patients required for clinical trials of our product candidates may be larger than we anticipate, enrollment in these clinical trials may be slower than we anticipate or participants may drop out of these clinical trials at a higher rate than we anticipate;
- our third-party contractors may fail to comply with regulatory requirements or meet their contractual obligations to us in a timely manner, or at all;
- we may decide, or regulators or IRBs may require us, to suspend or terminate clinical trials of our product candidates for various reasons, including noncompliance with regulatory requirements or a finding that the participants are being exposed to unacceptable health risks;
- regulators or IRBs may require us to perform additional or unanticipated clinical trials to obtain approval or we may be subject to additional post-marketing testing requirements to maintain regulatory approval;
- regulators may revise the requirements for approving our product candidates, or such requirements may not be as we anticipate;
- the cost of clinical trials of our product candidates may be greater than we anticipate;
- the supply or quality of our product candidates or other materials necessary to conduct clinical trials of our product candidates may be insufficient or inadequate;
- our product candidates may have undesirable side effects or other unexpected characteristics, causing us or our investigators, regulators or IRBs to suspend or terminate the trials; and
- regulators may withdraw their approval of a product or impose restrictions on its distribution, such as in the form of a risk evaluation and mitigation strategy, or REMS.

If we are required to conduct additional clinical trials or other testing of our product candidates beyond those that we currently contemplate, if we are unable to successfully complete clinical trials of our product candidates or other testing, if the results of these trials or tests are not positive or are only modestly positive or if there are safety concerns, we may:

- be delayed in obtaining marketing approval for our product candidates;
- not obtain marketing approval at all;
- obtain approval for indications or patient populations that are not as broad as intended or desired;
- obtain approval with labeling or a REMS that includes significant use or distribution restrictions or safety warnings;
- be subject to additional post-marketing testing requirements; or
- have the product removed from the market after obtaining marketing approval.

Our product development costs will also increase if we experience delays in testing or in obtaining marketing approvals. We do not know whether any of our preclinical studies or clinical trials will begin as planned, will need to be restructured or will be completed on schedule, or at all. We may also determine to change the design or protocol of one or more of our clinical trials, including to add additional patients or arms, which could result in increased costs and expenses and/or delays. Significant preclinical study or clinical trial delays also 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 and impair our ability to successfully commercialize our product candidates and may harm our business and results of operations.

Because we are developing some of our product candidates for the treatment of diseases in which there is little clinical experience and, in some cases, using new endpoints or methodologies, the FDA or other regulatory authorities may not consider the endpoints of our clinical trials to predict or provide clinically meaningful results.

There are currently no therapies approved to treat FSHD, and there may be no therapies approved to treat the underlying causes of diseases that we attempt to address or may address in the future. As a result, the design and conduct of clinical trials of product candidates for the treatment of these diseases may take longer, be more costly or be less effective as part of the novelty of development in these diseases. In some cases, we may use new or novel endpoints or methodologies, such as the optimized time up and go test we intend to use in our losmapimod clinical trials, which we refer to as the FSHD-TUG test, and the FDA or other regulatory authorities may not consider the endpoints of our clinical trials to provide clinically meaningful results. Even if applicable regulatory authorities do not object to our proposed endpoints in an earlier stage clinical trial, such regulatory authorities may require evaluation of additional or different clinical endpoints in later-stage clinical trials. Additionally, if we pursue accelerated approval for certain product candidates, the FDA or another regulatory authority may determine that the biomarker efficacy endpoint we select for evaluation is not sufficiently predictive of clinical benefit to support accelerated approval. For example, if we pursue accelerated approval with the FDA for losmapimod for the treatment of FSHD, the FDA may determine that our proposed biomarker efficacy endpoint of measuring DUX4-driven gene expression as a biomarker in muscle biopsies is inadequate to accurately capture treatment effects in muscle over time or is not sufficiently predictive of clinical benefit to support accelerated approval. The FDA may also determine that the measurement interval for our Phase 2b clinical trial is too short to evaluate the potential clinical benefit of losmapimod for FSHD where the progression of symptoms is relatively slow and chronic dosing is required.

Even if the FDA does find our clinical trial success criteria to be sufficiently validated and clinically meaningful, we may not achieve the pre-specified endpoint to a degree of statistical significance in any pivotal or other clinical trials we may conduct for our product candidates. Further, even if we do achieve the pre-specified criteria, our trials may produce results that are unpredictable or inconsistent with the results of the more traditional efficacy endpoints in the trial. The FDA also could give overriding weight to other efficacy endpoints over a primary endpoint, even if we achieve statistically significant results on that primary endpoint, if we do not do so on our secondary efficacy endpoints. The FDA also weighs the benefits of a product against its risks and the FDA may view the efficacy results in the context of safety as not being supportive of approval. Other regulatory authorities in Europe and other countries may make similar findings with respect to these endpoints.

If we experience delays or difficulties in the enrollment of patients in clinical trials, our receipt of necessary regulatory approvals could be delayed or prevented.

Identifying and qualifying patients to participate in clinical trials for our product candidates is critical to our success. Successful and timely completion of clinical trials will require that we enroll a sufficient number of patients who remain in the trial until its conclusion. We may not be able to initiate or continue clinical trials for our product candidates if we are unable to locate and enroll a sufficient number of eligible patients to participate in these trials as required by the FDA or similar regulatory authorities outside of the United States. Because of our primary focus on rare diseases, we may have difficulty enrolling a sufficient number of eligible patients.

Patient enrollment is affected by a variety of other factors, including:

- the prevalence and severity of the disease under investigation;
- the eligibility criteria for the trial in question;
- the perceived risks and benefits of the product candidate under trial;
- the requirements of the trial protocols, including invasive procedures such as muscle biopsies;

- the availability of existing treatments for the indications for which we are conducting clinical trials;
- the ability to recruit clinical trial investigators with the appropriate competencies and experience;
- the efforts to facilitate timely enrollment in clinical trials;
- the patient referral practices of physicians;
- the ability to monitor patients adequately during and after treatment;
- the proximity and availability of clinical trial sites for prospective patients;
- the conduct of clinical trials by competitors for product candidates that treat the same indications as our product candidates;
- the ability to identify specific patient populations for biomarker-defined trial cohort(s); and
- the cost to, or lack of adequate compensation for, prospective patients.

Our inability to locate and enroll a sufficient number of patients for our clinical trials would result in significant delays, could require us to abandon one or more clinical trials altogether and could delay or prevent our receipt of necessary regulatory approvals. Enrollment delays in our clinical trials may result in increased development costs for our product candidates, which would cause the value of our company to decline and limit our ability to obtain additional financing.

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

If our product candidates are associated with serious adverse events or undesirable side effects in clinical trials or have characteristics that are unexpected in clinical trials or preclinical testing, we may need to abandon their development or limit development to more narrow uses or subpopulations in which the serious adverse events, undesirable side effects or other characteristics are less prevalent, less severe or more acceptable from a risk-benefit perspective. In pharmaceutical development, many compounds that initially show promise in early-stage or clinical testing are later found to cause side effects that delay or prevent further development of the compound.

Additionally, if results of our clinical trials reveal unacceptable side effects, we, the FDA or the IRBs at the institutions in which our studies are conducted could suspend or terminate our clinical trials or the FDA or comparable foreign regulatory authorities could order us to cease clinical trials or deny approval of our product candidates for any or all targeted indications. Treatment-related side effects could also affect patient recruitment or the ability of enrolled patients to complete any of our clinical trials. If we elect or are forced to suspend or terminate any clinical trial of our product candidates, the commercial prospects of such product candidate will be harmed, and our ability to generate product revenue from such product candidate will be delayed or eliminated. Any of these occurrences could materially harm our business.

If any of our product candidates receives marketing approval and we, or others, later discover that the drug is less effective than previously believed or causes undesirable side effects that were not previously identified, our ability to market the drug could be compromised.

Clinical trials of our product candidates are conducted in carefully defined subsets of patients who have agreed to enter into clinical trials. Consequently, it is possible that our clinical trials may indicate an apparent positive effect of a product candidate that is greater than the actual positive effect, if any, or alternatively fail to identify undesirable side effects. If one or more of our product candidates receives regulatory approval, and we, or others, later discover that they are less effective than previously believed,

or cause undesirable side effects, a number of potentially significant negative consequences could result, including:

- withdrawal or limitation by regulatory authorities of approvals of such product;
- seizure of the product by regulatory authorities;
- recall of the product;
- restrictions on the marketing of the product or the manufacturing process for any component thereof;
- requirement by regulatory authorities of additional warnings on the label, such as a "black box" warning or contraindication;
- requirement that we implement a REMS or create a medication guide outlining the risks of such side effects for distribution to patients;
- commitment to expensive post-marketing studies as a prerequisite of approval by regulatory authorities of such product;
- the product may become less competitive;
- initiation of regulatory investigations and government enforcement actions;
- initiation of legal action against us to hold us liable for harm caused to patients; and
- harm to our reputation and resulting harm to physician or patient acceptance of our products.

Any of these events could prevent us from achieving or maintaining market acceptance of a particular product candidate, if approved, and could significantly harm our business, financial condition, and results of operations.

We may expend our limited resources to pursue a particular product candidate or indication and fail to capitalize on product candidates or indications that may be more profitable or for which there is a greater likelihood of success.

Because we have limited financial and managerial resources, we are focusing our research and development efforts on rare neuromuscular disorders, hemoglobinopathies and central nervous system diseases. As a result, we may forego or delay pursuit of opportunities with other product candidates or for other indications that later prove to have greater commercial potential. Our resource allocation decisions may cause us to fail to capitalize on viable commercial products or profitable market opportunities. Our spending on current and future research and development programs and product candidates for specific indications may not yield any commercially viable products. If we do not accurately evaluate the commercial potential or target market for a particular product candidate, we may relinquish valuable rights to that product candidate through collaboration, licensing or other royalty arrangements in cases in which it would have been more advantageous for us to retain sole development and commercialization rights to such product candidate. Failure to allocate resources or capitalize on strategies in a successful manner will have an adverse impact on our business.

We are conducting a Phase 1 clinical trial of losmapimod in patients with FSHD in Europe and currently plan to conduct additional clinical trials for our product candidates at sites outside the United States, and the FDA may not accept data from trials conducted in such locations.

We are currently conducting a Phase 1 clinical trial of losmapimod in patients with FSHD in Europe, and we plan to conduct additional clinical trials outside the United States. Although the FDA may accept data from clinical trials conducted outside the United States, acceptance of these data is subject to conditions imposed by the FDA. For example, the clinical trial must be well designed and conducted and be performed by qualified investigators in accordance with ethical principles. The trial population must

also adequately represent the U.S. population, and the data must be applicable to the U.S. population and U.S. medical practice in ways that the FDA deems clinically meaningful. In addition, while these clinical trials are subject to the applicable local laws, FDA acceptance of the data will depend on its determination that the trials also complied with all applicable U.S. laws and regulations. If the FDA does not accept the data from any trial that we conduct outside the United States, it would likely result in the need for additional trials, which would be costly and time-consuming and could delay or permanently halt our development of the applicable product candidates.

Risks Related to the Commercialization of our Product Candidates

Even if any of our product candidates receives marketing approval, it may fail to achieve the degree of market acceptance by physicians, patients, third-party payors and others in the medical community necessary for commercial success, and the market opportunity for any of our product candidates, if approved, may be smaller than we estimate.

If any of our product candidates receives marketing approval, it may nonetheless fail to gain sufficient market acceptance by physicians, patients, third-party payors and others in the medical community. Efforts to educate the medical community and third-party payors on the benefits of our product candidates may require significant resources and may not be successful. If our product candidates do not achieve an adequate level of acceptance, we may not generate significant product revenues and we may not become profitable. 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 of our product candidates compared to the advantages and relative risks of alternative treatments;
- the effectiveness of sales and marketing efforts;
- the cost of treatment in relation to alternative treatments, including any similar generic treatments;
- our ability to offer our products, if approved, for sale at competitive prices;
- the clinical indications for which the product is approved;
- the convenience and ease of administration compared to alternative treatments;
- the willingness of the target patient population to try new therapies and of physicians to prescribe these therapies;
- the strength of marketing and distribution support;
- the timing of market introduction of competitive products;
- the availability of third-party coverage and adequate reimbursement, and patients' willingness to pay out of pocket for required co-payments or in the absence of third-party coverage or adequate reimbursement;
- the prevalence and severity of any side effects; and
- any restrictions on the use of our products, if approved, together with other medications.

Our assessment of the potential market opportunity for our product candidates is based on industry and market data that we obtained from industry publications and research, surveys and studies conducted by third parties, one of which we commissioned. Industry publications and third-party research, surveys and studies generally indicate that their information has been obtained from sources believed to be reliable, although they do not guarantee the accuracy or completeness of such information. While we believe these industry publications and third-party research, surveys and studies are reliable, we have not independently verified such data. We commissioned Clarion Healthcare, LLC to conduct market research

with physicians and payors to better understand the commercial landscape and to assist in our commercial planning. A total of 14 physicians in the United States, the European Union and Asia and nine payors and payor experts in the United States and the European Union were surveyed. As the survey involved a limited number of physicians and payors, the results from such survey may be less reflective of market opportunity than a survey conducted with a larger sample size. Our estimates of the potential market opportunities for our product candidates include several key assumptions based on our industry knowledge, industry publications and third-party research, surveys and studies, which may be based on a small sample size and fail to accurately reflect market opportunities. While we believe that our internal assumptions are reasonable, no independent source has verified such assumptions. If any of our assumptions or estimates, or these publications, research, surveys or studies prove to be inaccurate, then the actual market for any of our product candidates may be smaller than we expect, and as a result our product revenue may be limited and it may be more difficult for us to achieve or maintain profitability.

If we are unable to establish sales, marketing and distribution capabilities or enter into sales, marketing and distribution agreements with third parties, we may not be successful in commercializing our product candidates if and when they are approved.

We do not have a sales or marketing infrastructure and have no experience in the sale, marketing or distribution of pharmaceutical products. To achieve commercial success for any product for which we have obtained marketing approval, we will need to establish a sales, marketing and distribution organization, either ourselves or through collaborations or other arrangements with third parties.

In the future, we expect to build a focused, specialty sales and marketing infrastructure to market some of our product candidates in the United States, if and when they are approved. There are risks involved with establishing our own sales, marketing and distribution capabilities. For example, recruiting and training a sales force is expensive and time-consuming and could delay any product launch. If the commercial launch of a product candidate for which we recruit a sales force and establish marketing capabilities is delayed or does not occur for any reason, we would have prematurely or unnecessarily incurred these commercialization expenses. These efforts may be costly, and our investment would be lost if we cannot retain or reposition our sales and marketing personnel.

Factors that may inhibit our efforts to commercialize our products on our own include:

- our inability to recruit, train and retain adequate numbers of effective sales, marketing, coverage or reimbursement, customer service, medical affairs and other support personnel;
- the inability of sales personnel to obtain access to physicians or persuade adequate numbers of physicians to prescribe any future products;
- the inability of reimbursement professionals to negotiate arrangements for formulary access, reimbursement and other acceptance by payors;
- the inability to price our products at a sufficient price point to ensure an adequate and attractive level of profitability;
- restricted or closed distribution channels that make it difficult to distribute our products to segments of the patient population;
- the lack of complementary products to be offered by sales personnel, which may put us at a competitive disadvantage relative to companies with more extensive product lines; and
- unforeseen costs and expenses associated with creating an independent sales and marketing organization.

If we are unable to establish our own sales, marketing and distribution capabilities and we enter into arrangements with third parties to perform these services, our product revenues and our profitability, if

any, are likely to be lower than if we were to market, sell and distribute any products that we develop ourselves. In addition, we may not be successful in entering into arrangements with third parties to sell, market and distribute our product candidates or may be unable to do so on terms that are acceptable to us. We likely will have little control over such third parties, and any of them may fail to devote the necessary resources and attention to sell and market our products effectively. If we do not establish sales, marketing and distribution capabilities successfully, either on our own or in collaboration with third parties, we will not be successful in commercializing our product candidates.

We face substantial competition, which may result in others discovering, developing or commercializing products before or more successfully than we do.

The development and commercialization of new drug products is highly competitive. We face competition with respect to our current product candidates, and will face competition with respect to any product candidates that we may seek to develop or commercialize in the future, from major pharmaceutical companies, specialty pharmaceutical companies and biotechnology companies worldwide. There are a number of large pharmaceutical and biotechnology companies that currently market and sell products or are pursuing the development of products for the treatment of many of the disease indications for which we are developing our product candidates. Some of these competitive products and therapies are based on scientific approaches that are the same as or similar to our approach, and others are based on entirely different approaches. Potential competitors also include academic institutions, government agencies and other public and private research organizations that conduct research, seek patent protection and establish collaborative arrangements for research, development, manufacturing and commercialization.

For example, we are aware of several product candidates in clinical development that could be competitive with product candidates that we may successfully develop and commercialize. Acceleron Pharma, Inc., or Acceleron, has a product candidate currently in Phase 2a clinical development for FSHD. Novartis AG, Global Blood Therapeutics, Inc., GlycoMimetics Inc., Pfizer, Inc., bluebird bio, Inc., Aruvant Sciences, Inc., EpiDestiny, Inc., or EpiDestiny (in collaboration with Novo Nordisk A/S), Imara, Inc. and Sangamo Therapeutics Inc., or Sangamo (in collaboration with Bioverativ Inc.), are developing therapeutic approaches for patients with sickle cell disease, or SCD. Acceleron (in collaboration with Celgene Corp.), Bellicum Pharmaceuticals, Inc., Kiadis Pharma, EpiDestiny (in collaboration with Novo Nordisk A/S), Orchard Therapeutics plc, Sangamo (in collaboration with Bioverativ, Inc.) and CRISPR Therapeutics AG (in collaboration with Vertex Pharmaceuticals, Inc.) are developing therapeutic approaches for patients with b-thalassemia.

See "Business—Competition" for additional information regarding competing products and product candidates.

Our commercial opportunity could be reduced or eliminated if our competitors develop and commercialize products that are safer, more effective, have fewer or less severe side effects, are more convenient or are less expensive than any products that we may develop. Our competitors also may obtain FDA or other regulatory approval for their products more rapidly than we may obtain approval for ours, which could result in our competitors establishing a strong market position before we are able to enter the market. In addition, our ability to compete may be affected in many cases by insurers or other third-party payors seeking to encourage the use of generic products. If our product candidates achieve marketing approval, we expect that they will be priced at a significant premium over competitive generic products.

Many of the companies against which we are competing or against which we may compete in the future have significantly greater financial resources and expertise in research and development, manufacturing, preclinical testing, conducting clinical trials, obtaining regulatory approvals and marketing approved products than we do.

Mergers and acquisitions in the pharmaceutical and biotechnology industries may result in even more resources being concentrated among a smaller number of our competitors. Smaller and other early-stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies. These third parties compete with us in recruiting and retaining qualified scientific and management personnel, establishing clinical trial sites and patient registration for clinical trials, as well as in acquiring technologies complementary to, or necessary for, our programs.

If the market opportunities for our product candidates are smaller than we believe they are, our revenue may be adversely affected, and our business may suffer. Because the target patient populations of our product candidates are small, and the addressable patient population even smaller, we must be able to successfully identify patients and capture a significant market share to achieve profitability and growth.

We focus our research and product development on treatments for rare diseases. Given the small number of patients who have the diseases that we are targeting, it is critical to our ability to grow and become profitable that we continue to successfully identify patients with these rare diseases. Our projections of both the number of people who have these diseases, as well as the subset of people with these diseases who have the potential to benefit from treatment with our product candidates, are based on our beliefs and estimates. These estimates have been derived from a variety of sources, including the scientific literature, surveys of clinics, patient foundations or market research that we conducted, and may prove to be incorrect or contain errors. New studies may change the estimated incidence or prevalence of these diseases. The number of patients may turn out to be lower than expected. The effort to identify patients with diseases we seek to treat is in early stages, and we cannot accurately predict the number of patients for whom treatment might be possible. Additionally, the potentially addressable patient population for each of our product candidates may be limited or may not be amenable to treatment with our product candidates, and new patients may become increasingly difficult to identify or gain access to, which would adversely affect our results of operations and our business. Further, even if we obtain significant market share for our product candidates, because the potential target populations are very small, we may never achieve profitability despite obtaining such significant market share.

Our target patient populations are relatively small, and there is currently no standard of care treatment directed at some of our target indications, such as FSHD. As a result, the pricing and reimbursement of our product candidates, if approved, is uncertain, but must be adequate to support commercial infrastructure. If we are unable to obtain adequate levels of reimbursement, our ability to successfully market and sell our product candidates will be adversely affected.

We expect to rely on contract manufacturing organizations to manufacture our product candidates. If we are unable to enter into such arrangements as expected or if such organizations do not meet our supply requirements, development and/or commercialization of our product candidates may be delayed.

We expect to rely on third parties to manufacture clinical supplies of our product candidates and commercial supplies of our products, if and when approved for marketing by applicable regulatory authorities, as well as for packaging, sterilization, storage, distribution and other production logistics. If we are unable to enter into such arrangements on the terms or timeline we expect, development and/or commercialization of our product candidates may be delayed. If these third parties do not successfully carry out their contractual duties, meet expected deadlines or manufacture our product candidates in accordance with regulatory requirements, if there are disagreements between us and such parties or if such parties are unable to expand capacities to support commercialization of any of our product candidates for which we obtain marketing approval, we may not be able to fulfill, or may be delayed in producing sufficient product candidates to meet, our supply requirements. These facilities may also be affected by natural disasters, such as floods or fire, or such facilities could face manufacturing issues, such as contamination or regulatory concerns following a regulatory inspection of such facility. In such instances, we may need to locate an appropriate replacement third-party facility and establish a contractual

relationship, which may not be readily available or on acceptable terms, which would cause additional delay and increased expense, including as a result of additional required FDA approvals, and may have a material adverse effect on our business.

Our third-party manufacturers will be subject to inspection and approval by the FDA before we can commence the manufacture and sale of any of our product candidates, and thereafter subject to FDA inspection from time to time. Failure by our third-party manufacturers to pass such inspections and otherwise satisfactorily complete the FDA approval regimen with respect to our product candidates may result in regulatory actions such as the issuance of FDA Form 483 notices of observations, warning letters or injunctions or the loss of operating licenses.

We or our third-party manufacturers may also encounter shortages in the raw materials or API necessary to produce our product candidates in the quantities needed for our clinical trials or, if our product candidates are approved, in sufficient quantities for commercialization or to meet an increase in demand, as a result of capacity constraints or delays or disruptions in the market for the raw materials or API, including shortages caused by the purchase of such raw materials or API by our competitors or others. The failure of us or our third-party manufacturers to obtain the raw materials or API necessary to manufacture sufficient quantities of our product candidates, may have a material adverse effect on our business.

Even if we are able to commercialize any product candidates, the products may become subject to unfavorable pricing regulations, third-party coverage or reimbursement practices or healthcare reform initiatives, which could harm our business.

The regulations that govern marketing approvals, pricing, coverage and reimbursement for new drug products vary widely from country to country. Current and future legislation may significantly change the approval requirements in ways that could involve additional costs and cause delays in obtaining approvals. Some countries require approval of the sale price of a drug before it can be marketed. In many countries, the pricing review period begins after marketing or product licensing approval is granted. In some foreign markets, prescription pharmaceutical pricing remains subject to continuing governmental control even after initial approval is granted. As a result, we might obtain marketing approval for a product in a particular country, but then be subject to price regulations that delay our commercial launch of the product, possibly for lengthy time periods, and negatively impact the revenues we are able to generate from the sale of the product in that country. Adverse pricing limitations may hinder our ability to recoup our investment in one or more product candidates, even if our product candidates obtain marketing approval.

Our ability to commercialize any product candidates successfully also will depend in part on the extent to which coverage and adequate reimbursement for these products and related treatments will be available from government health administration authorities, private health insurers and other organizations. Government authorities and third-party payors, such as private health insurers and health maintenance organizations, decide which medications they will pay for and establish reimbursement levels. A primary trend in the U.S. healthcare industry and elsewhere is cost containment. Government authorities and third-party payors have attempted to control costs by limiting coverage and the amount of reimbursement for particular medications. Increasingly, third-party payors are requiring that drug companies provide them with predetermined discounts from list prices and are challenging the prices charged for medical products. Coverage and reimbursement may not be available for any product that we commercialize and, even if these are available, the level of reimbursement may not be satisfactory. Reimbursement may affect the demand for, or the price of, any product candidate for which we obtain marketing approval. Obtaining and maintaining adequate reimbursement for our products may be difficult. We may be required to conduct expensive pharmacoeconomic studies to justify coverage and reimbursement or the level of reimbursement relative to other therapies. If coverage and adequate reimbursement are not available or reimbursement is

available only to limited levels, we may not be able to successfully commercialize any product candidate for which we obtain marketing approval.

There may be significant delays in obtaining coverage and reimbursement for newly approved drugs, and coverage may be more limited than the purposes for which the drug is approved by the FDA or similar regulatory authorities outside of the United States. Moreover, eligibility for coverage and reimbursement does not imply that a drug will be paid for in all cases or at a rate that covers our costs, including research, development, manufacture, sale and distribution expenses. Interim reimbursement levels for new drugs, if applicable, may also not be sufficient to cover our costs and may not be made permanent. Reimbursement rates may vary according to the use of the drug and the clinical setting in which it is used, may be based on reimbursement levels already set for lower cost drugs and may be incorporated into existing payments for other services. Net prices for drugs may be reduced by mandatory discounts or rebates required by government healthcare programs or private payors and by any future relaxation of laws that presently restrict imports of drugs from countries where they may be sold at lower prices than in the United States. Third-party payors often rely upon Medicare coverage policy and payment limitations in setting their own reimbursement policies. Our inability to promptly obtain coverage and adequate reimbursement rates from both government-funded and private payors for any approved products that we develop could have a material adverse effect on our operating results, our ability to raise capital needed to commercialize products and our overall financial condition.

There can be no assurance that our product candidates, even if they are approved for sale in the United States or in other countries, will be considered medically reasonable and necessary for a specific indication or cost-effective by third-party payors, or that coverage and an adequate level of reimbursement will be available or that third-party payors' reimbursement policies will not adversely affect our ability to sell our product candidates profitably.

Our future growth depends, in part, on our ability to penetrate foreign markets, where we would be subject to additional regulatory burdens and other risks and uncertainties that, if they materialize, could harm our business.

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

- economic weakness, including inflation, or political instability in particular economies and markets;
- the burden of complying with complex and changing foreign regulatory, tax, accounting and legal requirements, many of which vary between countries;
- different medical practices and customs in foreign countries affecting acceptance in the marketplace;
- tariffs and trade barriers, as well as other governmental controls and trade restrictions;
- other trade protection measures, import or export licensing requirements or other restrictive actions by U.S. or foreign governments;
- longer accounts receivable collection times;
- longer lead times for shipping;
- compliance with tax, employment, immigration and labor laws for employees living or traveling abroad;
- workforce uncertainty in countries where labor unrest is common;
- language barriers for technical training;
- reduced protection of intellectual property rights in some foreign countries, and related prevalence of generic alternatives to therapeutics;

- foreign currency exchange rate fluctuations and currency controls;
- differing foreign reimbursement landscapes;
- uncertain and potentially inadequate reimbursement of our products; and
- the interpretation of contractual provisions governed by foreign laws in the event of a contract dispute.

If risks related to any of these uncertainties materializes, it could have a material adverse effect on our business.

Clinical trial and product liability lawsuits against us could divert our resources and could cause us to incur substantial liabilities and to limit commercialization of any products that we may develop.

We face an inherent risk of clinical trial and product liability exposure related to the testing of our product candidates in human clinical trials, and we will face an even greater risk if we commercially sell any products that we may develop. While we currently have no products that have been approved for commercial sale, the current and future use of product candidates by us in clinical trials, and the sale of any approved products in the future, may expose us to liability claims. These claims might be made by patients that use the product, healthcare providers, pharmaceutical companies or others selling such products. If we cannot successfully defend ourselves against claims that our product candidates or products caused injuries, we will incur substantial liabilities. Regardless of merit or eventual outcome, liability claims may result in:

- decreased demand for any product candidates or products that we may develop;
- injury to our reputation and significant negative media attention;
- withdrawal of clinical trial participants;
- significant costs to defend any related litigation;
- substantial monetary awards to trial participants or patients;
- loss of revenue;
- reduced resources of our management to pursue our business strategy; and
- the inability to commercialize any products that we may develop.

We currently hold \$10 million in clinical trial liability insurance coverage in the aggregate, with a per incident limit of \$10 million, which may not be adequate to cover all liabilities that we may incur. We may need to increase our insurance coverage as we expand our clinical trials or if we commence commercialization of our product candidates. Insurance coverage is increasingly expensive. We may not be able to maintain insurance coverage at a reasonable cost or in an amount adequate to satisfy any liability that may arise. If a successful clinical trial or product liability claim or series of claims is brought against us for uninsured liabilities or in excess of insured liabilities, our assets may not be sufficient to cover such claims and our business operations could be impaired.

Risks Related to our Dependence on Third Parties

We rely, and expect to continue to rely, on third parties to conduct our clinical trials, and those third parties may not perform satisfactorily, including failing to meet deadlines for the completion of such trials, which may harm our business.

We currently rely on third-party clinical research organizations to conduct our ongoing Phase 1 clinical trial of losmapimod and plan to rely on third-party clinical research organizations or third-party research collaboratives to conduct our planned clinical trials. We do not plan to independently conduct clinical trials

of our other product candidates. We expect to continue to rely on third parties, such as clinical research organizations, clinical data management organizations, medical institutions and clinical investigators, to conduct our clinical trials. These agreements might terminate for a variety of reasons, including a failure to perform by the third parties. If we need to enter into alternative arrangements, our product development activities might be delayed.

Our reliance on these third parties for research and development activities will reduce our control over these activities but will not relieve us of our responsibilities. For example, we will remain responsible for ensuring that each of our clinical trials is conducted in accordance with the general investigational plan and protocols for the trial. Moreover, the FDA requires us to comply with standards, commonly referred to as good clinical practices, or GCPs, for conducting, recording and reporting the results of clinical trials to assure that data and reported results are credible and accurate and that the rights, integrity and confidentiality of trial participants are protected. We also are required to register ongoing clinical trials and post the results of completed clinical trials on a government-sponsored database, ClinicalTrials.gov, within specified timeframes. Failure to do so can result in fines, adverse publicity and civil and criminal sanctions.

If these third parties do not successfully carry out their contractual duties, meet expected deadlines or conduct our clinical trials in accordance with regulatory requirements or our stated protocols, we will not be able to obtain, or may be delayed in obtaining, marketing approvals for our product candidates and will not be able to, or may be delayed in our efforts to, successfully develop and commercialize our product candidates. Furthermore, these third parties may also have relationships with other entities, some of which may be our competitors.

We also expect to rely on other third parties to store and distribute drug supplies for our clinical trials. Any performance failure on the part of our distributors could delay clinical development or marketing approval of our product candidates or commercialization of our products, producing additional losses and depriving us of potential product revenue.

We plan to contract with third parties for the manufacture of our product candidates for preclinical and clinical testing and expect to continue to do so for commercialization. This reliance on third parties increases the risk that we will not have sufficient quantities of our product candidates or products or such quantities at an acceptable cost or quality, which could delay, prevent or impair our development or commercialization efforts.

We do not have any manufacturing facilities. Although we believe we have obtained sufficient losmapimod tablets from GSK to complete our planned Phase 2 clinical trials and that we have received a sufficient quantity of losmapimod API to complete further clinical trials in FSHD, we cannot be sure we have correctly estimated our drug product and API requirements or that such drug product or API will not expire before we want to use it. We intend to identify and engage a contract manufacturing organization to prepare our own API and to manufacture losmapimod tablets, but we may not be successful in entering into such arrangement or may be unable to do so on terms that are acceptable to us. Even if we have sufficient API to complete further clinical trials in FSHD, we would need to contract with a third-party manufacturer to convert the API into losmapimod tablets. While we believe that we have all the necessary information from GSK to enable any required technology transfer to a contract manufacturing organization, there can be no assurances that we will be able to effect such transfer in a timely manner.

We expect to rely on third parties for the manufacture of FTX-HbF and any future product candidates for preclinical and clinical testing, as well as for commercial manufacture if any of our product candidates receive marketing approval. This reliance on third parties increases the risk that we will not have sufficient quantities of our product candidates or products or such quantities at an acceptable cost or quality, which could delay, prevent or impair our development or commercialization efforts.

We also expect to rely on third-party manufacturers or third-party collaborators for the manufacture of commercial supply of any other product candidates for which we or our collaborators obtain marketing approval. 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 nonrenewal of the agreement by the third party at a time that is costly or inconvenient for us.

Third-party manufacturers may not be able to comply with current good manufacturing practices, or cGMP, regulations or similar regulatory requirements outside of the United States. Our failure, or the failure of our third-party manufacturers, to comply with applicable regulations could result in sanctions being imposed on us, including clinical holds, fines, injunctions, civil penalties, delays, suspension or withdrawal of approvals, license revocation, seizures or recalls of product candidates or products, operating restrictions and criminal prosecutions, any of which could significantly and adversely affect supplies of our products.

Our product candidates and any products that we may develop may compete with other product candidates and products for access to manufacturing facilities. There are a limited number of manufacturers that operate under cGMP regulations and that might be capable of manufacturing for us.

Any performance failure on the part of our existing or future manufacturers could delay clinical development or marketing approval. We do not currently have arrangements in place for redundant supply or a source for bulk drug substance. If any of our future contract manufacturers cannot perform as agreed, we may be required to replace such manufacturers. Although we believe that there are several potential alternative manufacturers who could manufacture our product candidates, we may incur added costs and delays in identifying and qualifying any such replacement.

Our current and anticipated future dependence upon others for the manufacture of our product candidates or products may adversely affect our future profit margins and our ability to commercialize any products that receive marketing approval on a timely and competitive basis.

We may enter into collaborations with third parties for the development or commercialization of our product candidates. If our collaborations are not successful, we may not be able to capitalize on the market potential of these product candidates and our business could be adversely affected.

While we have retained all rights to and are developing on our own our current product candidates, we may in the future enter into development, distribution or marketing arrangements with third parties with respect to our existing or future product candidates. Our likely collaborators for any sales, marketing, distribution, development, licensing or broader collaboration arrangements include large and mid-size pharmaceutical companies, regional and national pharmaceutical companies and biotechnology companies. We are not currently party to any such arrangement. However, if we do enter into any such arrangements with any third parties in the future, we will likely have limited control over the amount and timing of resources that our collaborators dedicate to the development or commercialization of our product candidates. Our ability to generate revenues from these arrangements will depend on our collaborators' abilities and efforts to successfully perform the functions assigned to them in these arrangements.

Collaborations that we enter into may not be successful, and any success will depend heavily on the efforts and activities of such collaborators. Collaborations pose a number of risks, including the following:

- collaborators have significant discretion in determining the amount and timing of efforts and resources that they will apply to these collaborations;
- collaborators may not perform their obligations as expected;
- collaborators may not pursue development of our product candidates or may elect not to continue or renew development programs based on results of clinical trials or other studies, changes in the collaborators' strategic focus or available funding, or external factors, such as an acquisition, that divert resources or create competing priorities;
- collaborators may not pursue commercialization of any product candidates that achieve regulatory approval or may elect not to continue or renew commercialization programs based on results of clinical trials or other studies, changes in the collaborators' strategic focus or available funding, or external factors, such as an acquisition, that may divert resources or create competing priorities;
- collaborators may delay clinical trials, provide insufficient funding for a clinical trial program, stop a clinical trial or abandon a product candidate, repeat or conduct new clinical trials or require a new formulation of a product candidate for clinical testing;
- we may not have access to, or may be restricted from disclosing, certain information regarding product candidates being developed or commercialized under a collaboration and, consequently, may have limited ability to inform our stockholders about the status of such product candidates on a discretionary basis;
- collaborators could independently develop, or develop with third parties, products that compete directly or indirectly with our product candidates and products if the collaborators believe that the competitive products are more likely to be successfully developed or can be commercialized under terms that are more economically attractive than ours;
- product candidates discovered in collaboration with us may be viewed by our collaborators as competitive with their own product candidates or products, which may cause collaborators to cease to devote resources to the commercialization of our product candidates;
- a collaborator may fail to comply with applicable regulatory requirements regarding the development, manufacture, distribution or marketing of a product candidate or product;
- a collaborator with marketing and distribution rights to one or more of our product candidates that achieve regulatory approval may not commit sufficient resources to the marketing and distribution of such product or products;
- disagreements with collaborators, including disagreements over intellectual property or proprietary rights, contract interpretation or the preferred course of development, might cause delays or terminations of the research, development or commercialization of product candidates, might lead to additional responsibilities for us with respect to product candidates, or might result in litigation or arbitration, any of which would be time-consuming and expensive;
- collaborators may not properly obtain, maintain, enforce, defend or protect our intellectual property or proprietary rights or may use our proprietary information in such a way as to potentially lead to disputes or legal proceedings that could jeopardize or invalidate our intellectual property or proprietary information or expose us to potential litigation;
- disputes may arise with respect to the ownership of intellectual property developed pursuant to our collaborations;

- collaborators may infringe, misappropriate or otherwise violate the intellectual property or proprietary rights of third parties, which may expose us to litigation and potential liability; and
- collaborations may be terminated for the convenience of the collaborator, and, if terminated, we could be required to raise additional capital to pursue further development or commercialization of the applicable product candidates.

Collaboration agreements may not lead to development or commercialization of product candidates in the most efficient manner, or at all. If any collaborations that we enter into do not result in the successful development and commercialization of products or if one of our collaborators terminates its agreement with us, we may not receive any future research funding or milestone or royalty payments under the collaboration. If we do not receive the funding we expect under these agreements, our development of our product candidates could be delayed and we may need additional resources to develop our product candidates. All of the risks relating to product development, regulatory approval and commercialization described in this prospectus also apply to the activities of our collaborators.

Additionally, subject to its contractual obligations to us, if a collaborator of ours is involved in a business combination, the collaborator might deemphasize or terminate the development or commercialization of any product candidate licensed to it by us. If one of our collaborators terminates its agreement with us, we may find it more difficult to attract new collaborators and our perception in the business and financial communities could be adversely affected.

If we are not able to establish or maintain collaborations, we may have to alter our development and commercialization plans and our business could be adversely affected.

For some of our product candidates, we may decide to collaborate with pharmaceutical or biotechnology companies for the development and potential commercialization of those product candidates. We face significant competition in seeking appropriate collaborators, and a number of more established companies may also be pursuing strategies to license or acquire third-party intellectual property rights that we consider attractive. These established companies may have a competitive advantage over us due to their size, financial resources and greater clinical development and commercialization capabilities. In addition, companies that perceive us to be a competitor may be unwilling to assign or license rights to us. Whether we reach a definitive agreement for a collaboration will depend, among other things, upon our assessment of the collaborator's resources and expertise, the terms and conditions of the proposed collaboration and the proposed collaborator's evaluation of a number of factors. Those factors may include the design or results of clinical trials, the likelihood of approval by the FDA or similar regulatory authorities outside the United States, the potential market for the subject product candidate, the costs and complexities of manufacturing and delivering such product candidate to patients, the potential of competing products, the existence of uncertainty with respect to our ownership of technology, which can exist if there is a challenge to such ownership without regard to the merits of the challenge, and industry and market conditions generally. The collaborator may also consider alternative product candidates or technologies for similar indications that may be available to collaborate on and whether such a collaboration could be more attractive than the one with us for our product candidate. We are also restricted by GSK's right of first negotiation under our current license agreement with them and may in the future be restricted under other license agreements from entering into agreements on certain terms with potential collaborators. Collaborations are complex and time-consuming to negotiate and document. In addition, there have been a significant number of recent business combinations among large pharmaceutical and biotechnology companies that have resulted in a reduced number of potential future collaborators.

If we are unable to reach agreements with suitable collaborators on a timely basis, on acceptable terms or at all, we may have to curtail the development of a product candidate, reduce or delay its development program or one or more of our other development programs, delay its potential commercialization or

reduce the scope of any sales or marketing activities, or increase our expenditures and undertake development or commercialization activities at our own expense. If we elect to fund and undertake development or commercialization activities on our own, we may need to obtain additional expertise and additional capital, which may not be available to us on acceptable terms or at all. If we fail to enter into collaborations and do not have sufficient funds or expertise to undertake the necessary development and commercialization activities, we may not be able to further develop our product candidates or bring them to market or continue to develop our product engine.

Risks Related to our Intellectual Property

If we are unable to obtain, maintain, enforce and protect patent protection for our technology and product candidates or if the scope of the patent protection obtained is not sufficiently broad, our competitors could develop and commercialize technology and products similar or identical to ours, and our ability to successfully develop and commercialize our technology and product candidates may be adversely affected.

Our success depends in large part on our ability to obtain and maintain protection of the intellectual property we may own solely and jointly with others or may license from others, particularly patents, in the United States and other countries with respect to any proprietary technology and product candidates we develop. We seek to protect our proprietary position by filing patent applications in the United States and abroad related to our product candidates that are important to our business and by in-licensing intellectual property related to our technologies and product candidates. If we are unable to obtain or maintain patent protection with respect to any proprietary technology or product candidate, our business, financial condition, results of operations and prospects could be materially harmed.

The patent prosecution process is expensive, time-consuming and complex, and we may not be able to file, prosecute, maintain, defend or license all necessary or desirable 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. Moreover, in some circumstances, we do not have the right to control the preparation, filing and prosecution of patent applications, or to maintain, enforce and defend the patents, covering technology that we license from third parties. Therefore, these in-licensed patents and applications may not be prepared, filed, prosecuted, maintained, defended and enforced in a manner consistent with the best interests of our business.

The patent position of pharmaceutical and biotechnology companies generally is highly uncertain, involves complex legal and factual questions and has in recent years been the subject of much litigation. In addition, the scope of patent protection outside of the United States is uncertain and laws of foreign countries may not protect our rights to the same extent as the laws of the United States or vice versa. For example, European patent law restricts the patentability of methods of treatment of the human body more than United States law does. With respect to both owned and in-licensed patent rights, we cannot predict whether the patent applications we and our licensors are currently pursuing will issue as patents in any particular jurisdiction or whether the claims of any issued patents will provide sufficient protection from competitors. Further, we may not be aware of all third-party intellectual property rights potentially relating to our product candidates. In addition, 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 published at all. Therefore, neither we nor our licensors can know with certainty whether either we or our licensors were the first to make the inventions claimed in the patents and patent applications we own or in-license now or in the future, or that either we or our licensors were the first to file for patent protection of such inventions. As a result, the issuance, scope, validity, enforceability and commercial value of our owned and in-licensed patent rights are highly uncertain. Moreover, our owned and in-licensed pending and future patent applications may not result in patents being issued which protect our technology and product candidates, in whole or in part, or which effectively prevent others from commercializing competitive technologies and products. 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 our ability to obtain, protect, maintain, defend and enforce our patent rights, narrow the scope of our patent protection and, more generally, could affect the value or narrow the scope of our patent rights.

Currently, our patent portfolio related to FTX-HbF is in its earliest stages, including only provisional patent applications which do not themselves issue as patents. We have no issued patents related to FTX-HbF or our SCD or b-thalassemia programs. In order to continue to pursue protection based on provisional patent applications, we will need to file Patent Cooperation Treaty applications, foreign applications and/or U.S. non-provisional patent applications prior to applicable deadlines. Even then, as highlighted above, patents may never issue from our patent applications, or the scope of any patent may not be sufficient to provide a competitive advantage. With respect to losmapimod, the patents to losmapimod licensed from GSK as a composition of matter and pharmaceutical composition are expected to expire on February 10, 2023. Our owned patent applications are not to the composition but, rather, are directed to certain methods of treating FSHD. We cannot be certain that any patents will be granted in respect of these patent applications. Even if such patent applications issue as patents, they will not prevent third parties from commercializing losmapimod for other indications.

Moreover, we or our licensors may be subject to a third-party preissuance submission of prior art to the United States Patent and Trademark Office, or USPTO, or become involved in opposition, derivation, revocation, 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 technology or 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. If the breadth or strength of protection provided by our patents and patent applications is threatened, regardless of the outcome, it could dissuade companies from collaborating with us to license, develop or commercialize current or future product candidates.

Additionally, the coverage claimed in a patent application can be significantly reduced before the patent is issued, and its scope can be reinterpreted after issuance. Even if our owned and in-licensed 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. The issuance of a patent is not conclusive as to its inventorship, scope, validity or enforceability, and our owned and in-licensed 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 technology and products, or limit the duration of the patent protection of our technology and product candidates. Such proceedings also may result in substantial cost and require significant time from our management and employees, even if the eventual outcome is favorable to us. 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. Furthermore, our competitors may be able to circumvent our owned or in-licensed patents by developing similar or alternative technologies or products in a non-infringing manner. As a result, our owned and in-licensed patent portfolio may not provide us with sufficient rights to exclude others from commercializing technology and products similar or identical to any of our technology and product candidates.

Patent terms may be inadequate to protect our competitive position on our product candidates for an adequate amount of time.

Patents have a limited lifespan. In the United States, if all maintenance fees are timely paid, the natural expiration of a patent is generally 20 years from its earliest U.S. non-provisional filing date. Various extensions may be available, but the life of a patent, and the protection it affords, is limited. Even if patents covering our product candidates are obtained, once the patent life has expired, we may be open to competition from competitive products, including generics or biosimilars. 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 owned and licensed patent portfolio may not provide us with sufficient rights to exclude others from commercializing products similar or identical to ours. For example, the composition of matter patents covering losmapimod, licensed from GSK, are expected to expire on February 10, 2023. Given the near term expiration date of these patents, and the fact that safe harbor protections in many jurisdictions permit third parties to engage in development, including clinical trials, these patents may not provide us with any meaningful competitive advantage.

If we are unable to obtain licenses from third parties on commercially reasonable terms or fail to comply with our obligations under such agreements, our business could be harmed.

It may be necessary for us to use the patented or proprietary technology of third parties to commercialize our products, in which case we would be required to obtain a license from these third parties. If we are unable to license such technology, or if we are forced to license such technology on unfavorable terms, our business could be materially harmed. If we are unable to obtain a necessary license, we may be unable to develop or commercialize the affected product candidates, which could materially harm our business and the third parties owning such intellectual property rights could seek either an injunction prohibiting our sales or an obligation on our part to pay royalties and/or other forms of compensation. Even if we are able to obtain a license, it may be non-exclusive, thereby giving our competitors access to the same technologies licensed to us.

If we are unable to obtain rights to required third-party intellectual property rights or maintain the existing intellectual property rights we have, we may be required to expend significant time and resources to redesign our technology, product candidates, or the methods for manufacturing them or to develop or license replacement technology, all of which may not be feasible on a technical or commercial basis. If we are unable to do so, we may be unable to develop or commercialize the affected technology and product candidates, which could harm our business, financial condition, results of operations and prospects significantly.

Additionally, if we fail to comply with our obligations under license agreements, our counterparties may have the right to terminate these agreements, in which event we might not be able to develop, manufacture or market, or may be forced to cease developing, manufacturing or marketing, any product that is covered by these agreements or may face other penalties under such agreements. Such an occurrence could materially adversely affect the value of the product candidate being developed under any such agreement. Termination of these agreements or reduction or elimination of our rights under these agreements, or restrictions on our ability to freely assign or sublicense our rights under such agreements when it is in the interest of our business to do so, may result in our having to negotiate new or reinstated agreements with less favorable terms, cause us to lose our rights under these agreements, including our rights to important intellectual property or technology or impede, or delay or prohibit the further development or commercialization of one or more product candidates that rely on such agreements.

If we do not obtain patent term extension in the United States under the Hatch-Waxman Act and in foreign countries under similar legislation, thereby potentially extending the term of our marketing exclusivity for any product candidates we may develop, our business may be materially harmed.

In the United States, the patent term of a patent that covers an FDA-approved drug may be eligible for limited patent term extension, which permits patent term restoration as compensation for the patent term lost during the FDA regulatory review process. The Drug Price Competition and Patent Term Restoration Act of 1984, also known as the Hatch-Waxman Act, permits a patent term extension of up to five years beyond the expiration of the patent. The length of the patent term extension is related to the length of time the drug is under regulatory review. Patent extension cannot extend the remaining term of a patent beyond a total of 14 years from the date of product approval, and only one patent applicable to an approved drug may be extended and only those claims covering the approved drug, a method for using it, or a method for manufacturing it may be extended. Similar provisions are available in Europe and certain other non-United States jurisdictions to extend the term of a patent that covers an approved drug. While, in the future, if and when our product candidates receive FDA approval, we expect to apply for patent term extensions on patents covering those product candidates, there is no guarantee that the applicable authorities will agree with our assessment of whether such extensions should be granted, and even if granted, the length of such extensions. We may not be granted patent term extension either in the United States or in any foreign country because of, for example, failing to exercise due diligence during the testing phase or regulatory review process, failing to apply within applicable deadlines, failing to apply prior to expiration of relevant patents or otherwise failing to satisfy applicable requirements. Moreover, the term of extension, as well as the scope of patent protection during any such extension, afforded by the governmental authority could be less than we request. If we are unable to obtain any patent term extension or the term of any such extension is less than we request, our competitors may obtain approval of competing products following the expiration of our patent rights, and our business, financial condition, results of operations and prospects could be materially harmed.

It is possible that we will not obtain patent term extension under the Hatch-Waxman Act for a U.S. patent covering any of our product candidates that we may identify even where that patent is eligible for patent term extension, or if we obtain such an extension, it may be for a shorter period than we had sought. Further, for our licensed patents, we may not have the right to control prosecution, including filing with the USPTO a petition for patent term extension under the Hatch-Waxman Act. Thus, if one of our licensed patents is eligible for patent term extension under the Hatch-Waxman Act, we may not be able to control whether a petition to obtain a patent term extension is filed, or obtained, from the USPTO.

Also, there are detailed rules and requirements regarding the patents that may be submitted to the FDA for listing in the Approved Drug Products with Therapeutic Equivalence Evaluations, or the Orange Book. We may be unable to obtain patents covering our product candidates that contain one or more claims that satisfy the requirements for listing in the Orange Book. Even if we submit a patent for listing in the Orange Book, the FDA may decline to list the patent, or a manufacturer of generic drugs may challenge the listing. If one of our product candidates is approved and a patent covering that product candidate is not listed in the Orange Book, a manufacturer of generic drugs would not have to provide advance notice to us of any abbreviated new drug application filed with the FDA to obtain permission to sell a generic version of such product candidate.

Changes to patent laws in the United States and other jurisdictions could diminish the value of patents in general, thereby impairing our ability to protect our products.

Changes in either the patent laws or interpretation of patent laws in the United States, including patent reform legislation such as the Leahy-Smith America Invents Act, or the Leahy-Smith Act, could increase the uncertainties and costs surrounding the prosecution of our owned and in-licensed patent applications and the maintenance, enforcement or defense of our owned and in-licensed issued patents.

The Leahy-Smith Act includes a number of significant changes to United States patent law. These changes include provisions that affect the way patent applications are prosecuted, redefine prior art, provide more efficient and cost-effective avenues for competitors to challenge the validity of patents, and enable third-party submission of prior art to the USPTO during patent prosecution and additional procedures to attack the validity of a patent at USPTO-administered post-grant proceedings, including post-grant review, *inter partes* review, and derivation proceedings. Assuming that other requirements for patentability are met, prior to March 2013, in the United States, the first to invent the claimed invention was entitled to the patent, while outside the United States, the first to file a patent application was entitled to the patent. After March 2013, under the Leahy-Smith Act, the United States transitioned to a first-to-file system in which, assuming that the other statutory requirements for patentability are met, the first inventor to file a patent application will be entitled to the patent on an invention regardless of whether a third party was the first to invent the claimed invention. As such, 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 our issued patents, all of which could have a material adverse effect on our business, financial condition, results of operations and prospects.

In addition, the patent positions of companies in the development and commercialization of biologics and pharmaceuticals are particularly uncertain. Recent U.S. Supreme Court rulings have narrowed the scope of patent protection available in certain circumstances and weakened the rights of patent owners in certain situations. This combination of events has created uncertainty with respect to the validity and enforceability 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 could have a material adverse effect on our patent rights and our ability to protect, defend and enforce our patent rights in the future.

Although we or our licensors are not currently involved in any litigation, we may become involved in lawsuits to protect or enforce our patent or other intellectual property rights, which could be expensive, time-consuming and unsuccessful.

Competitors and other third parties may infringe, misappropriate or otherwise violate our or our licensor's issued patents or other intellectual property. As a result, we or our licensors may need to file infringement, misappropriation or other intellectual property related claims, which can be expensive and time-consuming. Any claims we assert against perceived infringers could provoke such parties to assert counterclaims against us alleging that we infringe, misappropriate or otherwise violate their intellectual property. In addition, in a patent infringement proceeding, such parties could counterclaim that the patents we or our licensors have asserted are invalid or unenforceable. In patent litigation in the United States, defendant counterclaims alleging invalidity 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, 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. Third parties may institute such claims before administrative bodies in the United States or abroad, even outside the context of litigation. Such mechanisms include re-examination, post-grant review, *inter partes* review, interference proceedings, derivation proceedings, and equivalent proceedings in foreign jurisdictions (e.g., opposition proceedings). The outcome following legal assertions of invalidity and unenforceability is unpredictable.

An adverse result in any such proceeding could put one or more of our owned or in-licensed patents at risk of being invalidated or interpreted narrowly, and could put any of our owned or in-licensed patent applications at risk of not yielding an issued patent. A court may also refuse to stop the third party from using the technology at issue in a proceeding on the grounds that our owned or in-licensed patents do not cover such technology. 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 or trade secrets could be compromised by disclosure during this type of litigation. Any of the foregoing could allow such third parties to develop and commercialize competing technologies and products and have a material adverse impact on our business, financial condition, results of operations and prospects.

Interference or derivation proceedings provoked by third parties or brought by us or declared by the USPTO may be necessary to determine the priority of inventions with respect to our patents or patent applications. An unfavorable outcome could require us to cease using the related technology or to attempt to license rights to it from the prevailing party. Our business could be harmed if the prevailing party does not offer us a license on commercially reasonable terms or at all, or if a non-exclusive license is offered and our competitors gain access to the same technology. 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.

Third parties may initiate legal proceedings alleging that we are infringing, misappropriating or otherwise violating their intellectual property rights, the outcome of which would be uncertain and could have a material adverse effect on the success of our business.

Our commercial success depends upon our ability and the ability of our collaborators to develop, manufacture, market and sell our product candidates and use our proprietary technologies without infringing, misappropriating or otherwise violating the intellectual property and proprietary rights of third parties. There is considerable patent and other intellectual property litigation in the pharmaceutical and biotechnology industries. We may become party to, or threatened with, adversarial proceedings or litigation regarding intellectual property rights with respect to our technology and product candidates, including interference proceedings, post grant review, *inter partes* review, and derivation proceedings before the USPTO and similar proceedings in foreign jurisdictions such as oppositions before the European Patent Office. Numerous U.S. and foreign issued patents and pending patent applications, which are owned by third parties, exist in the fields in which we are pursuing development candidates. As the biotechnology and pharmaceutical industries expand and more patents are issued, the risk increases that our technologies or product candidates that we may identify may be subject to claims of infringement of the patent rights of third parties.

The legal threshold for initiating litigation or contested proceedings is low, so that even lawsuits or proceedings with a low probability of success might be initiated and require significant resources to defend. Litigation and contested proceedings can also be expensive and time-consuming, and our adversaries in these proceedings may have the ability to dedicate substantially greater resources to prosecuting these legal actions than we can. The risks of being involved in such litigation and proceedings may increase if and as our product candidates near commercialization and as we gain the greater visibility associated with being a public company. Third parties may assert infringement claims against us based on existing patents or patents that may be granted in the future, regardless of merit. We may not be aware of all such intellectual property rights potentially relating to our technology and product candidates and their uses, or we may incorrectly conclude that third party intellectual property is invalid or that our activities and product candidates do not infringe such intellectual property. Thus, we do not know with certainty that our technology and product candidates, or our development and commercialization thereof, do not and will not infringe, misappropriate or otherwise violate any third party's intellectual property.

Third parties may assert that we are employing their proprietary technology without authorization. There may be third-party patents or patent applications with claims to materials, formulations or methods,

such as methods of manufacture or methods for treatment, related to the discovery, use or manufacture of the product candidates that we may identify or related to our technologies. Because patent applications can take many years to issue, there may be currently pending patent applications which may later result in issued patents that the product candidates that we may identify may infringe. In addition, third parties may obtain patents in the future and claim that use of our technologies infringes upon these patents. Moreover, as noted above, there may be existing patents that we are not aware of or that we have incorrectly concluded are invalid or not infringed by our activities. If any third-party patents were held by a court of competent jurisdiction to cover, for example, the manufacturing process of the product candidates that we may identify, any molecules formed during the manufacturing process or any final product itself, the holders of any such patents may be able to block our ability to commercialize such product candidate unless we obtained a license under the applicable patents, or until such patents expire.

Parties making claims against us may obtain injunctive or other equitable relief, which could effectively block our ability to further develop and commercialize the product candidates that we may identify. Defense of these claims, regardless of their merit, would involve substantial litigation expense and would be a substantial diversion of employee resources from our business. In the event of a successful claim of infringement against us, we may have to pay substantial damages, including treble damages and attorneys' fees for willful infringement, pay royalties, redesign our infringing products or obtain one or more licenses from third parties, which may be impossible or require substantial time and monetary expenditure.

We may choose to take a license or, if we are found to infringe, misappropriate or otherwise violate a third party's intellectual property rights, we could also be required to obtain a license from such third party to continue developing, manufacturing and marketing our technology and product candidates. However, we may not be able to obtain any required license on commercially reasonable terms or at all. Even if we were able to obtain a license, it could be non-exclusive, thereby giving our competitors and other third parties access to the same technologies licensed to us and could require us to make substantial licensing and royalty payments. We could be forced, including by court order, to cease developing, manufacturing and commercializing the infringing technology or product. In addition, we could be found liable for significant monetary damages, including treble damages and attorneys' fees, if we are found to have willfully infringed a patent or other intellectual property right and could be forced to indemnify our customers or collaborators. A finding of infringement could prevent us from commercializing our product candidates or force us to cease some of our business operations, which could materially harm our business. In addition, we may be forced to redesign our product candidates, seek new regulatory approvals and indemnify third parties pursuant to contractual agreements. Claims that we have misappropriated the confidential information or trade secrets of third parties could have a similar material adverse effect on our business, financial condition, results of operations and prospects.

Intellectual property litigation or other legal proceedings relating to intellectual property could cause us to spend substantial resources and distract our personnel from their normal responsibilities.

Even if resolved in our favor, litigation or other legal proceedings relating to intellectual property claims may cause us to incur significant expenses, and could distract our technical and management personnel from their normal responsibilities. In addition, there could be public announcements of the results of hearings, motions or other interim proceedings or developments and if securities analysts or investors perceive these results to be negative, it could have a substantial adverse effect on the price of our common stock. Such litigation or proceedings could substantially increase our operating losses and reduce the resources available for development activities or any future sales, marketing or distribution activities. We may not have sufficient financial or other resources to conduct such litigation or proceedings adequately. Some of our competitors may be able to sustain the costs of such litigation or proceedings more effectively than we can because of their greater financial resources and may also have an advantage in such proceedings due to their more mature and developed intellectual property portfolios. Uncertainties

resulting from the initiation and continuation of intellectual property litigation or other proceedings could compromise our ability to compete in the marketplace.

Obtaining and maintaining 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, renewal and annuity fees and various other government fees on any issued patent and pending patent application must be paid to the USPTO and foreign patent agencies in several stages or annually over the lifetime of our owned and in-licensed patents and patent applications. The USPTO and various foreign governmental patent agencies require compliance with a number of procedural, documentary, fee payment and other similar provisions during the patent application process. In certain circumstances, we rely on our licensing partners to pay these fees to, or comply with the procedural and documentary rules of, the relevant patent agency. With respect to our patents, we rely on an annuity service, outside firms and outside counsel to remind us of the due dates and to make payment after we instruct them to do so. While an inadvertent lapse can in many cases be cured by payment of a late fee or by other means in accordance with the applicable rules, there are situations in which noncompliance 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. Non-compliance events that could result in abandonment or lapse of a patent or patent application include failure to respond to official actions within prescribed time limits, non-payment of fees and failure to properly legalize and submit formal documents. In such an event, potential competitors might be able to enter the market with similar or identical products or technology. If we or our licensors fail to maintain the patents and patent applications covering our product candidates, it would have a material adverse effect on our business, financial condition, results of operations and prospects.

If we fail to comply with our obligations in our intellectual property licenses and funding arrangements with third parties, or otherwise experience disruptions to our business relationships with our licensors, we could lose intellectual property rights that are important to our business.

We are party to license and funding agreements, such as the GSK Agreement, that impose, and we may enter into additional licensing and funding arrangements with third parties that may impose, diligence, development and commercialization timelines, milestone payment, royalty, insurance and other obligations on us. Under our existing licensing and funding agreements, we are obligated to pay royalties on net product sales of product candidates or related technologies to the extent they are covered by the agreements. If we fail to comply with such obligations under current or future license and funding agreements, our counterparties may have the right to terminate these agreements or require us to grant them certain rights. Such an occurrence could materially adversely affect the value of any product candidate being developed under any such agreement. Termination of these agreements or reduction or elimination of our rights under these agreements may result in our having to negotiate new or reinstated agreements with less favorable terms, or cause us to lose our rights under these agreements, including our rights to important intellectual property or technology, which would have a material adverse effect on our business, financial condition, results of operations and prospects. We also have licenses and agreements to certain technologies used in our product engine, all of which are non-exclusive. While we still face all of the risks described herein with respect to those agreements, we cannot prevent third parties from also accessing those technologies. In addition, our licenses may place restrictions on our future business opportunities. For example, under our license with GSK, GSK has certain rights of first negotiation if we wish to sublicense any of the patent or data rights licensed by GSK to us to a third party for use outside the United States. This may prevent or delay certain transactions, which could have an adverse effect on the development and commercialization of losmapimod and on our business.

Disputes may arise regarding intellectual property subject to a licensing agreement, including:

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

In addition, the agreements under which we currently license intellectual property or technology from third parties are complex, and certain provisions in such agreements may be susceptible to multiple interpretations. The resolution of any contract interpretation disagreement that may arise could narrow what we believe to be the scope of our rights to the relevant intellectual property or technology, or increase what we believe to be our financial or other obligations under the relevant agreement, either of which could have a material adverse effect on our business, financial condition, results of operations and prospects. Moreover, if disputes over intellectual property that we have licensed prevent or impair our ability to maintain our current licensing arrangements on commercially acceptable terms, we may be unable to successfully develop and commercialize the affected technology and product candidates, which could have a material adverse effect on our business, financial conditions, results of operations and prospects.

Our current or future licensors may have relied on third-party consultants or collaborators or on funds from third parties such that our licensors are not the sole and exclusive owners of the patents and patent applications we in-license. If other third parties have ownership rights to patents or patent applications we in-license, they may be able to license such patents to our competitors, and our competitors could market competing products and technology. This could have a material adverse effect on our competitive position, business, financial conditions, results of operations and prospects.

In spite of our best efforts, our licensors might conclude that we have materially breached our license agreements and might therefore terminate the license agreements, thereby removing our ability to develop and commercialize product candidates and technology covered by these license agreements. If these in-licenses are terminated, or if the underlying intellectual property fails to provide the intended exclusivity, competitors would have the freedom to seek regulatory approval of, and to market, products and technologies identical to ours. This could have a material adverse effect on our competitive position, business, financial condition, results of operations and prospects.

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

Filing, prosecuting and defending patents on product candidates in all countries throughout the world would be prohibitively expensive, and the laws of foreign countries may not protect our rights to the same extent as the laws of 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, and even where such protection is nominally available, judicial and governmental enforcement of such intellectual property rights may be lacking. Consequently, we may not be able to prevent third parties from practicing our inventions in all countries outside the United States, or from selling or importing products made using our inventions in and into the United States or other jurisdictions. Competitors may use our technologies in jurisdictions where we have not obtained patent protection to develop their own products and, further, may export otherwise infringing products to territories where we have patent protection or licenses but

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

Many companies have encountered significant problems in protecting and defending intellectual property rights in foreign jurisdictions. The legal systems of certain countries, particularly certain developing countries, do not favor the enforcement of patents, trade secrets, and other intellectual property protection, particularly those relating to biotechnology products, which could make it difficult for us to stop the infringement of our patents or marketing of competing products in violation of our intellectual property and proprietary rights generally. In addition, certain jurisdictions do not protect to the same extent or at all inventions that constitute new methods of treatment.

Proceedings to enforce our intellectual property and proprietary rights in foreign jurisdictions could result in substantial costs and divert our efforts and attention from other aspects of our business, could put our patents at risk of being invalidated or interpreted narrowly, could put 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 and proprietary rights around the world may be inadequate to obtain a significant commercial advantage from the intellectual property that we develop or license.

Many countries have compulsory licensing laws under which a patent owner may be compelled to grant licenses to third parties. In addition, many countries limit the enforceability of patents against government agencies or government contractors. In these countries, the patent owner may have limited remedies, which could materially diminish the value of such patent. If we or any of our licensors is forced to grant a license to third parties with respect to any patents relevant to our business, our competitive position may be impaired, and our business, financial condition, results of operations and prospects may be adversely affected.

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

We or our licensors may be subject to claims that former employees, collaborators or other third parties have an interest in our owned or in-licensed patents, trade secrets or other intellectual property as an inventor or co-inventor. For example, we or our licensors may have inventorship disputes arise from conflicting obligations of employees, consultants or others who are involved in developing our product candidates. Litigation may be necessary to defend against these and other claims challenging inventorship or our or our licensors' ownership of our owned or in-licensed patents, trade secrets or other intellectual property. If we or our licensors 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, intellectual property that is important to our product candidates. 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. Any of the foregoing could have a material adverse effect on our business, financial condition, results of operations and prospects.

We may be subject to claims by third parties asserting that our employees, consultants or contractors have wrongfully used or disclosed confidential information of third parties, or we have wrongfully used or disclosed alleged trade secrets of their current or former employers or claims asserting we have misappropriated their intellectual property, or claiming ownership of what we regard as our own intellectual property.

Many of our employees, consultants and contractors were previously employed at universities or other pharmaceutical or biotechnology companies, including our competitors or potential competitors. Although we try to ensure that our employees, consultants and contractors do not use the proprietary information or know-how of others in their work for us, we may be subject to claims that these individuals or we have used

or disclosed intellectual property, including trade secrets or other proprietary information, of any such individual's current or former employer. Litigation may be necessary to defend against these claims.

In addition, while it is our policy to require our employees, consultants and contractors who may be involved in the development of intellectual property to execute agreements assigning such intellectual property to us, we may be unsuccessful in executing such an agreement with each party who in fact develops intellectual property that we regard as our own. Our intellectual property assignment agreements with them may not be self-executing or may be breached, and we may be forced to bring claims against third parties, or defend claims they may bring against us, to determine the ownership of what we regard as our intellectual property. Such claims could have a material adverse effect on our business, financial conditions, results of operations and prospects.

If we fail in prosecuting or defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights or personnel, which could have a material adverse effect on our competitive business position and prospects. Such intellectual property rights could be awarded to a third party, and we could be required to obtain a license from such third party to commercialize our technology or products, which license may not be available on commercially reasonable terms, or at all, or such license may be non-exclusive. Even if we are successful in prosecuting or defending against such claims, litigation could result in substantial costs and be a distraction to our management and employees.

If we are unable to protect the confidentiality of our trade secrets, our business and competitive position would be harmed.

In addition to seeking patents for our product candidates, we also rely on trade secrets and confidentiality agreements to protect our unpatented know-how, technology and other proprietary information, to maintain our competitive position, including certain aspects of our proprietary product engine. We seek to protect our trade secrets and other proprietary technology, in part, by entering into non-disclosure and confidentiality agreements with parties who have access to them, such as our employees, corporate collaborators, outside scientific collaborators, contract research organizations, contract manufacturers, consultants, advisors and other third parties. We also enter into confidentiality and invention or patent assignment agreements with our employees and consultants, but we cannot guarantee that we have entered into such agreements with each party that may have or has had access to our trade secrets or proprietary technology. Despite these efforts, 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. Detecting the disclosure or misappropriation of a trade secret and enforcing a claim that a party illegally disclosed or misappropriated a trade secret is difficult, expensive and time-consuming, and the outcome is unpredictable. In addition, some courts inside and outside of the United States are less willing or unwilling to protect trade secrets. If any of our trade secrets were to be lawfully obtained or independently developed by a competitor or other third party, we would have no right to prevent them, or those to whom they communicate it, from using that technology or information to compete with us. If any of our trade secrets were to be disclosed to or independently developed by a competitor or other third party, our competitive position would be materially and adversely harmed.

Intellectual property rights do not necessarily address all potential threats.

The degree of future protection afforded by our intellectual property rights is uncertain because intellectual property rights have limitations and may not adequately protect our business or permit us to maintain our competitive advantage. For example:

- portions of our product engine are protected by trade secrets, but much of our product engine is not protected by intellectual property, including patents, trade secrets and know-how, and we may not be able to develop, acquire or in-license any patentable technologies or other intellectual property related to the unprotected portions of our product engine;

- others may be able to make product candidates that are similar to ours but that are not covered by the claims of the patents that we own;
- we, or our license partners or current or future collaborators, might not have been the first to make the inventions covered by the issued patent or pending patent applications that we license or may own in the future;
- we, or our license partners or current or future collaborators, might not have been the first to file patent applications covering certain of our or their inventions;
- others may independently develop similar or alternative technologies or duplicate any of our technologies without infringing our owned or in-licensed intellectual property rights;
- it is possible that our owned and in-licensed pending patent applications or those we may own or in-license in the future will not lead to issued patents;
- issued patents that we hold rights to may be held invalid or unenforceable, including as a result of legal challenges by our competitors;
- our competitors might conduct research and development activities in countries where we do not have patent rights and then use the information learned from such activities to develop competitive products for sale in our major commercial markets;
- we cannot ensure that any of our patents, or any of our pending patent applications, if issued, or those of our licensors, will include claims having a scope sufficient to protect our product candidates;
- we cannot ensure that any patents issued to us or our licensors will provide a basis for an exclusive market for our commercially viable product candidates or will provide us with any competitive advantages;
- we cannot ensure that our commercial activities or product candidates will not infringe upon the patents of others;
- we cannot ensure that we will be able to successfully commercialize our product candidates on a substantial scale, if approved, before the relevant patents that we own or license expire;
- we may not develop additional proprietary technologies that are patentable;
- the patents of others may harm our business; and
- we may choose not to file a patent in order to maintain certain trade secrets or know-how, and a third party may subsequently file a patent covering such intellectual property.

Should any of these events occur, they could have a material adverse effect on our business, financial condition, results of operations and prospects.

Risks Related to Regulatory Approval of our Product Candidates and Other Legal Compliance Matters

Even if we complete the necessary preclinical studies and clinical trials, the marketing approval process is expensive, time-consuming and uncertain and may prevent us from obtaining approvals for the commercialization of some or all of our product candidates. If we are not able to obtain, or if there are delays in obtaining, required regulatory approvals, we will not be able to commercialize our product candidates, and our ability to generate revenue will be materially impaired.

Our product candidates and the activities associated with their development and commercialization, including design, testing, manufacture, packaging, recordkeeping, labeling, storage, approval, advertising, promotion, sale and distribution, export, import and adverse event reporting, are subject to comprehensive regulation by the FDA and other regulatory agencies in the United States and by the EMA and similar

regulatory authorities outside of the United States. Marketing approval of drugs in the United States requires the submission of a new drug application, or NDA, to the FDA and we are not permitted to market any drug candidate in the United States until we obtain approval from the FDA of the NDA for that product. An NDA must be supported by extensive clinical and preclinical data, as well as extensive information regarding pharmacology, chemistry, manufacturing and controls. We have not submitted an application for or received marketing approval for any of our product candidates in the United States or in any other jurisdiction.

We have only limited experience in filing and supporting the applications necessary to gain marketing approvals and expect to rely on third-party clinical research organizations or other third-party consultants or vendors to assist us in this process. Securing marketing approval requires the submission of extensive preclinical and clinical data and supporting information to regulatory authorities for each therapeutic indication to establish the product candidate's safety and efficacy. Securing marketing approval also requires the submission of information about the product manufacturing process to, and inspection of manufacturing facilities by, the regulatory authorities. Our product candidates may not be effective, may be only moderately effective or may prove to have undesirable or unintended side effects, toxicities or other characteristics that may preclude our obtaining marketing approval or prevent or limit commercial use. If any of our product candidates receives marketing approval, the accompanying label may limit the approved use of our drug, which could limit sales of the product.

The process of obtaining marketing approvals, both in the United States and abroad, is expensive, may take many years, if approval is obtained at all, and can vary substantially based upon a variety of factors, including the type, complexity and novelty of the product candidates involved. Changes in marketing approval policies during the development period, changes in or the enactment of additional statutes or regulations, or changes in regulatory review for each submitted product application, may cause delays in the approval or rejection of an application. Regulatory authorities have substantial discretion in the approval process and may refuse to accept any application or may decide that our data is insufficient for approval and require additional preclinical, clinical or other studies. In addition, varying interpretations of the data obtained from preclinical and clinical testing could delay, limit or prevent marketing approval of a product candidate. Any marketing approval we ultimately obtain may be limited or subject to restrictions or post-approval commitments that render the approved product not commercially viable.

If we experience delays in obtaining approval or if we fail to obtain approval of our product candidates, the commercial prospects for our product candidates may be harmed and our ability to generate revenues will be materially impaired.

We may not be able to obtain or maintain orphan drug designation or exclusivity for our product candidates and, even if we do, that exclusivity may not prevent the FDA or the EMA from approving other competing products.

We plan to apply for orphan drug designation for FSHD in the United States and Europe, and we may seek orphan drug designation for our other current or future product candidates. Regulatory authorities in some jurisdictions, including the United States and Europe, may designate drugs for relatively small patient populations as orphan drugs. Under the Orphan Drug Act, the FDA may designate a product as an orphan drug if it is a drug intended to treat a rare disease or condition, which is generally defined as a patient population of fewer than 200,000 individuals in the United States.

Generally, if a product with an orphan drug designation subsequently receives the first marketing approval for the indication for which it has such designation, the product is entitled to a period of marketing exclusivity, which precludes the FDA 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 ten years in Europe. The exclusivity period in Europe 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.

Even if we obtain orphan drug exclusivity for a product, that exclusivity may not effectively protect the product from competition because competing drugs containing a different active ingredient can be approved for the same condition. In addition, even after an orphan drug is approved, the FDA can subsequently approve the same drug for the same condition if the FDA concludes that the later drug is clinically superior in that it is shown to be safer, more effective or makes a major contribution to patient care.

On August 3, 2017, the U.S. Congress passed the FDA Reauthorization Act of 2017, or FDARA. FDARA, among other things, codified the FDA's pre-existing regulatory interpretation to require that a drug sponsor demonstrate the clinical superiority of an orphan drug that is otherwise the same as a previously approved drug for the same rare disease in order to receive orphan drug exclusivity. The new legislation reverses prior precedent holding that the Orphan Drug Act unambiguously requires that the FDA recognize the orphan exclusivity period regardless of a showing of clinical superiority. The FDA may further reevaluate the Orphan Drug Act and its regulations and policies. We do not know if, when or how the FDA may change the orphan drug regulations and policies in the future, and it is uncertain how any changes might affect our business. Depending on what changes the FDA may make to its orphan drug regulations and policies, our business could be adversely impacted.

A Fast Track designation by the FDA may not lead to a faster development or regulatory review or approval process.

We may seek Fast Track designation for some of our product candidates. If a drug is intended for the treatment of a serious or life-threatening condition and the drug demonstrates the potential to address unmet medical needs for this condition, the drug sponsor may apply for FDA Fast Track designation. The FDA has broad discretion whether or not to grant this designation, so even if we believe a particular product candidate is eligible for this designation, we cannot assure you that the FDA would decide to grant it. Even if we do receive Fast Track designation, we may not experience a faster development process, review or approval compared to conventional FDA procedures. The FDA may withdraw Fast Track designation if it believes that the designation is no longer supported by data from our clinical development program.

A Breakthrough Therapy designation by the FDA for our product candidates may not lead to a faster development or regulatory review or approval process, and it does not increase the likelihood that our product candidates will receive marketing approval.

We may seek a Breakthrough Therapy designation for some of our product candidates. A Breakthrough Therapy is defined as a drug that is intended, alone or in combination with one or more other drugs, to treat a serious or life-threatening disease or condition, and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. For drugs and biologics that have been designated as breakthrough therapies, interaction and communication between the FDA and the sponsor of the trial can help to identify the most efficient path for clinical development while minimizing the number of patients placed in ineffective control regimens. Drugs designated as breakthrough therapies by the FDA are also eligible for accelerated approval.

Designation as a breakthrough therapy is within the discretion of the FDA. Accordingly, even if we believe one of our product candidates meets the criteria for designation as a breakthrough therapy, the FDA may disagree and instead determine not to make such designation. Even if we receive Breakthrough Therapy designation, the receipt of such designation for a product candidate may not result in a faster development process, review or approval compared to drugs considered for approval under conventional FDA procedures and does not assure ultimate approval by the FDA. In addition, even if one or more of

our product candidates qualify as breakthrough therapies, the FDA may later decide that the products no longer meet the conditions for qualification or decide that the time period for FDA review or approval will not be shortened.

Accelerated approval by the FDA, even if granted for our product candidates, may not lead to a faster development or regulatory review or approval process and it does not increase the likelihood that our product candidates will receive marketing approval.

We may seek approval of our product candidates using the FDA's accelerated approval pathway. A product may be eligible for accelerated approval if it treats a serious or life-threatening condition and generally provides a meaningful advantage over available therapies. In addition, it must demonstrate an effect on a biomarker efficacy endpoint that is reasonably likely to predict clinical benefit or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, or IMM, that is reasonably likely to predict an effect on IMM or other clinical benefit. The FDA or other applicable regulatory agency makes the determination regarding whether a biomarker efficacy endpoint is reasonably likely to predict long-term clinical benefit.

Prior to seeking such accelerated approval, we will seek feedback from the FDA and otherwise evaluate our ability to seek and receive such accelerated approval. As a condition of approval, the FDA may require that a sponsor of a drug or biologic product candidate receiving accelerated approval perform adequate and well-controlled post-marketing clinical trials. These confirmatory trials must be completed with due diligence and we may be required to evaluate different or additional endpoints in these post-marketing confirmatory trials. In addition, the FDA currently requires as a condition for accelerated approval pre-approval of promotional materials, which could adversely impact the timing of the commercial launch of the product.

There can be no assurance that the FDA will agree with our biomarker efficacy endpoints or intermediate clinical endpoints, such as measuring DUX4-driven gene expression in muscle tissue biopsies or measuring the fraction of muscle tissue by replaced by fat, or that we will decide to pursue or submit an NDA for accelerated approval or any other form of expedited development, review or approval. Similarly, there can be no assurance that, after feedback from FDA, we will continue to pursue or apply for accelerated approval or any other form of expedited development, review or approval, even if we initially decide to do so. Furthermore, if we decide to submit an application for accelerated approval or under another expedited regulatory designation, there can be no assurance that such submission or application will be accepted or that any expedited review or approval will be granted on a timely basis, or at all.

Moreover, as noted above, for drugs granted accelerated approval, the FDA typically requires post-marketing confirmatory trials to evaluate the anticipated effect on IMM or other clinical benefit. These confirmatory trials must be completed with due diligence. We may be required to evaluate additional or different clinical endpoints in these post-marketing confirmatory trials. These confirmatory trials may require enrollment of more patients than we currently anticipate and will result in additional costs, which may be greater than the estimated costs we currently anticipate. The FDA may withdraw approval of a product candidate approved under the accelerated approval pathway if, for example, the trial required to verify the predicted clinical benefit of our product candidate fails to verify such benefit or does not demonstrate sufficient clinical benefit to justify the risks associated with the drug. The FDA may also withdraw approval if other evidence demonstrates that our product candidate is not shown to be safe or effective under the conditions of use, we fail to conduct any required post approval trial of our product candidate with due diligence or we disseminate false or misleading promotional materials relating to our product candidate. A failure to obtain accelerated approval or any other form of expedited development, review or approval for our product candidates, or withdrawal of a product candidate, would result in a longer time period for commercialization of such product candidate, could increase the cost of development of such product candidate and could harm our competitive position in the marketplace.

Even if we do receive accelerated approval, we may not experience a faster development or regulatory review or approval process, and receiving accelerated approval does not provide assurance of ultimate FDA approval.

Failure to obtain marketing approval in foreign jurisdictions would prevent our product candidates from being marketed abroad.

In order to market and sell our products in the European Union and many other foreign jurisdictions, we or our potential third-party collaborators must obtain separate marketing approvals and comply with numerous and varying regulatory requirements. The approval procedure varies among countries and can involve additional testing. The time required to obtain approval may differ substantially from that required to obtain FDA approval. The regulatory approval process outside of the United States generally includes all of the risks associated with obtaining FDA approval. In addition, in many countries outside of the United States, it is required that the product be approved for reimbursement before the product can be approved for sale in that country. We or our potential third-party collaborators may not obtain approvals from regulatory authorities outside of the United States on a timely basis, if at all. Approval by the FDA does not ensure approval by regulatory authorities in other countries or jurisdictions, and approval by one regulatory authority outside of the United States does not ensure approval by regulatory authorities in other countries or jurisdictions or by the FDA. However, a failure or delay in obtaining regulatory approval in one country may have a negative effect on the regulatory process in other countries. We may not be able to file for marketing approvals and may not receive necessary approvals to commercialize our products in any market.

Additionally, on June 23, 2016, the electorate in the United Kingdom voted in favor of leaving the European Union, commonly referred to as Brexit. On March 29, 2017, the United Kingdom formally notified the European Union of its intention to withdraw pursuant to Article 50 of the Lisbon Treaty. The United Kingdom had a period of a maximum of two years from the date of its formal notification to negotiate the terms of its withdrawal from, and future relationship with, the European Union. If no formal withdrawal agreement can be reached between the United Kingdom and the European Union, then it is expected that the United Kingdom's membership of the European Union would automatically terminate on the deadline, which was initially March 29, 2019. That deadline has been extended to October 31, 2019 to allow the parties to negotiate a withdrawal agreement, which has proven to be extremely difficult to date. Discussions between the United Kingdom and the European Union will continue to focus on withdrawal issues and transition agreements. However, limited progress to date in these negotiations and ongoing uncertainty within the government of the United Kingdom sustains the possibility of the United Kingdom leaving the European Union without a withdrawal agreement and associated transition period in place, which is likely to cause significant market and economic disruption.

Since a significant proportion of the regulatory framework in the United Kingdom is derived from European Union directives and regulations, Brexit could materially impact the regulatory regime with respect to the approval of our product candidates in the United Kingdom or the European Union. Any delay in obtaining, or an inability to obtain, any marketing approvals, as a result of Brexit or otherwise, would prevent us from commercializing our product candidates in the United Kingdom and/or the European Union and restrict our ability to generate revenue and achieve and sustain profitability. If any of these outcomes occur, we may be forced to restrict or delay efforts to seek regulatory approval in the United Kingdom and/or European Union for our product candidates, which could significantly and materially harm our business.

Any product candidate for which we obtain marketing approval could be subject to post-marketing restrictions or withdrawal from the market and we may be subject to substantial penalties if we fail to comply with regulatory requirements or if we experience unanticipated problems with our products, when and if any of them are approved.

Any product candidate for which we obtain marketing approval, along with the manufacturing processes, post-approval clinical data, labeling, advertising and promotional activities for such product, will be subject to continual requirements of and review by the FDA and other regulatory authorities. These requirements include submissions of safety and other post-marketing information and reports, registration and listing requirements, cGMP requirements relating to manufacturing, quality control, quality assurance and corresponding maintenance of records and documents, requirements regarding the distribution of samples to physicians and recordkeeping. Even if marketing approval of a product candidate is granted, the approval may be subject to limitations on the indicated uses for which the product may be marketed or to the conditions of approval, including the requirement to implement a REMS. If any of our product candidates receives marketing approval, the accompanying label may limit the approved use of our drug, which could limit sales of the product.

The FDA may also impose requirements for costly post-marketing studies or clinical trials and surveillance to monitor the safety or efficacy of the product, including the adoption and implementation of REMS. The FDA and other agencies, including the Department of Justice, or the DOJ, closely regulate and monitor the post-approval marketing and promotion of drugs to ensure they are marketed and distributed only for the approved indications and in accordance with the provisions of the approved labeling. The FDA and DOJ impose stringent restrictions on manufacturers' communications regarding off-label use, and if we do not market our products for their approved indications, we may be subject to enforcement action for off-label marketing. Violations of the Federal Food, Drug and Cosmetic Act, or FDCA, and other statutes, including the False Claims Act, relating to the promotion and advertising of prescription drugs may lead to investigations and enforcement actions alleging violations of federal and state healthcare fraud and abuse laws, as well as state consumer protection laws.

In addition, later discovery of previously unknown adverse events or other problems with our products, manufacturers or manufacturing processes, or failure to comply with regulatory requirements, may have various consequences, including:

- suspension of or restrictions on such products, manufacturers or manufacturing processes;
- restrictions and warnings on the labeling or marketing of a product;
- restrictions on product distribution or use;
- requirements to conduct post-marketing studies or clinical trials;
- warning letters or untitled letters;
- withdrawal of the products from the market;
- refusal to approve pending applications or supplements to approved applications that we submit;
- recall of products;
- fines, restitution or disgorgement of profits or revenues;
- suspension of any ongoing clinical trials;
- suspension or withdrawal of marketing approvals;
- damage to relationships with any potential collaborators;

- unfavorable press coverage and damage to our reputation;
- refusal to permit the import or export of our products;
- product seizure or detention;
- injunctions or the imposition of civil or criminal penalties; or
- litigation involving patients using our products.

Non-compliance with European Union requirements regarding safety monitoring or pharmacovigilance, and with requirements related to the development of products for the pediatric population, can also result in significant financial penalties. Similarly, failure to comply with the European Union's requirements regarding the protection of personal information can also lead to significant penalties and sanctions.

In addition, manufacturers of approved products and those manufacturers' facilities are required to comply with extensive FDA requirements, including ensuring that quality control and manufacturing procedures conform to cGMPs applicable to drug manufacturers or quality assurance standards applicable to medical device manufacturers, which include requirements relating to quality control and quality assurance as well as the corresponding maintenance of records and documentation and reporting requirements. We, any contract manufacturers we may engage in the future, our future collaborators and their contract manufacturers will also be subject to other regulatory requirements, including submissions of safety and other post-marketing information and reports, registration and listing requirements, requirements regarding the distribution of samples to clinicians, recordkeeping, and costly post-marketing studies or clinical trials and surveillance to monitor the safety or efficacy of the product such as the requirement to implement a REMS.

The efforts of the Trump administration to pursue regulatory reform may limit the FDA's ability to engage in oversight and implementation activities in the normal course, and that could negatively impact our business.

The Trump administration has taken several executive actions, including the issuance of a number of executive orders, that could impose significant burdens on, or otherwise materially delay, the FDA's ability to engage in routine regulatory and oversight activities such as implementing statutes through rulemaking, issuance of guidance, and review and approval of marketing applications. On January 30, 2017, President Trump issued an executive order, applicable to all executive agencies, including the FDA, requiring that for each notice of proposed rulemaking or final regulation to be issued in fiscal year 2017, the agency shall identify at least two existing regulations to be repealed, unless prohibited by law. These requirements are referred to as the "two-for-one" provisions. This executive order includes a budget neutrality provision that requires the total incremental cost of all new regulations in the 2017 fiscal year, including repealed regulations, to be no greater than zero, except in limited circumstances. For fiscal years 2018 and beyond, the executive order requires agencies to identify regulations to offset any incremental cost of a new regulation. In interim guidance issued by the Office of Information and Regulatory Affairs within the Office of Management and on February 2, 2017, the Trump administration indicates that the "two-for-one" provisions may apply not only to agency regulations, but also to significant agency guidance documents. It is difficult to predict how these requirements will be implemented, and the extent to which they will impact the FDA's ability to exercise its regulatory authority. If these executive actions impose constraints on FDA's ability to engage in oversight and implementation activities in the normal course, our business may be negatively impacted.

Our relationships with healthcare providers, physicians and third-party payors will be subject to applicable anti-kickback, fraud and abuse, false claims, transparency, health information privacy and security, and other healthcare laws and regulations, which, in the event of a violation, could expose us to criminal sanctions, civil penalties, contractual damages, reputational harm, administrative burdens and diminished profits and future earnings.

If we obtain regulatory approval and commercialize any products, healthcare providers, physicians and third-party payors will play a primary role in the recommendation and prescription of any product candidates for which we obtain marketing approval. Our future arrangements with healthcare providers, physicians and third-party payors may expose us to broadly applicable fraud and abuse and other healthcare laws and regulations that may constrain the business or financial arrangements and relationships through which we market, sell and distribute any products for which we obtain marketing approval. In addition, we may be subject to transparency laws and patient privacy regulation by U.S. federal and state governments and by governments in foreign jurisdictions in which we conduct our business. Restrictions under applicable federal and state healthcare laws and regulations include the following:

- the federal Anti-Kickback Statute prohibits, among other things, persons from knowingly and willfully soliciting, offering, receiving or providing remuneration, directly or indirectly, in cash or in kind, to induce or reward, or in return for, either the referral of an individual for, or the purchase, order or recommendation or arranging of, any good or service, for which payment may be made under a federal healthcare program such as Medicare and Medicaid;
- the federal False Claims Act imposes criminal and civil penalties, including through civil whistleblower or *qui tam* actions, against individuals or entities for, among other things, knowingly presenting, or causing to be presented, false or fraudulent claims for payment by a federal healthcare program or making a false statement or record material to payment of a false claim or avoiding, decreasing or concealing an obligation to pay money to the federal government, with potential liability including mandatory treble damages and significant per-claim penalties, currently set at \$5,500 to \$11,000 per false claim;
- the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, imposes criminal and civil liability for executing a scheme to defraud any healthcare benefit program or making false statements relating to healthcare matters;
- HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act of 2009, and their respective implementing regulations, also imposes obligations, including mandatory contractual terms, with respect to safeguarding the privacy, security and transmission of individually identifiable health information;
- the FDCA, which prohibits, among other things, the adulteration or misbranding of drugs, biologics and medical devices;
- the federal Physician Payments Sunshine Act requires applicable manufacturers of covered drugs to report payments and other transfers of value to physicians and teaching hospitals; and
- analogous state and foreign laws and regulations, such as state anti-kickback and false claims laws and transparency statutes, may apply to sales or marketing arrangements and claims involving healthcare items or services reimbursed by non-governmental third-party payors, including private insurers.

Some state laws require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government and may require drug manufacturers to report information related to payments and other transfers of value to physicians and other healthcare providers or marketing expenditures. Additionally,

some state and local laws require the registration of pharmaceutical sales representatives in the jurisdiction. State and foreign laws also govern the privacy and security of health information in some circumstances, many of which differ from each other in significant ways and often are not preempted by HIPAA, thus complicating compliance efforts.

Efforts to ensure that our business arrangements with third parties will comply with applicable healthcare laws and regulations will involve substantial costs. It is possible that governmental authorities will conclude that our business practices may not comply with current or future statutes, regulations or case law involving applicable fraud and abuse or other healthcare laws and regulations. If our operations, including anticipated activities that would be conducted by our sales team, are found to be in violation of any of these laws or any other governmental regulations that may apply to us, we may be subject to significant civil, criminal and administrative penalties, damages, fines, imprisonment, exclusion of products from government funded healthcare programs, such as Medicare and Medicaid, and the curtailment or restructuring of our operations. If any of the physicians or other healthcare providers or entities with whom we expect to do business is found to be not in compliance with applicable laws, they may be subject to criminal, civil or administrative sanctions, including exclusions from participation in government funded healthcare programs.

Compliance with global privacy and data security requirements could result in additional costs and liabilities to us or inhibit our ability to collect and process data globally, and the failure to comply with such requirements could subject us to significant fines and penalties, which may have a material adverse effect on our business, financial condition or results of operations.

The regulatory framework for the collection, use, safeguarding, sharing, transfer and other processing of information worldwide is rapidly evolving and is likely to remain uncertain for the foreseeable future. Globally, virtually every jurisdiction in which we operate has established its own data security and privacy frameworks with which we must comply. For example, the collection, use, disclosure, transfer, or other processing of personal data regarding individuals in the European Union, including personal health data, is subject to the EU General Data Protection Regulation, or the GDPR, which took effect across all member states of the European Economic Area, or EEA, in May 2018. The GDPR is wide-ranging in scope and imposes numerous requirements on companies that process personal data, including requirements relating to processing health and other sensitive data, obtaining consent of the individuals to whom the personal data relates, providing information to individuals regarding data processing activities, implementing safeguards to protect the security and confidentiality of personal data, providing notification of data breaches, and taking certain measures when engaging third-party processors. The GDPR increases our obligations with respect to clinical trials conducted in the EEA by expanding the definition of personal data to include coded data and requiring changes to informed consent practices and more detailed notices for clinical trial subjects and investigators. In addition, the GDPR also imposes strict rules on the transfer of personal data to countries outside the European Union, including the United States and, as a result, increases the scrutiny that clinical trial sites located in the EEA should apply to transfers of personal data from such sites to countries that are considered to lack an adequate level of data protection, such as the United States. The GDPR also permits data protection authorities to require destruction of improperly gathered or used personal information and/or impose substantial fines for violations of the GDPR, which can be up to four percent of global revenues or 20 million Euros, whichever is greater, and it also confers a private right of action on data subjects and consumer associations to lodge complaints with supervisory authorities, seek judicial remedies, and obtain compensation for damages resulting from violations of the GDPR. In addition, the GDPR provides that EU member states may make their own further laws and regulations limiting the processing of personal data, including genetic, biometric or health data.

Given the breadth and depth of changes in data protection obligations, preparing for and complying with the GDPR's requirements is rigorous and time intensive and requires significant resources and a review of our technologies, systems and practices, as well as those of any third-party collaborators, service

providers, contractors or consultants that process or transfer personal data collected in the European Union. The GDPR and other changes in laws or regulations associated with the enhanced protection of certain types of sensitive data, such as healthcare data or other personal information from our clinical trials, could require us to change our business practices and put in place additional compliance mechanisms, may interrupt or delay our development, regulatory and commercialization activities and increase our cost of doing business, and could lead to government enforcement actions, private litigation and significant fines and penalties against us and could have a material adverse effect on our business, financial condition or results of operations. Similarly, failure to comply with federal and state laws regarding privacy and security of personal information could expose us to fines and penalties under such laws. Even if we are not determined to have violated these laws, government investigations into these issues typically require the expenditure of significant resources and generate negative publicity, which could harm our reputation and our business.

Recently enacted and future legislation may increase the difficulty and cost for us to obtain marketing approval of and commercialize our product candidates and affect the prices we may obtain for any products that are approved in the United States or foreign jurisdictions.

In the United States and some foreign jurisdictions, there have been a number of legislative and regulatory changes and proposed changes regarding the healthcare system that could prevent or delay marketing approval of our product candidates, restrict or regulate post-approval activities and affect our ability to profitably sell any product candidates for which we obtain marketing approval. The pharmaceutical industry has been a particular focus of these efforts and has been significantly affected by legislative initiatives. Current laws, as well as other healthcare reform measures that may be adopted in the future, may result in more rigorous coverage criteria and in additional downward pressure on the price that we receive for any FDA approved product.

In the United States, the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, or the MMA, changed the way Medicare covers and pays for pharmaceutical products. The legislation expanded Medicare coverage for drug purchases by the elderly and introduced a new reimbursement methodology based on average sales prices for physician-administered drugs. In addition, this legislation provided authority for limiting the number of drugs that will be covered in any therapeutic class. Cost reduction initiatives and other provisions of this legislation could decrease the coverage and price that we receive for any approved products. While the MMA applies only to drug benefits for Medicare beneficiaries, private payors often follow Medicare coverage policy and payment limitations in setting their own reimbursement rates. Therefore, any reduction in reimbursement that results from the MMA may result in a similar reduction in payments from private payors.

In March 2010, President Obama signed into law the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act of 2010, or collectively the ACA. Among the provisions of the ACA of potential importance to our business, including, without limitation, our ability to commercialize and the prices we may obtain for any of our product candidates that are approved for sale, are the following:

- an annual, non-deductible fee on any entity that manufactures or imports specified branded prescription drugs and biologic agents, apportioned among these entities according to their market share in certain government healthcare programs, although this fee would not apply to sales of certain products approved exclusively for orphan indications;
- an increase in the statutory minimum rebates a manufacturer must pay under the Medicaid Drug Rebate Program;
- expansion of healthcare fraud and abuse laws, including the civil False Claims Act and the federal Anti-Kickback Statute, new government investigative powers and enhanced penalties for noncompliance;

- a Medicare Part D coverage gap discount program, in which manufacturers must agree to offer 70% point-of-sale discounts off negotiated prices;
- extension of manufacturers' Medicaid rebate liability;
- expansion of eligibility criteria for Medicaid programs;
- expansion of the entities eligible for discounts under the Public Health Service pharmaceutical pricing program;
- requirements to report certain financial arrangements with physicians and teaching hospitals;
- a requirement to annually report drug samples that manufacturers and distributors provide to physicians; and
- a Patient-Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research.

In addition, other legislative changes have been proposed and adopted since the ACA was enacted. These changes include the Budget Control Act of 2011, which, among other things, led to aggregate reductions to Medicare payments to providers of up to 2% per fiscal year that started in 2013 and, due to subsequent legislative amendments to the statute, will stay in effect through 2027 unless additional congressional action is taken, and the American Taxpayer Relief Act of 2012, which, among other things, reduced Medicare payments to several types of providers and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. These new laws may result in additional reductions in Medicare and other healthcare funding and otherwise affect the prices we may obtain for any of our product candidates for which we may obtain regulatory approval or the frequency with which any such product candidate is prescribed or used. Further, there have been several recent U.S. congressional inquiries and proposed state and federal legislation designed to, among other things, bring more transparency to drug pricing, review the relationship between pricing and manufacturer patient programs, reduce the costs of drugs under Medicare and reform government reimbursement methodologies for drug products.

We expect that these healthcare reforms, as well as other healthcare reform measures that may be adopted in the future, may result in additional reductions in Medicare and other healthcare funding, more rigorous coverage criteria, new payment methodologies and additional downward pressure on the price that we receive for any approved product and/or the level of reimbursement physicians receive for administering any approved product we might bring to market. Reductions in reimbursement levels may negatively impact the prices we receive or the frequency with which our products are prescribed or administered. Any reduction in reimbursement from Medicare or other government programs may result in a similar reduction in payments from private payors.

With enactment of the TCJA, which was signed by the President on December 22, 2017, Congress repealed the "individual mandate." The repeal of this provision, which requires most Americans to carry a minimal level of health insurance, is effective as of 2019. According to the Congressional Budget Office, the repeal of the individual mandate will cause an estimated 13 million fewer Americans to be insured in 2027 and premiums in insurance markets may rise. Additionally, on January 22, 2018, President Trump signed a continuing resolution on appropriations for fiscal year 2018 that delayed the implementation of certain ACA-mandated fees, including the so-called "Cadillac" tax on certain high cost employer-sponsored insurance plans, the annual fee imposed on certain health insurance providers based on market share, and the medical device excise tax on non-exempt medical devices. Further, the Bipartisan Budget Act of 2018, among other things, amends the ACA, effective January 1, 2019, to increase from 50% to 70% the point-of-sale discount that is owed by pharmaceutical manufacturers who participate in Medicare Part D and to close the coverage gap in most Medicare drug plans, commonly referred to as the "donut hole".

The Trump administration has also taken executive actions to undermine or delay implementation of the ACA. Since January 2017, President Trump has signed two Executive Orders designed to delay the implementation of certain provisions of the ACA or otherwise circumvent some of the requirements for health insurance mandated by the ACA. One Executive Order directs federal agencies with authorities and responsibilities under the ACA to waive, defer, grant exemptions from, or delay the implementation of any provision of the ACA that would impose a fiscal or regulatory burden on states, individuals, healthcare providers, health insurers, or manufacturers of pharmaceuticals or medical devices. The second Executive Order terminates the cost-sharing subsidies that reimburse insurers under the ACA. Several state Attorneys General filed suit to stop the administration from terminating the subsidies, but their request for a restraining order was denied by a federal judge in California on October 25, 2017.

In addition, the Centers for Medicare & Medicaid Services, or CMS, has recently proposed regulations that would give states greater flexibility in setting benchmarks for insurers in the individual and small group marketplaces, which may have the effect of relaxing the essential health benefits required under the ACA for plans sold through such marketplaces. Further, on June 14, 2018, U.S. Court of Appeals for the Federal Circuit ruled that the federal government was not required to pay more than \$12 billion in ACA risk corridor payments to third-party payors who argued were owed to them. The effects of this gap in reimbursement on third-party payors, the viability of the ACA marketplace, providers, and potentially our business, are not yet known. On November 30, 2018, CMS announced a proposed rule that would amend the Medicare Advantage and Medicare Part D prescription drug benefit regulations to reduce out of pocket costs for plan enrollees and allow Medicare plans to negotiate lower rates for certain drugs. Among other things, the proposed rule changes would allow Medicare Advantage plans to use pre authorization (PA) and step therapy (ST) for six protected classes of drugs, with certain exceptions; permit plans to implement PA and ST in Medicare Part B drugs; and change the definition of "negotiated prices" as well as add a definition of "price concession" in the regulations. It is unclear whether these proposed changes will be accepted, and if so, what effect such changes will have on our business. Litigation and legislation over the ACA are likely to continue, with unpredictable and uncertain results.

Further, on December 14, 2018, a U.S. District Court judge in the Northern District of Texas ruled that the individual mandate portion of the ACA is an essential and inseparable feature of the ACA, and therefore because the mandate was repealed as part of the TCJA, the remaining provisions of the ACA are invalid as well. The Trump administration and CMS have both stated that the ruling will have no immediate effect, and on December 30, 2018 the same judge issued an order staying the judgment pending appeal. The Trump administration has recently represented to the Court of Appeals considering this judgment that it does not oppose the lower court's ruling. It is unclear how this decision and any subsequent appeals and other efforts to repeal and replace the ACA will impact the ACA and our business. Litigation and legislation over the ACA are likely to continue, with unpredictable and uncertain results.

The costs of prescription pharmaceuticals have also been the subject of considerable discussion in the United States, and members of Congress and the Trump administration have stated that they will address such costs through new legislative and administrative measures. To date, there have been several recent U.S. congressional inquiries and proposed and enacted state and federal legislation designed to, among other things, bring more transparency to drug pricing, review the relationship between pricing and manufacturer patient programs, reduce the costs of drugs under Medicare and reform government program reimbursement methodologies for drug products. At the federal level, the Trump administration's budget proposal for fiscal year 2019 contains further drug price control measures that could be enacted during the 2019 budget process or in other future legislation, including, for example, measures to permit Medicare Part D plans to negotiate the price of certain drugs under Medicare Part B, to allow some states to negotiate drug prices under Medicaid, and to eliminate cost sharing for generic drugs for low-income patients. While any proposed measures will require authorization through additional legislation to become effective, Congress and the Trump administration have each indicated that it will continue to seek new

legislative and/or administrative measures to control drug costs. At the state level, legislatures are increasingly passing legislation and implementing regulations designed to control pharmaceutical and biological product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing.

Specifically, there have been several recent U.S. congressional inquiries and proposed federal and proposed and enacted state legislation designed to, among other things, bring more transparency to drug pricing, review the relationship between pricing and manufacturer patient programs, reduce the costs of drugs under Medicare and reform government program reimbursement methodologies for drug products. At the federal level, Congress and the Trump administration have each indicated that it will continue to seek new legislative and/or administrative measures to control drug costs. For example, on May 11, 2018, the Trump administration issued a plan to lower drug prices. Under this blueprint for action, the Trump administration indicated that the Department of Health and Human Services, or HHS, will: take steps to end the gaming of regulatory and patent processes by drug makers to unfairly protect monopolies; advance biosimilars and generics to boost price competition; evaluate the inclusion of prices in drug makers' advertisements to enhance price competition; speed access to and lower the cost of new drugs by clarifying policies for sharing information between insurers and drug makers; avoid excessive pricing by relying more on value-based pricing by expanding outcome-based payments in Medicare and Medicaid; work to give Part D plan sponsors more negotiation power with drug makers; examine which Medicare Part B drugs could be negotiated for a lower price by Part D plans, and improving the design of the Part B Competitive Acquisition Program; update Medicare's drug-pricing dashboard to increase transparency; prohibit Part D contracts that include "gag rules" that prevent pharmacists from informing patients when they could pay less out-of-pocket by not using insurance; and require that Part D plan members be provided with an annual statement of plan payments, out-of-pocket spending, and drug price increases. More recently, on January 31, 2019, the HHS Office of Inspector General proposed modifications to the federal Anti-Kickback Statute discount safe harbor for the purpose of reducing the cost of drug products to consumers which, among other things, if finalized, will affect discounts paid by manufacturers to Medicare Part D plans, Medicaid managed care organizations and pharmacy benefit managers working with these organizations.

At the state level, individual states are increasingly aggressive in passing legislation and implementing regulations designed to control pharmaceutical and biological product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing. In addition, regional healthcare authorities and individual hospitals are increasingly using bidding procedures to determine what pharmaceutical products and which suppliers will be included in their prescription drug and other healthcare programs. These measures could reduce the ultimate demand for our products, once approved, or put pressure on our product pricing. 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.

Legislative and regulatory proposals have been made to expand post-approval requirements and restrict sales and promotional activities for pharmaceutical products. We cannot be sure whether additional legislative changes will be enacted, or whether the FDA regulations, guidance or interpretations will be changed, or what the impact of such changes on the marketing approvals of our product candidates, if any, may be. Increased scrutiny by the U.S. Congress of the FDA's approval process may significantly delay or prevent marketing approval, as well as subject us to more stringent product labeling and post-marketing testing and other requirements.

Governments outside of the United States tend to impose strict price controls, which may adversely affect our revenues, if any.

In some countries, particularly the countries of the European Union, the pricing of prescription pharmaceuticals is subject to governmental control. In these countries, pricing negotiations with governmental authorities can take considerable time after the receipt of marketing approval for a product. To obtain reimbursement or pricing approval in some countries, we may be required to conduct a clinical trial that compares the cost-effectiveness of our product candidate to other available therapies. If reimbursement of our products is unavailable or limited in scope or amount, or if pricing is set at unsatisfactory levels, our business could be harmed, possibly materially.

If we or any third-party manufacturers we engage now or in the future fail to comply with environmental, health and safety laws and regulations, we could become subject to fines or penalties or incur costs or liabilities that could harm our business.

We and third-party manufacturers we engage now are, and any third-party manufacturers we may engage in the future will be, subject to numerous environmental, health and safety laws and regulations, including those governing laboratory procedures and the handling, use, storage, treatment and disposal of hazardous materials and wastes. Our operations involve the use of hazardous and flammable materials, including chemicals and biological materials. Our operations also produce hazardous waste products. We generally contract with third parties for the disposal of these materials and wastes. We cannot eliminate the risk of contamination or injury from these materials. In the event of contamination or injury resulting from our use of hazardous materials, we could be held liable for any resulting damages, and any liability could exceed our resources. Liability under certain environmental laws governing the release and cleanup of hazardous materials is joint and several and could be imposed without regard to fault. We also could incur significant costs associated with civil or criminal fines and penalties or become subject to injunctions limiting or prohibiting our activities for failure to comply with such laws and regulations.

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

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

Further, with respect to the operations of our current and any future third-party contract manufacturers, it is possible that if they fail to operate in compliance with applicable environmental, health and safety laws and regulations or properly dispose of wastes associated with our products, we could be held liable for any resulting damages, suffer reputational harm or experience a disruption in the manufacture and supply of our product candidates or products. In addition, our supply chain may be adversely impacted if any of our third-party contract manufacturers become subject to injunctions or other sanctions as a result of their non-compliance with environmental, health and safety laws and regulations.

We are subject to anti-corruption laws, as well as export control laws, customs laws, sanctions laws and other laws governing our operations. If we fail to comply with these laws, we could be subject to civil or criminal penalties, other remedial measures and legal expenses, be precluded from developing manufacturing and selling certain products outside the United States or be required to develop and implement costly compliance programs, which could adversely affect our business, results of operations and financial condition.

Our operations are subject to anti-corruption laws, including the U.K. Bribery Act 2010, or Bribery Act, the U.S. Foreign Corrupt Practices Act, or FCPA, and other anti-corruption laws that apply in countries where we do business and may do business in the future. The Bribery Act, FCPA and these other laws generally prohibit us, our officers, and our employees and intermediaries from bribing, being bribed or making other prohibited payments to government officials or other persons to obtain or retain business or gain some other business advantage. Compliance with the FCPA, in particular, is expensive and difficult, particularly in countries in which corruption is a recognized problem. In addition, the FCPA presents particular challenges in the pharmaceutical industry, because, in many countries, hospitals are operated by the government, and doctors and other hospital employees are considered foreign officials. Certain payments to hospitals in connection with clinical trials and other work have been deemed to be improper payments to government officials and have led to FCPA enforcement actions.

We may in the future operate in jurisdictions that pose a high risk of potential Bribery Act or FCPA violations, and we may participate in collaborations and relationships with third parties whose actions could potentially subject us to liability under the Bribery Act, FCPA or local anti-corruption laws. In addition, we cannot predict the nature, scope or effect of future regulatory requirements to which our international operations might be subject or the manner in which existing laws might be administered or interpreted. If we expand our operations outside of the United States, we will need to dedicate additional resources to comply with numerous laws and regulations in each jurisdiction in which we plan to operate.

We are also subject to other laws and regulations governing our international operations, including regulations administered by the governments of the United Kingdom and the United States, and authorities in the European Union, including applicable export control regulations, economic sanctions on countries and persons, customs requirements and currency exchange regulations, collectively referred to as the Trade Control laws. In addition, various laws, regulations and executive orders also restrict the use and dissemination outside of the United States, or the sharing with certain non-U.S. nationals, of information classified for national security purposes, as well as certain products and technical data relating to those products. If we expand our presence outside of the United States, it will require us to dedicate additional resources to comply with these laws, and these laws may preclude us from developing, manufacturing, or selling certain products and product candidates outside of the United States, which could limit our growth potential and increase our development costs.

There is no assurance that we will be completely effective in ensuring our compliance with all applicable anti-corruption laws, including the Bribery Act, the FCPA or other legal requirements, including Trade Control laws. If we are not in compliance with the Bribery Act, the FCPA and other anti-corruption laws or Trade Control laws, we may be subject to criminal and civil penalties, disgorgement and other sanctions and remedial measures, and legal expenses, which could have an adverse impact on our business, financial condition, results of operations and liquidity. The Securities and Exchange Commission, or SEC, also may suspend or bar issuers from trading securities on U.S. exchanges for violations of the FCPA's accounting provisions. Any investigation of any potential violations of the Bribery Act, the FCPA, other anti-corruption laws or Trade Control laws by United Kingdom, U.S. or other authorities could also have an adverse impact on our reputation, our business, results of operations and financial condition.

Our employees, independent contractors, consultants and vendors may engage in misconduct or other improper activities, including non-compliance with regulatory standards and requirements and insider trading, which could cause significant liability for us and harm our reputation.

We are exposed to the risk of fraud or other misconduct by our employees, independent contractors, consultants and vendors. Misconduct by these partners could include intentional failures to comply with FDA regulations or similar regulations of comparable foreign regulatory authorities, provide accurate information to the FDA or comparable foreign regulatory authorities, comply with manufacturing standards, comply with federal and state healthcare fraud and abuse laws and regulations and similar laws and regulations established and enforced by comparable foreign regulatory authorities, report financial information or data accurately or disclose unauthorized activities to us. Employee misconduct could also involve the improper use of information obtained in the course of clinical trials, which could result in regulatory sanctions and serious harm to our reputation. This could include violations of HIPAA, other U.S. federal and state law, and requirements of non-U.S. jurisdictions, including the European Union Data Protection Directive. We are also exposed to risks in connection with any insider trading violations by employees or others affiliated with us. It is not always possible to identify and deter employee misconduct, and the precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to be in compliance with such laws, standards, regulations, guidance or codes of conduct. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business and results of operations, including the imposition of significant fines or other sanctions.

Our internal computer systems, or those of our collaborators or other contractors or consultants, may fail or suffer security breaches, which could result in a material disruption of our product development programs.

Our internal computer systems and those of any collaborators, contractors or consultants are vulnerable to damage from computer viruses, unauthorized access, natural disasters, terrorism, war and telecommunication and electrical failures. Such systems are also vulnerable to service interruptions or to security breaches from inadvertent or intentional actions by our employees, third-party vendors and/or business partners, or from cyber-attacks by malicious third parties. Cyber-attacks are increasing in their frequency, sophistication and intensity, and have become increasingly difficult to detect. Cyber-attacks could include the deployment of harmful malware, ransomware, denial-of-service attacks, unauthorized access to or deletion of files, social engineering and other means to affect service reliability and threaten the confidentiality, integrity and availability of information. For example, we make extensive use of cloud-based storage systems, and in October 2018, we experienced a breach of one such system. While this breach did not result in the permanent loss or theft of any of our critical information or any other material consequences, it could have, and while we took steps to remediate this breach, such as establishing multi-factor authentication and implementing improvements to our data securities protocols, we cannot guarantee that the measures we have taken to date, and actions we may take in the future, will be sufficient to remediate any future breaches. Cyber-attacks also could include phishing attempts or e-mail fraud to cause payments or information to be transmitted to an unintended recipient.

While we have not experienced any material system failure, accident, cyber-attack or security breach to date, if such an event were to occur and cause interruptions in our operations, it could result in a material disruption of our development programs and our business operations, whether due to a loss of our trade secrets or other proprietary information or other similar disruptions. For example, the loss of clinical trial data from completed or future clinical trials could result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce the data. To the extent that any disruption or security breach were to result in a loss of, or damage to, our data or applications, or inappropriate disclosure of confidential or proprietary information, we could incur liability, our competitive position could be harmed and the further development and commercialization of our product candidates could be delayed.

Risks Related to Employee Matters and Managing Growth

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

We are highly dependent on the research and development, clinical, financial, operational and other business expertise of our executive officers, as well as the other principal members of our management, scientific and clinical teams. Although we have entered into employment offer letters with our executive officers, each of them may terminate their employment with us at any time. We do not maintain "key person" insurance for any of our executives or other employees. Recruiting and retaining qualified scientific, clinical, manufacturing, accounting, legal and sales and marketing personnel will also be critical to our success.

The loss of the services of our executive officers or other key employees could impede the achievement of our research, development and commercialization objectives and seriously harm our ability to successfully implement our business strategy. Furthermore, replacing executive officers and key employees may be difficult and may take an extended period of time because of the limited number of individuals in our industry with the breadth of skills and experience required to successfully develop, gain regulatory approval of and commercialize products. Competition to hire from this limited pool is intense, and we may be unable to hire, train, retain or motivate these key personnel on acceptable terms given the competition among numerous pharmaceutical and biotechnology companies for similar personnel. We also experience competition for the hiring of scientific and clinical personnel from universities and research institutions. In addition, we rely on consultants and advisors, including scientific and clinical advisors, to assist us in formulating our research and development and commercialization strategy. Our consultants and advisors may be employed by employers other than us and may have commitments under consulting or advisory contracts with other entities that may limit their availability to us. Our success as a public company also depends on implementing and maintaining internal controls and the accuracy and timeliness of our financial reporting. If we are unable to continue to attract and retain high quality personnel, our ability to pursue our growth strategy will be limited.

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

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

Risks Related to our Common Stock

After this offering, our executive officers, directors and principal stockholders, if they choose to act together, will continue to have the ability to control all matters submitted to stockholders for approval.

Upon the closing of this offering, our executive officers and directors and our stockholders who owned more than 5% of our outstanding common stock before this offering will, in the aggregate, beneficially own shares representing approximately 52.9% of our capital stock (or 51.5% if the underwriters exercise their option to purchase additional shares in full). As a result, if these stockholders were to choose to act

together, they would be able to control all matters submitted to our stockholders for approval, as well as our management and affairs. For example, these persons, if they choose to act together, would control the election of directors and approval of any merger, consolidation or sale of all or substantially all of our assets.

This concentration of ownership control may:

- delay, defer or prevent a change in control;
- entrench our management and board of directors; or
- delay or prevent a merger, consolidation, takeover or other business combination involving us that other stockholders may desire.

Provisions in our corporate charter documents and under Delaware law could make an acquisition of our company, which may be beneficial to our stockholders, more difficult and may prevent attempts by our stockholders to replace or remove our current directors and members of management.

Provisions in our certificate of incorporation and our bylaws that will become effective upon the closing of this offering may discourage, delay or prevent a merger, acquisition or other change in control of our company that stockholders may consider favorable, including transactions in which you might otherwise receive a premium for your shares. These provisions could also limit the price that investors might be willing to pay in the future for shares of our common stock, thereby depressing the market price of our common stock. In addition, because our board of directors is responsible for appointing the members of our management team, these provisions may frustrate or prevent any attempts by our stockholders to replace or remove our current management by making it more difficult for stockholders to replace members of our board of directors. Among other things, these provisions:

- establish a classified board of directors such that only one of three classes of directors is elected each year;
- allow the authorized number of our directors to be changed only by resolution of our board of directors;
- limit the manner in which stockholders can remove directors from our board of directors;
- establish advance notice requirements for stockholder proposals that can be acted on at stockholder meetings and nominations to our board of directors;
- require that stockholder actions must be effected at a duly called stockholder meeting and prohibit actions by our stockholders by written consent;
- limit who may call stockholder meetings;
- authorize our board of directors to issue preferred stock without stockholder approval, which could be used to institute a "poison pill" that would work to dilute the stock ownership of a potential hostile acquirer, effectively preventing acquisitions that have not been approved by our board of directors; and
- require the approval of the holders of at least 75% of the votes that all our stockholders would be entitled to cast to amend or repeal specified provisions of our certificate of incorporation or bylaws that will become effective upon the closing of this offering.

Moreover, because we are incorporated in Delaware, we are governed by the provisions of Section 203 of the Delaware General Corporation Law, or the DGCL, which prohibits a person who owns in excess of 15% of our outstanding voting stock from merging or combining with us for a period of three years after the date of the transaction in which the person acquired in excess of 15% of our outstanding voting stock, unless the merger or combination is approved in a prescribed manner.

If you purchase shares of common stock in this offering, you will suffer immediate dilution of your investment.

The initial public offering price of our common stock is substantially higher than the pro forma as adjusted net tangible book value per share of our common stock. Therefore, if you purchase shares of our common stock in this offering, you will pay a price per share that substantially exceeds our pro forma as adjusted net tangible book value per share after this offering. To the extent outstanding options are exercised, you will incur further dilution. Based on the initial public offering price of \$16.00 per share, you will experience immediate dilution of \$10.45 per share, representing the difference between our pro forma as adjusted net tangible book value per share, after giving effect to this offering, and the initial public offering price.

An active trading market for our common stock may not develop.

Prior to this offering, there has been no public market for our common stock. The initial public offering price for our common stock was determined through negotiations with the underwriters. Although our common stock has been approved for listing on the Nasdaq Global Market, an active trading market for our shares may never develop or be sustained following this offering. If an active market for our common stock does not develop, it may be difficult for you to sell shares you purchase in this offering without depressing the market price for the shares or at all.

If securities analysts do not publish or cease publishing research or reports or publish misleading, inaccurate or unfavorable research about our business or if they publish negative evaluations of our stock, the price and trading volume of our stock could decline.

The trading market for our common stock will rely, in part, on the research and reports that industry or financial analysts publish about us or our business. We do not currently have, and may never obtain, research coverage by industry or financial analysts. If no, or few, analysts commence coverage of us, the trading price of our stock would likely decrease. Even if we do obtain analyst coverage, if one or more of the analysts covering our business downgrade their evaluations of our stock or publish inaccurate or unfavorable research about our business, or provides more favorable relative recommendations about our competitors, the price of our stock could decline. If one or more of these analysts cease to cover our stock, we could lose visibility in the market for our stock, which in turn could cause our stock price and trading volume to decline.

The price of our common stock may be volatile and fluctuate substantially, which could result in substantial losses for purchasers of our common stock in this offering.

Our stock price is likely to be volatile. The stock market in general and the market for smaller biopharmaceutical companies in particular have experienced extreme volatility that has often been unrelated to the operating performance of particular companies. As a result of this volatility, you may not be able to sell your common stock at or above the initial public offering price. The market price for our common stock may be influenced by many factors, including:

- results of or developments in preclinical studies and clinical trials of our product candidates or those of our competitors or potential collaborators;
- our success in commercializing our product candidates, if and when approved;
- the success of competitive products or technologies;
- regulatory or legal developments in the United States and other countries;
- developments or disputes concerning patent applications, issued patents or other intellectual property or proprietary rights;
- the recruitment or departure of key personnel;

- the level of expenses related to any of our product candidates or clinical development programs;
- the results of our efforts to discover, develop, acquire or in-license products, product candidates, technologies or data referencing rights, the costs of commercializing any such products and the costs of development of any such product candidates or technologies;
- actual or anticipated changes in estimates as to financial results, development timelines or recommendations by securities analysts;
- variations in our financial results or the financial results of companies that are perceived to be similar to us;
- changes in the structure of healthcare payment systems;
- market conditions in the pharmaceutical and biotechnology sectors;
- general economic, industry and market conditions; and
- the other factors described in this "Risk Factors" section.

In the past, following periods of volatility in the market price of a company's securities, securities class-action litigation has often been instituted against that company. Any lawsuit to which we are a party, with or without merit, may result in an unfavorable judgment. We also may decide to settle lawsuits on unfavorable terms. Any such negative outcome could result in payments of substantial damages or fines, damage to our reputation or adverse changes to our offerings or business practices. Such litigation may also cause us to incur other substantial costs to defend such claims and divert management's attention and resources. Furthermore, negative public announcements of the results of hearings, motions or other interim proceedings or developments could have a negative effect on the market price of our common stock.

We have broad discretion in the use of the net proceeds from this offering and may not use them effectively.

Our management will have broad discretion in the application of the net proceeds from this offering and could spend the proceeds in ways that do not improve our results of operations or enhance the value of our common stock. The failure by our management to apply these funds effectively could result in financial losses that could cause the price of our common stock to decline and delay the development of our product candidates. Pending their use, we may invest the net proceeds from this offering in a manner that does not produce income or that loses value.

A significant portion of our total outstanding shares are eligible to be sold into the market in the near future, which could cause the market price of our common stock to drop significantly, even if our business is doing well.

Sales of a substantial number of shares of our common stock in the public market, or the perception in the market that the holders of a large number of shares intend to sell shares, could reduce the market price of our common stock. After this offering, we will have 23,340,014 shares of common stock outstanding based on the number of shares outstanding as of June 30, 2019. This includes the 4,500,000 shares that we are selling in this offering, which may be resold in the public market immediately without restriction, unless purchased by our affiliates or existing stockholders. The remaining shares are currently restricted as a result of securities laws or lock-up agreements but will become eligible to be sold at various times after the offering. Moreover, beginning 180 days after the completion of this offering, holders of an aggregate of 16,357,132 shares of our common stock will have rights, subject to specified conditions, to require us to file registration statements covering their shares or to include their shares in registration statements that we may file for ourselves or other stockholders. We also intend to register all shares of common stock that we may issue under our equity compensation plans. Once we register these shares, they can be freely sold in the public market upon issuance, subject to volume limitations applicable to affiliates and the lock-up agreements described in the "Underwriters" section of this prospectus.

We are an "emerging growth company," and the reduced disclosure requirements applicable to emerging growth companies may make our common stock less attractive to investors.

We are an "emerging growth company," or EGC, as defined in the Jumpstart Our Business Startups Act of 2012, or the JOBS Act. We may remain an EGC until the end of the fiscal year in which the fifth anniversary of this offering occurs, although if the market value of our common stock that is held by non-affiliates exceeds \$700 million as of any June 30 before that time or if we have annual gross revenues of \$1.07 billion or more in any fiscal year, we would cease to be an EGC as of December 31 of the applicable year. We also would cease to be an EGC if we issue more than \$1 billion of non-convertible debt over a three-year period. For so long as we remain an EGC, we are permitted and intend to rely on exemptions from certain disclosure requirements that are applicable to other public companies that are not EGCs. These exemptions include:

- being permitted to provide only two years of audited financial statements in this prospectus, in addition to any required unaudited interim financial statements, with correspondingly reduced "Management's Discussion and Analysis of Financial Condition and Results of Operations" disclosure;
- not being required to comply with the auditor attestation requirements in the assessment of our internal control over financial reporting;
- not being required to comply with any requirement that may be adopted by the Public Company Accounting Oversight Board regarding mandatory audit firm rotation or a supplement to the auditor's report providing additional information about the audit and the financial statements;
- reduced disclosure obligations regarding executive compensation; and
- exemptions from the requirements of holding a nonbinding advisory vote on executive compensation and stockholder approval of any golden parachute payments not previously approved.

We have taken advantage of reduced reporting obligations in this prospectus. In particular, in this prospectus, we have provided only two years of audited financial statements and have not included all of the executive compensation related information that would be required if we were not an EGC.

We cannot predict whether investors will find our common stock less attractive if we rely on these exemptions. If some investors find our common stock less attractive as a result, there may be a less active trading market for our common stock and our stock price may be more volatile.

In addition, the JOBS Act permits an EGC to take advantage of an extended transition period to comply with new or revised accounting standards applicable to public companies until those standards would otherwise apply to private companies. We have elected not to "opt out" of such extended transition period, which means that when a standard is issued or revised and it has different application dates for public or private companies, we will adopt the new or revised standard at the time private companies adopt the new or revised standard and will do so until such time that we either (i) irrevocably elect to "opt out" of such extended transition period or (ii) no longer qualify as an EGC.

We will incur increased costs as a result of operating as a public company, and our management will be required to devote substantial time to new compliance initiatives and corporate governance practices.

As a public company, and particularly after we are no longer an EGC, we will incur significant legal, accounting and other expenses that we did not incur as a private company. The Sarbanes-Oxley Act of 2002, the Dodd-Frank Wall Street Reform and Consumer Protection Act, the listing requirements of the Nasdaq Global Market and other applicable securities rules and regulations impose various requirements on public companies, including establishment and maintenance of effective disclosure and financial controls and corporate governance practices. Our management and other personnel will need to devote a

substantial amount of time to these compliance initiatives. Moreover, these rules and regulations will increase our legal and financial compliance costs, particularly as we hire additional financial and accounting employees to meet public company internal control and financial reporting requirements, and will make some activities more time-consuming and costly. For example, we expect that these rules and regulations may make it more difficult and more expensive for us to obtain director and officer liability insurance, which in turn could make it more difficult for us to attract and retain qualified members of our board of directors.

We are evaluating these rules and regulations, and cannot predict or estimate the amount of additional costs we may incur or the timing of such costs. These rules and regulations are often subject to varying interpretations, in many cases due to their lack of specificity, and, as a result, their application in practice may evolve over time as new guidance is provided by regulatory and governing bodies. This could result in continuing uncertainty regarding compliance matters and higher costs necessitated by ongoing revisions to disclosure and governance practices.

Pursuant to Section 404 of the Sarbanes-Oxley Act of 2002, or Section 404, we will be required to furnish a report by our management on our internal control over financial reporting. However, while we remain an EGC, we will not be required to include an attestation report on internal control over financial reporting issued by our independent registered public accounting firm. To achieve compliance with Section 404 within the prescribed period, we will be engaged in a process to document and evaluate our internal control over financial reporting, which is both costly and challenging. In this regard, we will need to continue to dedicate internal resources, including through hiring additional financial and accounting personnel, potentially engage outside consultants and adopt a detailed work plan to assess and document the adequacy of internal control over financial reporting, continue steps to improve control processes as appropriate, validate through testing that controls are functioning as documented and implement a continuous reporting and improvement process for internal control over financial reporting. Despite our efforts, there is a risk that we will not be able to conclude, within the prescribed timeframe or at all, that our internal control over financial reporting is effective as required by Section 404. If we identify one or more material weaknesses in our internal control over financial reporting, it could result in an adverse reaction in the financial markets due to a loss of confidence in the reliability of our financial statements.

Because we do not anticipate paying any cash dividends on our capital stock in the foreseeable future, capital appreciation, if any, will be your sole source of gain.

We have never declared or paid cash dividends on our capital stock. We currently intend to retain all of our future earnings, if any, to finance the growth and development of our business. As a result, capital appreciation, if any, of our common stock will be your sole source of gain for the foreseeable future.

Our certificate of incorporation that will become effective upon the closing of this offering designates the state courts in the State of Delaware as the sole and exclusive forum for certain types of actions and proceedings that may be initiated by our stockholders, which could discourage lawsuits against the company and our directors, officers and employees.

Our certificate of incorporation that will become effective upon the closing of this offering provides that, unless we consent in writing to the selection of an alternative forum, the Court of Chancery of the State of Delaware (or, if the Court of Chancery of the State of Delaware does not have jurisdiction, the federal district court for the District of Delaware) will be the sole and exclusive forum for (1) any derivative action or proceeding brought on our behalf, (2) any action asserting a claim of breach of a fiduciary duty owed by any of our directors, officers, employees or stockholders to our company or our stockholders, (3) any action asserting a claim arising pursuant to any provision of the DGCL or as to which the DGCL confers jurisdiction on the Court of Chancery of the State of Delaware or (4) any action asserting a claim arising pursuant to any provision of our certificate of incorporation or bylaws (in each case, as they may be amended from time to time) or governed by the internal affairs doctrine. This

exclusive forum provision will not apply to actions arising under the Securities Act of 1933, as amended, or the Securities Exchange Act of 1934, as amended.

This exclusive forum provision may limit the ability of our stockholders to bring a claim in a judicial forum that such stockholders find favorable for disputes with us or our directors, officers or employees, which may discourage such lawsuits against us and our directors, officers and employees. Alternatively, if a court were to find the choice of forum provision contained in our certificate of incorporation to be inapplicable or unenforceable in an action, we may incur additional costs associated with resolving such action in other jurisdictions, which could materially adversely affect our business, financial condition and operating results.

CAUTIONARY NOTE REGARDING FORWARD-LOOKING STATEMENTS AND INDUSTRY DATA

This prospectus contains forward-looking statements that involve substantial risks and uncertainties. All statements, other than statements of historical fact, contained in this prospectus, including statements regarding our strategy, future operations, future financial position, future revenue, projected costs, prospects, plans and objectives of management, are forward-looking statements. The words "anticipate," "believe," "continue" "could," "estimate," "expect," "intend," "may," "might," "plan," "potential," "predict," "project," "should," "target," "would," and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words.

The forward-looking statements in this prospectus include, among other things, statements about:

- our ongoing Phase 1 clinical trial and planned Phase 2b clinical trial and Phase 2 open label clinical trial of losmapimod;
- our IND-enabling studies and planned Phase 1 clinical trial of FTX-HbF;
- the initiation, timing, progress and results of our drug target discovery screening programs;
- the initiation, timing, progress and results of our current and future preclinical studies and clinical trials and our research and development programs;
- our plans to develop and, if approved, subsequently commercialize losmapimod and any other product candidates, including in combination with other drugs and therapies;
- the timing of and our ability to submit applications for, obtain and maintain regulatory approvals for losmapimod and other product candidates;
- our expectations regarding our ability to fund our operating expenses and capital expenditure requirements with our cash and cash equivalents and proceeds of this offering;
- the potential advantages of our product candidates;
- the rate and degree of market acceptance and clinical utility of our products;
- our estimates regarding the potential market opportunity for our product candidates;
- our commercialization, marketing and manufacturing capabilities and strategy;
- our intellectual property position;
- our ability to identify additional products, product candidates or technologies with significant commercial potential that are consistent with our commercial objectives;
- our expectations related to the use of proceeds from this offering;
- our estimates regarding expenses, future revenue, timing of any future revenue, capital requirements and needs for additional financing;
- the impact of government laws and regulations;
- our competitive position;
- developments relating to our competitors and our industry;
- our ability to maintain and establish collaborations or obtain additional funding; and
- our expectations regarding the time during which we will be an emerging growth company under the JOBS Act.

We may not actually achieve the plans, intentions or expectations disclosed in our forward-looking statements, and you should not place undue reliance on our forward-looking statements. Actual results or

events could differ materially from the plans, intentions and expectations disclosed in the forward-looking statements we make. We have included important factors in the cautionary statements included in this prospectus, particularly in the "Risk Factors" section, that we believe could cause actual results or events to differ materially from the forward-looking statements that we make. Our forward-looking statements do not reflect the potential impact of any future acquisitions, mergers, dispositions, collaborations, joint ventures or investments we may make or enter into.

You should read this prospectus and the documents that we reference in this prospectus and have filed as exhibits to the registration statement of which this prospectus is a part completely and with the understanding that our actual future results may be materially different from what we expect. The forward-looking statements contained in this prospectus are made as of the date of this prospectus, and we do not assume any obligation to update any forward-looking statements, whether as a result of new information, future events or otherwise, except as required by applicable law.

This prospectus includes statistical and other industry and market data that we obtained from industry publications and research, surveys and studies conducted by third parties as well as our own estimates of potential market opportunities. All of the market data used in this prospectus involves a number of assumptions and limitations, and you are cautioned not to give undue weight to such data. Industry publications and third-party research, surveys and studies generally indicate that their information has been obtained from sources believed to be reliable, although they do not guarantee the accuracy or completeness of such information. Our estimates of the potential market opportunities for our product candidates include several key assumptions based on our industry knowledge, industry publications, third-party research and other surveys, which may be based on a small sample size and may fail to accurately reflect market opportunities. While we believe that our internal assumptions are reasonable, no independent source has verified such assumptions.

USE OF PROCEEDS

We estimate that the net proceeds from our issuance and sale of 4,500,000 shares of our common stock in this offering will be approximately \$63.9 million, based on the initial public offering price of \$16.00 per share, after deducting underwriting discounts and commissions and estimated offering expenses payable by us. If the underwriters exercise their option to purchase additional shares of our common stock in full, we estimate that the net proceeds from this offering will be approximately \$73.9 million.

As of March 31, 2019, we had cash and cash equivalents of \$62.5 million. We currently estimate that we will use the net proceeds from this offering, together with our existing cash and cash equivalents, as follows:

- approximately \$45.0 million to advance losmapimod for FSHD;
- approximately \$15.0 million to advance our hemoglobinopathies program;
- approximately \$30.0 million to fund our ongoing product engine and discovery efforts; and
- the remainder for working capital and other general corporate purposes.

This expected use of net proceeds from this offering and our existing cash and cash equivalents represents our intentions based upon our current plans and business conditions, which could change in the future as our plans and business conditions evolve. The amounts and timing of our actual expenditures may vary significantly depending on numerous factors, including the progress of our development programs, the status of and results from clinical trials, the timing of regulatory submissions and the outcome of regulatory review, as well as any collaborations that we may enter into with third parties for our product candidates, and any unforeseen cash needs. As a result, our management will retain broad discretion over the allocation of the net proceeds from this offering.

Based on our planned use of the net proceeds from this offering, together with our existing cash and cash equivalents, we estimate that such funds will be sufficient to fund our operating expenses and capital expenditure requirements into the third quarter of 2021. We anticipate that the net proceeds from this offering together with our existing cash and cash equivalents will be sufficient to allow us to complete our ongoing clinical trials, including our Phase 2b clinical trial, of losmapimod and conduct IND-enabling studies for and initiate a Phase 1 clinical trial of FTX-HbF. We will require additional capital to advance losmapimod through additional clinical trials, if required, to advance FTX-HbF through necessary clinical trials and to commercialize any of our product candidates, if we receive regulatory approval. We have based these estimates on assumptions that may prove to be wrong, including assumptions regarding the clinical trials necessary for FDA approval of our product candidates, and we could use our capital resources sooner than we currently expect. Due to the numerous risks and uncertainties associated with product development, including the risks and uncertainties with respect to successful enrollment and completion of clinical trials, at this time, we cannot reasonably estimate the amount of additional funding that will be necessary to complete the clinical development of losmapimod or any future product candidates. If we receive regulatory approval for losmapimod or other product candidates, we expect to incur significant commercialization expenses related to product manufacturing, sales, marketing and distribution.

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

DIVIDEND POLICY

We have never declared or paid cash dividends on our common stock. We currently intend to retain all available funds and any future earnings to fund the development and expansion of our business and we do not anticipate paying any cash dividends in the foreseeable future. Any future determination to declare and pay dividends will be made at the discretion of our board of directors and will depend on then-existing conditions, including our results of operations, financial condition, contractual restrictions, capital requirements, business prospects and other factors our board of directors may deem relevant.

CAPITALIZATION

The following table sets forth our cash and cash equivalents and our capitalization as of March 31, 2019:

- on an actual basis;
- on a pro forma basis to give effect to (i) the automatic conversion of all outstanding shares of our preferred stock into an aggregate of 16,071,418 shares of common stock upon the closing of this offering and (ii) the filing and effectiveness of our certificate of incorporation; and
- on a pro forma as adjusted basis to give further effect to our issuance and sale of 4,500,000 shares of our common stock in this offering at the initial public offering price of \$16.00 per share, after deducting underwriting discounts and commissions and estimated offering expenses payable by us.

You should read the information in this table together with our consolidated financial statements and the related notes appearing at the end of this prospectus and the "Selected Consolidated Financial Data" and "Management's Discussion and Analysis of Financial Condition and Results of Operations" sections of this prospectus.

	As of March 31, 2019		
	Actual	Pro Forma	Pro Forma As Adjusted
	(in thousands, except share and per share data)		
Cash and cash equivalents	\$ 62,452	\$ 62,452	\$ 126,312
Convertible preferred stock (Series A and B), \$0.001 par value; 112,500,000 shares authorized, issued and outstanding, actual; no shares authorized, issued or outstanding, pro forma and pro forma as adjusted	165,136	—	—
Stockholders' (deficit) equity			
Preferred stock, \$0.001 par value; no shares authorized, issued or outstanding, actual; 5,000,000 shares authorized, no shares issued or outstanding, pro forma and pro forma as adjusted	—	—	—
Common stock, \$0.001 par value; 147,500,000 shares authorized, 2,747,842 shares issued and 1,721,966 shares outstanding, actual; 200,000,000 shares authorized, 18,819,260 shares issued and 17,793,384 shares outstanding, pro forma; 200,000,000 shares authorized, 23,319,260 shares issued and 22,293,384 shares outstanding, pro forma as adjusted	2	18	22
Additional paid-in capital	5,278	170,398	234,254
Accumulated deficit	(104,967)	(104,967)	(104,967)
Total stockholders' (deficit) equity	(99,687)	65,449	129,309
Total capitalization	\$ 65,449	\$ 65,449	\$ 129,309

The table above does not include:

- 1,528,387 shares of common stock issuable upon the exercise of stock options outstanding as of March 31, 2019, at a weighted average exercise price of \$7.60 per share, and an additional 93,995 shares of common stock issuable upon the exercise of stock options granted subsequent to March 31, 2019, at a weighted average exercise price of \$11.06 per share;
- 366,623 shares of common stock available for future issuance as of March 31, 2019 under our 2016 Stock Incentive Plan, as amended, or the 2016 Plan; and

- 2,017,142 and 252,142 additional shares of our common stock available for future issuance under our 2019 Stock Incentive Plan, of which our board of directors has granted options to purchase an aggregate of 308,486 shares of common stock to certain of our employees and non-employee directors effective upon the commencement of trading of our common stock on the Nasdaq Global Market, and our 2019 Employee Stock Purchase Plan, respectively, as well as any automatic increases in the number of shares of common stock reserved for future issuance under these plans.

DILUTION

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

Our historical net tangible book value (deficit) as of March 31, 2019 was \$(99.9) million, or \$(36.36) per share of common stock. Our historical net tangible book value (deficit) is the amount of our total tangible assets less our total liabilities and the carrying value of our preferred stock, which is not included within stockholders' (deficit) equity. Historical net tangible book value (deficit) per share represents historical net tangible book value (deficit) divided by the 2,747,842 shares of common stock outstanding as of March 31, 2019, including 1,025,876 shares of unvested restricted stock subject to repurchase by us.

Our pro forma net tangible book value as of March 31, 2019 was \$65.3 million, or \$3.47 per share of common stock. Pro forma net tangible book value represents the amount of our total tangible assets less our total liabilities, after giving effect to the automatic conversion of all outstanding shares of our preferred stock into an aggregate of 16,071,418 shares of common stock upon the closing of this offering. Pro forma net tangible book value per share represents pro forma net tangible book value divided by the total number of shares outstanding as of March 31, 2019, after giving effect to the pro forma adjustments described above.

After giving further effect to our issuance and sale of 4,500,000 shares of our common stock in this offering at the initial public offering price of \$16.00 per share, and after deducting underwriting discounts and commissions and estimated offering expenses payable by us, our pro forma as adjusted net tangible book value as of March 31, 2019 would have been \$129.3 million, or \$5.55 per share. This represents an immediate increase in pro forma as adjusted net tangible book value per share of \$2.08 to existing stockholders and immediate dilution of \$10.45 in pro forma as adjusted net tangible book value per share to new investors purchasing shares of common stock in this offering. Dilution per share to new investors is determined by subtracting pro forma as adjusted net tangible book value per share after this offering from the initial public offering price per share paid by new investors. The following table illustrates this dilution on a per share basis:

Initial public offering price per share	\$ 16.00
Historical net tangible book value (deficit) per share as of March 31, 2019	\$ (36.36)
Increase per share attributable to the pro forma adjustments described above	<u>39.83</u>
Pro forma net tangible book value per share as of March 31, 2019	\$ 3.47
Increase in pro forma as adjusted net tangible book value per share attributable to new investors purchasing shares of common stock in this offering	<u>2.08</u>
Pro forma as adjusted net tangible book value per share immediately after this offering	\$ 5.55
Dilution per share to new investors purchasing shares of common stock in this offering	<u>\$ 10.45</u>

If the underwriters exercise their option to purchase additional shares in full, our pro forma as adjusted net tangible book value per share after this offering would be \$5.81, representing an immediate increase in pro forma as adjusted net tangible book value per share of \$2.34 to existing stockholders and immediate dilution in pro forma as adjusted net tangible book value per share of \$10.19 to new investors purchasing shares of common stock in this offering, based on the initial public offering price of \$16.00 per share, and after deducting underwriting discounts and commissions and estimated offering expenses payable by us.

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The following table summarizes, as of March 31, 2019, on the pro forma as adjusted basis described above, the total number of shares of common stock purchased from us on an as converted to common stock basis, the total consideration paid or to be paid and the average price per share paid or to be paid by existing stockholders and by new investors in this offering at the initial public offering price of \$16.00 per share, before deducting underwriting discounts and commissions and estimated offering expenses payable by us. As the table shows, new investors purchasing shares of common stock in this offering will pay an average price per share substantially higher than our existing stockholders paid.

	Shares Purchased		Total Consideration		Average Price Per Share
	Number	Percent	Amount	Percentage	
Existing stockholders	18,819,260	81%	\$ 140,076,300	66%	7.44
Investors purchasing shares of common stock in this offering	4,500,000	19%	72,000,000	34%	16.00
Total	23,319,260	100%	\$ 212,076,300	100%	

The table above assumes no exercise of the underwriters' option to purchase additional shares in this offering. If the underwriters exercise their option to purchase additional shares in full, the number of shares of our common stock held by existing stockholders would be reduced to 78% of the total number of shares of our common stock outstanding after this offering, and the number of shares of common stock held by new investors purchasing shares of common stock in this offering would be increased to 22% of the total number of shares of our common stock outstanding after this offering.

The tables and discussion above are based on 2,747,842 shares of our common stock outstanding as of March 31, 2019, including 1,025,876 shares of unvested restricted stock subject to repurchase by us, and exclude:

- 1,528,387 shares of common stock issuable upon the exercise of stock options outstanding as of March 31, 2019, at a weighted average exercise price of \$7.60 per share, and an additional 93,995 shares of common stock issuable upon the exercise of stock options granted subsequent to March 31, 2019, at a weighted average exercise price of \$11.06 per share;
- 366,623 shares of common stock available for future issuance as of March 31, 2019 under our 2016 Plan; and
- 2,017,142 and 252,142 additional shares of our common stock available for future issuance under our 2019 Stock Incentive Plan, of which our board of directors has granted options to purchase an aggregate of 308,486 shares of common stock to certain of our employees and non-employee directors effective upon the commencement of trading of our common stock on the Nasdaq Global Market, and our 2019 Employee Stock Purchase Plan, respectively, as well as any automatic increases in the number of shares of common stock reserved for future issuance under these plans.

To the extent that outstanding stock options are exercised, new stock options are issued, or we issue additional shares of common stock in the future, there will be further dilution to investors purchasing shares of common stock in this offering. In addition, we may choose to raise additional capital because of market conditions or strategic considerations, even if we believe that we have sufficient funds for our current or future operating plans. If we raise additional capital through the sale of equity or convertible debt securities, the issuance of these securities could result in further dilution to our stockholders.

SELECTED CONSOLIDATED FINANCIAL DATA

You should read the following selected consolidated financial data together with our consolidated financial statements and the related notes appearing at the end of this prospectus and the "Management's Discussion and Analysis of Financial Condition and Results of Operations" section of this prospectus. We have derived the consolidated statement of operations data for the years ended December 31, 2017 and 2018 and the consolidated balance sheet data as of December 31, 2017 and 2018 from our annual consolidated financial statements appearing at the end of this prospectus. The consolidated statement of operations data for the three months ended March 31, 2018 and 2019 and the consolidated balance sheet data as of March 31, 2019 have been derived from our interim consolidated financial statements appearing at the end of this prospectus and have been prepared on the same basis as the annual consolidated financial statements. In the opinion of management, the interim data reflect all normal recurring adjustments necessary for the fair presentation of the financial information in those statements. Our historical results are not necessarily indicative of the results that may be expected in the future, and our results for any interim period are not necessarily indicative of the results that should be expected for any full year or any other period.

	Year Ended December 31,		Three Months Ended March 31,	
	2017	2018	2018	2019
(in thousands, except per share data)				
Consolidated Statement of Operations Data:				
Operating expenses:				
Research and development	\$ 18,494	\$ 25,184	\$ 5,573	\$ 34,629
General and administrative	4,499	8,314	1,737	2,598
Total operating expenses	<u>22,993</u>	<u>33,498</u>	<u>7,310</u>	<u>37,227</u>
Loss from operations	<u>(22,993)</u>	<u>(33,498)</u>	<u>(7,310)</u>	<u>(37,227)</u>
Other income, net:				
Interest income, net	1	518	—	377
Other income	28	392	370	7
Net loss and comprehensive loss	<u>\$ (22,964)</u>	<u>\$ (32,588)</u>	<u>\$ (6,940)</u>	<u>\$ (36,843)</u>
Cumulative convertible preferred stock dividends	<u>\$ (2,407)</u>	<u>\$ (6,559)</u>	<u>(828)</u>	<u>(3,041)</u>
Net loss attributable to common stockholders	<u>\$ (25,371)</u>	<u>\$ (39,147)</u>	<u>\$ (7,768)</u>	<u>\$ (39,884)</u>
Net loss per share attributable to common stockholders, basic and diluted ⁽¹⁾	<u>\$ (35.68)</u>	<u>\$ (31.14)</u>	<u>\$ (7.62)</u>	<u>\$ (24.29)</u>
Weighted average number of common shares used in net loss per share attributable to common stockholders, basic and diluted ⁽¹⁾	<u>711</u>	<u>1,257</u>	<u>1,019</u>	<u>1,642</u>
Pro forma net loss per share attributable to common stockholders, basic and diluted ⁽¹⁾		<u>\$ (2.98)</u>		<u>\$ (2.17)</u>
Pro forma weighted average number of common shares used in net loss per share attributable to common stockholders, basic and diluted ⁽¹⁾		<u>10,951</u>		<u>16,940</u>

- (1) See Note 12 to our annual and interim consolidated financial statements appearing at the end of this prospectus for details on the calculation of basic and diluted net loss per share attributable to common stockholders and unaudited basic and diluted pro forma net loss per share attributable to common stockholders.

	As of December 31,		As of
	2017	2018	March 31,
	(in thousands)		
Consolidated Balance Sheet Data:			
Cash and cash equivalents	\$ 407	\$ 72,797	\$ 62,452
Working (deficit) capital ⁽¹⁾	(1,447)	69,866	59,306
Total assets	4,340	85,771	75,588
Convertible preferred stock	34,587	139,670	165,136
Total stockholders' deficit	(33,265)	(63,670)	(99,687)

(1) We define working (deficit) capital as current assets less current liabilities.

MANAGEMENT'S DISCUSSION AND ANALYSIS OF FINANCIAL CONDITION AND RESULTS OF OPERATIONS

You should read the following discussion and analysis of our financial condition and results of operations together with the "Selected Consolidated Financial Data" section of this prospectus and our consolidated financial statements and related notes appearing at the end of this prospectus. Some of the information contained in this discussion and analysis or set forth elsewhere in this prospectus, including information with respect to our plans and strategy for our business and related financing, includes forward-looking statements that involve risks and uncertainties. As a result of many factors, including those factors set forth in the "Risk Factors" section of this prospectus, our actual results could differ materially from the results described in or implied by the forward-looking statements contained in the following discussion and analysis.

Overview

We are a clinical-stage biopharmaceutical company focused on improving the lives of patients with genetically defined diseases in areas of high unmet medical need, with an initial focus on rare diseases. We have developed a proprietary product engine that we employ to systematically identify and validate cellular drug targets that can potentially modulate gene expression to treat the known root cause of genetically defined diseases. We are using our product engine to identify targets that can be drugged by small molecules regardless of the particular underlying mechanism of gene mis-expression. We have identified drug targets to treat the root causes of facioscapulohumeral muscular dystrophy, or FSHD, and certain hemoglobinopathies, namely sickle cell disease, or SCD, and β -thalassemia. We expect to initiate a Phase 2b clinical trial of losmapimod, our product candidate for FSHD, in mid-2019. We commenced a Phase 1 clinical trial in February 2019 to obtain safety and tolerability data for losmapimod in patients with FSHD. We plan to submit an investigational new drug application, or IND, for FTX-HbF, our product candidate for certain hemoglobinopathies, in mid-2020.

Since inception, our operations have focused on organizing and staffing our company, business planning, raising capital, establishing our intellectual property, building our discovery platform, including our proprietary compound library and product engine, identifying drug targets and potential product candidates, in-licensing, producing drug substance and drug product material for use in clinical trials and conducting pre-clinical studies and early clinical trials. To date, we have funded our operations primarily through the issuance of convertible notes and convertible preferred stock. Since inception, we have raised an aggregate of \$140.0 million of gross proceeds to fund our operations through the issuance of convertible notes and convertible preferred stock.

We have incurred significant operating losses since our inception and we expect to continue to incur significant operating losses for the foreseeable future. Our ability to generate product revenue sufficient to achieve profitability, if ever, will depend heavily on the successful development and eventual commercialization of one or more of our product candidates. Our net losses were \$23.0 million and \$32.6 million for the years ended December 31, 2017 and 2018, respectively, and \$36.8 million for the three months ended March 31, 2019. As of March 31, 2019, we had an accumulated deficit of \$105.0 million. We expect our expenses and operating losses will increase substantially over the next several years in connection with our ongoing activities, as we:

- continue our clinical development of losmapimod, including our ongoing Phase 1 clinical trial and planned Phase 2b clinical trial and Phase 2 open label clinical trial;
- continue IND-enabling studies and prepare for a planned Phase 1 clinical trial of FTX-HbF;
- advance clinical-stage product candidates into later stage trials;
- pursue the discovery of drug targets for other rare diseases and the subsequent development of any resulting product candidates;

- seek regulatory approvals for any product candidates that successfully complete clinical trials;
- scale up our manufacturing processes and capabilities, or arrange for a third party to do so on our behalf, to support our clinical trials of our product candidates and commercialization of any of our product candidates for which we obtain marketing approval;
- establish a sales, marketing and distribution infrastructure to commercialize any products for which we may obtain regulatory approval;
- acquire or in-license products, product candidates, technologies and/or data referencing rights;
- make any milestone payments to affiliates of GlaxoSmithKline plc, or GSK, under our right of reference and license agreement with GSK upon the achievement of specified clinical or regulatory milestones;
- maintain, expand, enforce, defend and protect our intellectual property;
- hire additional clinical, quality control and scientific personnel; and
- add operational, financial and management information systems and personnel, including personnel to support our product development and planned future commercialization efforts and our operations as a public company.

As a result, we will need substantial additional funding to support our continuing operations and pursue our growth strategy. Until such time as we can generate significant revenue from product sales, if ever, we expect to finance our operations through the sale of equity, debt financings or other capital sources, including collaborations with other companies or other strategic transactions. We may be unable to raise additional funds or enter into such other agreements or arrangements when needed on favorable terms, or at all. If we fail to raise capital or enter into such agreements as, and when, needed, we may have to significantly delay, scale back or discontinue the development and commercialization of one or more of our product candidates, or grant rights to develop and market our product candidates even if we would otherwise prefer to develop and market such product candidates ourselves.

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

As of March 31, 2019, we had \$62.5 million in cash and cash equivalents. We believe that the anticipated net proceeds from this offering, together with our existing cash and cash equivalents, will enable us to fund our operating expenses and capital expenditure requirements into the third quarter of 2021. We have based this estimate on assumptions that may prove to be wrong, and we could exhaust our available capital resources sooner than we expect. See "—Liquidity and Capital Resources."

Without giving effect to the anticipated net proceeds from this offering, based on our current operating plan, we expect that our existing cash and cash equivalents will be sufficient to fund our operating expenses and capital expenditure requirements into the first quarter of 2020. To finance our operations beyond that point we will need to raise additional capital, which cannot be assured. We have concluded that this circumstance raises substantial doubt about our ability to continue as a going concern for at least one year from the date that our consolidated financial statements for the year ended December 31, 2018 and our consolidated financial statements for the three months ended March 31, 2019 were issued. See Note 1 to our annual and interim consolidated financial statements appearing at the end of this prospectus for additional information on our assessment.

Components of Results of Operations

Revenue

We have not generated any revenue from product sales and do not expect to generate any revenue from the sale of products for several years, if at all. If our development efforts for our current or future product candidates are successful and result in marketing approval, we may generate revenue in the future from product sales. We cannot predict if, when or to what extent we will generate revenue from the commercialization and sale of our product candidates. We may never succeed in obtaining regulatory approval for any of our product candidates.

We may also in the future enter into license or collaboration agreements for our product candidates or intellectual property, and we may generate revenue in the future from payments as a result of such license or collaboration agreements.

Operating Expenses

Research and Development Expenses

Research and development expenses represent costs incurred by us for the discovery, development, and manufacture of our product candidates and include:

- external research and development expenses incurred under agreements with contract research organizations, or CROs, contract manufacturing organizations, or CMOs, and consultants;
- salaries, payroll taxes, employee benefits and stock-based compensation expenses for individuals involved in research and development efforts;
- laboratory supplies;
- in-process research and development, or IPR&D, expenses, which relate to IPR&D acquired as part of an asset acquisition for which there is no alternative future use;
- costs related to compliance with regulatory requirements; and
- facilities, depreciation and other allocated expenses, which include direct and allocated expenses for rent, maintenance of facilities, insurance and other operating costs.

We expense research and development costs as incurred. We recognize expenses for certain development activities, such as clinical trials and manufacturing, based on an evaluation of the progress to completion of specific tasks using data such as patient enrollment or other information provided to us by our vendors. Payments for these activities are based on the terms of the individual agreements, which may differ from the pattern of expenses incurred. Nonrefundable advance payments for goods or services to be received in the future for use in research and development activities are recorded as prepaid expenses. These amounts are recognized as an expense as the goods are delivered or the related services are performed, or until it is no longer expected that the goods will be delivered or the services rendered.

External costs represent a significant portion of our research and development expenses, which we track on a program-by-program basis following the nomination of a development candidate. Our internal research and development expenses consist primarily of personnel-related expenses, including stock-based compensation expense. We do not track our internal research and development expenses on a program-by-program basis as the resources are deployed across multiple projects.

The following table summarizes our external research and development expenses by program following nomination as a development candidate for the years ended December 31, 2017 and 2018, and for the three months ended March 31, 2018 and 2019. Pre-development candidate expenses, unallocated expenses and internal research and development expenses are classified separately. We nominated

losmapimod as a development candidate in December 2017. FSHD external expenses include IPR&D expenses.

(in thousands)	Year Ended December 31, 2017	Year Ended December 31, 2018	Three Months Ended March 31, 2018	Three Months Ended March 31, 2019
FSHD external expenses	\$ 134	\$ 3,108	\$ 454	\$ 27,802
Pre-development candidate expenses and unallocated expenses	11,143	13,534	3,058	4,029
Internal research and development expenses	7,217	8,542	2,061	2,798
Total research and development expenses	<u>\$ 18,494</u>	<u>\$ 25,184</u>	<u>\$ 5,573</u>	<u>\$ 34,629</u>

The successful development of our product candidates is highly uncertain. At this time, we cannot reasonably estimate or know the nature, timing, and estimated costs of the efforts that will be necessary to complete the remainder of the development of our product candidates. We are also unable to predict when, if ever, material net cash inflows will commence from our product candidates, if approved. This is due to the numerous risks and uncertainties associated with developing our product candidates, including the uncertainty related to:

- the timing and progress of preclinical and clinical development activities;
- the number and scope of preclinical and clinical programs we decide to pursue;
- our ability to raise additional funds necessary to complete clinical development of and commercialize our product candidates;
- our ability to maintain our current research and development programs and to establish new ones;
- our ability to establish new licensing or collaboration arrangements;
- the progress of the development efforts of parties with whom we may enter into collaboration arrangements;
- the successful initiation and completion of clinical trials with safety, tolerability and efficacy profiles that are satisfactory to the U.S. Food and Drug Administration, or FDA, or any comparable foreign regulatory authority;
- the receipt and related terms of regulatory approvals from applicable regulatory authorities;
- the availability of raw materials and active pharmaceutical ingredient, or API, for use in production of our product candidates;
- our ability to establish and operate a manufacturing facility, or secure manufacturing supply through relationships with third parties;
- our ability to consistently manufacture our product candidates in quantities sufficient for use in clinical trials;
- our ability to obtain and maintain intellectual property protection and regulatory exclusivity, both in the United States and internationally;
- our ability to maintain, enforce, defend and protect our rights in our intellectual property portfolio;
- the commercialization of our product candidates, if and when approved;
- our ability to obtain and maintain third-party coverage and adequate reimbursement for our product candidates, if approved;
- the acceptance of our product candidates, if approved, by patients, the medical community and third-party payors;
- competition with other products; and
- a continued acceptable safety profile of our products following receipt of any regulatory approvals.

A change in the outcome of any of these variables with respect to the development of any of our product candidates would significantly change the costs and timing associated with the development of that product candidate, and potentially other candidates.

Research and development activities account for a significant portion of our operating expenses. We expect our research and development expenses to increase significantly in future periods as we continue to implement our business strategy, which includes advancing losmapimod and FTX-HbF through clinical development, expanding our research and development efforts, including hiring additional personnel to support our research and development efforts, and seeking regulatory approvals for our product candidates that successfully complete clinical trials. In addition, product candidates in later stages of clinical development generally incur higher development costs than those in earlier stages of clinical development, primarily due to the increased size and duration of later-stage clinical trials. As a result, we expect our research and development expenses to increase as our product candidates advance into later stages of clinical development. However, we do not believe that it is possible at this time to accurately project total program-specific expenses through commercialization. There are numerous factors associated with the successful commercialization of any of our product candidates, including future trial design and various regulatory requirements, many of which cannot be determined with accuracy at this time based on our stage of development.

General and Administrative Expenses

General and administrative expenses consist of personnel-related costs, including salaries, benefits and stock-based compensation expense, for our personnel in executive, finance and accounting, human resources, business operations and other administrative functions, legal fees related to patent, intellectual property and corporate matters, fees paid for accounting and tax services, consulting fees and facility-related costs not otherwise included in research and development expenses.

We expect our general and administrative expenses will increase for the foreseeable future to support our expanded infrastructure and increased costs of expanding our operations and operating as a public company. These increases will likely include increased expenses related to accounting, audit, legal, regulatory and tax-related services associated with maintaining compliance with exchange listing and SEC requirements, director and officer insurance premiums, and investor relations costs associated with operating as a public company.

Other Income, Net

Other income, net consists primarily of interest income related to our investments in cash equivalents and proceeds from the sale of drug material to a third party during February 2018.

Results of Operations**Comparison of the Three Months Ended March 31, 2018 and 2019**

The following summarizes our results of operations for the three months ended March 31, 2018 and 2019, along with the changes in those items in dollars:

(in thousands)	Three Months Ended		Change
	March 31,		
	2018	2019	\$
Operating expenses:			
Research and development	\$ 5,573	\$ 34,629	\$ 29,056
General and administrative	1,737	2,598	861
Total operating expenses	7,310	37,227	29,917
Loss from operations	(7,310)	(37,227)	(29,917)
Other income, net	370	384	14
Net loss	\$ (6,940)	\$ (36,843)	\$ (29,903)

Research and Development Expenses

Research and development expense increased by \$29.0 million from \$5.6 million for the three months ended March 31, 2018 to \$34.6 million for the three months ended March 31, 2019. The increase in research and development expense was primarily attributable to the following:

- \$25.6 million in increased IPR&D expenses associated with the recognition of the fair value attributable to the right of reference and license agreement with GSK during the three months ended March 31, 2019;
- \$1.8 million in increased costs for external clinical activities as we advanced losmapimod into a Phase 1 clinical trial and conducted preparatory studies in anticipation of initiating Phase 2 clinical trials in mid-2019;
- \$0.8 million in increased personnel-related costs due to increased headcount, including \$0.2 million of increased stock-based compensation expense; and
- \$0.3 million in increased laboratory supplies to support our expanding research efforts.

General and Administrative Expenses

General and administrative expenses increased by \$0.9 million from \$1.7 million for the three months ended March 31, 2018 to \$2.6 million for the three months ended March 31, 2019. The increase in general and administrative expenses was primarily attributable to the following:

- \$0.6 million in increased personnel-related costs, primarily due to increased general and administrative headcount to support the growth of our research and development organization, including \$0.2 million of increased stock-based compensation expense; and
- \$0.2 million in increased consulting and professional fees, including for legal services, market research, recruiting, accounting, and tax.

Other Income, Net

Other income, net increased by less than \$0.1 million from \$0.4 million for the three months ended March 31, 2018 to \$0.4 million for the three months ended March 31, 2019. Other income, net during the three months ended March 31, 2019 was primarily attributable to investment income of \$0.4 million from cash equivalents. During the three months ended March 31, 2018, other income, net related primarily to the sale of drug material to a third party for \$0.4 million.

Comparison of the Years Ended December 31, 2017 and 2018

The following summarizes our results of operations for the years ended December 31, 2017 and 2018, along with the changes in those items in dollars:

(in thousands)	Year Ended December 31,		Change
	2017	2018	\$
Operating expenses:			
Research and development	\$ 18,494	\$ 25,184	\$ 6,690
General and administrative	4,499	8,314	3,815
Total operating expenses	22,993	33,498	10,505
Loss from operations	(22,993)	(33,498)	(10,505)
Other income, net	29	910	881
Net loss	\$ (22,964)	\$ (32,588)	\$ (9,624)

Research and Development Expenses

Research and development expense increased by \$6.7 million from \$18.5 million for the year ended December 31, 2017 to \$25.2 million for the year ended December 31, 2018. The increase in research and development expense was primarily attributable to the following:

- \$2.4 million in increased facility-related costs, including rent and other costs related to our new facility lease that commenced in December 2017, depreciation and other utility and maintenance costs;
- \$1.6 million in increased external manufacturing costs related to losmapimod and increased chemistry efforts for our hemoglobinopathies program;
- \$1.3 million in increased personnel-related costs due to increased headcount, including \$0.3 million of increased stock-based compensation expense;
- \$0.9 million in increased costs for preparatory studies in anticipation of initiating losmapimod clinical trials in 2019; and
- \$0.4 million in increased laboratory supplies to support our expanding research efforts.

General and Administrative Expenses

General and administrative expenses increased by \$3.8 million from \$4.5 million for the year ended December 31, 2017 to \$8.3 million for the year ended December 31, 2018. The increase in general and administrative expenses was primarily attributable to the following:

- \$1.9 million in increased personnel-related costs, primarily due to increased general and administrative headcount to support the growth of our research and development organization, including \$0.5 million of increased stock-based compensation expense;
- \$1.1 million in increased consulting and professional fees, including for legal services, market research, recruiting, accounting and tax; and
- \$0.4 million in increased facility-related costs, including rent and other costs related to our new facility lease that commenced in December 2017, depreciation and other utility and maintenance costs.

Other Income, Net

Other income, net increased by \$0.9 million from less than \$0.1 million for the year ended December 31, 2017 to \$0.9 million for the year ended December 31, 2018. The increase in other income, net was primarily attributable to an increase in investment income of \$0.5 million during the year ended

December 31, 2018 due to higher cash equivalents in 2018 and the sale of drug material to a third party in February 2018 for \$0.4 million.

Liquidity and Capital Resources

Sources of Liquidity

We have incurred significant operating losses since our inception and expect to continue to incur significant operating losses for the foreseeable future and may never become profitable. We have not yet commercialized any of our product candidates, which are in various phases of preclinical and clinical development, and we do not expect to generate revenue from sales of any products for several years, if at all. We have primarily funded our operations through March 31, 2019 with aggregate gross proceeds of \$140.0 million from the issuance of convertible notes and convertible preferred stock. As of March 31, 2019, we had cash and cash equivalents of \$62.5 million.

Cash Flows

The following table provides information regarding our cash flows for the years ended December 31, 2017 and 2018, and for the three months ended March 31, 2018 and 2019:

(in thousands)	Year Ended December 31, 2017	Year Ended December 31, 2018	Three Months Ended March 31, 2018	Three Months Ended March 31, 2019
Net cash used in operating activities	\$ (20,074)	\$ (22,562)	\$ (6,632)	\$ (9,897)
Net cash used in investing activities	(1,908)	(8,981)	(783)	(401)
Net cash provided by (used in) financing activities	17,662	105,025	12,640	(47)
Net (decrease) increase in cash, cash equivalents, and restricted cash	<u>\$ (4,320)</u>	<u>\$ 73,482</u>	<u>\$ 5,225</u>	<u>\$ (10,345)</u>

Net Cash Used in Operating Activities

Net cash used in operating activities was \$9.9 million during the three months ended March 31, 2019 compared to net cash used in operating activities of \$6.6 million during the three months ended March 31, 2018. The increase in net cash used in operating activities of \$3.3 million was due to an increase in net loss of \$29.9 million for the three months ended March 31, 2019 as compared to the three months ended March 31, 2018, partially offset by a net increase in non-cash expenses of \$26.3 million primarily due to an increase in IPR&D expenses of \$25.6 million and an increase in stock-based compensation expense of \$0.4 million, and a net increase in cash provided by changes in our operating assets and liabilities of \$0.3 million.

Net cash used in operating activities was \$22.6 million during the year ended December 31, 2018 compared to net cash used in operating activities of \$20.1 million during the year ended December 31, 2017. The increase in net cash used in operating activities of \$2.5 million was due to an increase in net loss of \$9.6 million for the year ended December 31, 2018 as compared to the year ended December 31, 2017, partially offset by a net increase in cash provided by changes in our operating assets and liabilities of \$5.7 million, primarily due to the receipt of \$4.6 million during the year ended December 31, 2018 associated with the leasehold improvement allowance related to our new facility lease that commenced in December 2017, and a net increase in non-cash expenses of \$1.4 million.

Net Cash Used in Investing Activities

Net cash used in investing activities was \$0.4 million during the three months ended March 31, 2019 compared to net cash used in investing activities of \$0.8 million during the three months ended March 31, 2018. Net cash used in investing activities for the three months ended March 31, 2019 and 2018 primarily consisted of purchases of property and equipment.

Net cash used in investing activities was \$9.0 million during the year ended December 31, 2018 compared to net cash used in investing activities of \$1.9 million during the year ended December 31, 2017. Net cash used in investing activities for the years ended December 31, 2018 and 2017 consisted of purchases of property and equipment. The increase in net cash used in investing activities of \$7.1 million was primarily due to an increase in purchases of property and equipment associated with our new facility lease that commenced in December 2017.

Net Cash Provided by (Used in) Financing Activities

Net cash used in financing activities was less than \$0.1 million during the three months ended March 31, 2019 compared to net cash provided by financing activities of \$12.6 million during the three months ended March 31, 2018. The cash provided by financing activities during the three months ended March 31, 2018 was primarily the result of \$12.7 million of net proceeds received from private placements of our Series A preferred stock. The net cash used in financing activities for the three months ended March 31, 2019 was primarily the result of the payment of costs associated with the issuance of Series B preferred stock.

Net cash provided by financing activities was \$105.0 million during the year ended December 31, 2018 compared to \$17.7 million during the year ended December 31, 2017. The cash provided by financing activities during the year ended December 31, 2018 was primarily the result of \$105.1 million of net proceeds received from private placements of our Series A and Series B preferred stock. The cash provided by financing activities for the year ended December 31, 2017 was primarily the result of \$17.6 million of net proceeds received from private placements of our Series A preferred stock.

Funding Requirements

We expect our expenses to increase substantially in connection with our ongoing research and development activities, particularly as we continue the research and development of, initiate clinical trials of, and seek marketing approval for, our product candidates. In addition, upon the closing of this offering, we expect to incur additional costs associated with operating as a public company. As a result, we expect to incur substantial operating losses and negative operating cash flows for the foreseeable future.

Based on our current operating plan, we expect that the anticipated net proceeds from this offering, together with our existing cash and cash equivalents, will enable us to fund our operating expenses and capital expenditure requirements into the third quarter of 2021. However, we have based this estimate on assumptions that may prove to be wrong and we could exhaust our capital resources sooner than we expect.

Our funding requirements and timing and amount of our operating expenditures will depend largely on:

- the progress, costs and results of our ongoing Phase 1 clinical trial of losmapimod;
- the scope, progress, results and costs of discovery research, preclinical development, laboratory testing and clinical trials for our product candidates, including our planned Phase 2b clinical trial and planned Phase 2 open label clinical trial of losmapimod and our planned Phase 1 clinical trial of FTX-HbF;
- the number of and development requirements for other product candidates that we pursue;
- the costs, timing and outcome of regulatory review of our product candidates;
- our ability to enter into contract manufacturing arrangements for supply of API and manufacture of our product candidates and the terms of such arrangements;
- our ability to establish and maintain strategic collaborations, licensing or other arrangements and the financial terms of such arrangements;
- the payment or receipt of milestones and receipt of other collaboration-based revenues, if any;

- the costs and timing of future commercialization activities, including product manufacturing, sales, marketing and distribution, for any of our product candidates for which we may receive marketing approval;
- the amount and timing of revenue, if any, received from commercial sales of our product candidates for which we receive marketing approval;
- the costs and timing of preparing, filing and prosecuting patent applications, maintaining and enforcing our intellectual property and proprietary rights and defending any intellectual property-related claims; and
- the extent to which we acquire or in-license other products, product candidates, technologies or data referencing rights.

A change in the outcome of any of these or other variables with respect to the development of any of our product candidates could significantly change the costs and timing associated with the development of that product candidate. We will need to continue to rely on additional financing to achieve our business objectives.

In addition to the variables described above, if and when any of our product candidates successfully complete development, we will incur substantial additional costs associated with regulatory filings, marketing approval, post-marketing requirements, maintaining our intellectual property rights, and regulatory protection, in addition to other commercial costs. We cannot reasonably estimate these costs at this time.

Until such time, if ever, as we can generate substantial product revenue, we expect to finance our cash needs through a combination of equity or debt financings and collaboration arrangements. We currently have no credit facility or committed sources of capital. To the extent that we raise additional capital through the future sale of equity securities, the ownership interests of our stockholders will be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect the rights of our existing common stockholders. If we raise additional funds through the issuance of debt securities, these securities could contain covenants that would restrict our operations. We may require additional capital beyond our currently anticipated amounts, and additional capital may not be available on reasonable terms, or at all. If we raise additional funds through collaboration arrangements or other strategic transactions in the future, we may have to relinquish valuable rights to our technologies, future revenue streams or product candidates, or grant licenses on terms that may not be favorable to us. If we are unable to raise additional funds through equity or debt financings when needed, we may be required to delay, limit, reduce or terminate development or future commercialization efforts or grant rights to develop and market product candidates that we would otherwise prefer to develop and market ourselves.

Contractual Obligations

The following table summarizes our contractual obligations as of December 31, 2018 and the effects that these obligations are expected to have on our liquidity and cash flows in future periods:

(in thousands)	Total	Less Than 1 Year	1 to 3 Years	3 to 5 Years	More Than 5 Years
Operating lease commitments ⁽¹⁾	\$ 23,966	\$ 2,219	\$ 4,639	\$ 4,921	\$ 12,187
Capital lease obligation	124	53	71	—	—
	<u>\$ 24,090</u>	<u>\$ 2,272</u>	<u>\$ 4,710</u>	<u>\$ 4,921</u>	<u>\$ 12,187</u>

- (1) Represents future minimum lease payments under our non-cancelable operating lease, which expires in June 2028. The minimum lease payments above do not include any related common area maintenance charges or real estate taxes.

Under our right of reference and license agreement that we entered into in February 2019 with affiliates of GSK, we have payment obligations that are contingent upon the occurrence of future events

such as our achievement of specified clinical, regulatory and sales milestones and are required to make royalty payments in connection with the sale of products developed under the agreement. Specifically, we may owe GSK up to \$37.5 million in certain specified clinical and regulatory milestones, of which \$2.5 million is due upon the initiation of a Phase 2 clinical trial, and up to \$60.0 million in certain specified sales milestones and royalties on product sales, if any. We have not included any such contingent milestone or royalty payment obligations in the table above, which is presented as of December 31, 2018. In addition, the amount (in the case of potential royalty payments), timing and likelihood of such payments are not always known. For additional information regarding this license agreement, including our payment obligations thereunder, see "Business—Right of Reference and License Agreement with GlaxoSmithKline," Note 14 to our annual consolidated financial statements included elsewhere in this prospectus and Note 9 to our interim consolidated financial statements included elsewhere in this prospectus.

We enter into contracts in the normal course of business with CROs, CMOs and other third parties for clinical trials, pre-clinical research studies, synthetic chemistry and testing and manufacturing services. These contracts are generally cancelable by us upon up to 30 days' prior written notice. Payments due upon cancellation consist only of payments for services provided or expenses incurred, including noncancelable obligations of our service providers, up to and through the date of cancellation. These payments are not included in the preceding table as the amount and timing of these payments are not known.

Off-Balance Sheet Arrangements

We did not have, during the periods presented, and we do not currently have, any off-balance sheet arrangements, as defined in the rules and regulations of the SEC.

Critical Accounting Policies and Estimates

Our management's discussion and analysis of our financial condition and results of operations are based on our consolidated financial statements, which have been prepared in accordance with accounting principles generally accepted in the United States. The preparation of these consolidated financial statements requires us to make judgments and estimates that affect the reported amounts of assets and liabilities, the disclosure of contingent assets and liabilities at the date of the consolidated financial statements, and the reported amounts of expenses during the reported periods. Our estimates are based on our historical experience, known trends and events, and on various other factors that we believe are reasonable under the circumstances, the results of which form the basis for making judgments about the carrying value of assets and liabilities and amount of expense recognized that are not readily apparent from other sources. Actual results may differ from these estimates under different assumptions or conditions. We evaluate our estimates and assumptions on an ongoing basis. The effects of material revisions in estimates, if any, will be reflected in the consolidated financial statements prospectively from the date of change in estimates.

We believe that the accounting policies discussed below are critical to understanding our historical and future performance, as these policies relate to the most significant areas involving management's judgments and estimates. See Note 2 to our annual consolidated financial statements included elsewhere in this prospectus for a description of our other significant accounting policies.

Accrued Research and Development Expenses

As part of the process of preparing our consolidated financial statements, we are required to estimate our accrued expenses as of each balance sheet date. This process involves reviewing open contracts and purchase orders, communicating with our personnel to identify services that have been performed on our behalf and estimating the level of service performed and the associated cost incurred for the service when we have not yet been invoiced or otherwise notified of the actual cost. The majority of our service providers invoice us monthly in arrears for services performed or when contractual milestones are met. We make estimates of our accrued expenses as of each balance sheet date based on facts and circumstances known to us at that time. We periodically confirm the accuracy of our estimates with the service providers

and make adjustments if necessary. The significant estimates in our accrued research and development expenses include the costs incurred for services performed by our vendors in connection with research and development activities for which we have not yet been invoiced.

We base our expenses related to research and development activities on our estimates of the services received and efforts expended pursuant to quotes and contracts with vendors that conduct research and development on our behalf. The financial terms of these agreements are subject to negotiation, vary from contract to contract and may result in uneven payment flows. There may be instances in which payments made to our vendors will exceed the level of services provided and result in a prepayment of the research and development expense. In accruing service fees, we estimate the time period over which services will be performed and the level of effort to be expended in each period. If the actual timing of the performance of services or the level of effort varies from our estimate, we adjust the accrual or prepaid expense accordingly. Non-refundable advance payments for goods and services that will be used in future research and development activities are expensed when the activity has been performed or when the goods have been received rather than when the payment is made.

Although we do not expect our estimates to be materially different from amounts actually incurred, if our estimates of the status and timing of services performed differ from the actual status and timing of services performed, it could result in us reporting amounts that are too high or too low in any particular period. To date, there have been no material differences between our estimates of such expenses and the amounts actually incurred.

Stock-Based Compensation

We measure stock-based compensation expense related to all restricted stock awards and stock options based on the fair value of the award on the date of grant. We recognize compensation expense for these awards over the requisite service period, which is generally the vesting period of the respective award. Generally, we issue awards with only service-based vesting conditions and record the expense for these awards using the straight-line method. We have also granted certain stock-based awards with performance-based vesting conditions. We recognize compensation expense for awards with performance-based vesting conditions over the remaining service period using an accelerated attribution method when management determines that achievement of the performance condition is probable. At each reporting date, we evaluate if the achievement of a performance-based milestone is probable based on the expected satisfaction of the performance conditions.

We determine the fair value of restricted stock awards based on the estimated fair value of our common stock on the date of grant, less any applicable purchase price. We estimate the fair value of stock options granted using the Black-Scholes option-pricing model. The determination of the grant date fair value of stock options using an option pricing model is affected principally by our estimated fair value of our common stock and requires management to make a number of other assumptions, including the expected term of the option, the estimated volatility of the underlying shares, the risk-free interest rate, and expected dividends. The assumptions used in the determination of the grant date fair value of stock options represent management's best estimates at the time of measurement. As a result of the lack of a public market for the trading of our common stock and a lack of company-specific historical and implied volatility data, we base the estimate of expected volatility on the historical volatility of a representative group of publicly traded companies for which historical information is available. The historical volatility is calculated based on a period of time commensurate with the assumption used for the expected term. We use the simplified method to calculate the expected term for all stock options. We utilize this method as we do not have sufficient historical exercise data to provide a reasonable basis upon which to estimate the expected term. The risk-free interest rate is based on a U.S. treasury instrument whose term is consistent with the expected term of the stock options. The expected dividend yield is assumed to be zero as we have never paid dividends and do not have current plans to pay any dividends on common stock.

In future periods, we expect stock-based compensation expense to increase, due in part to our existing unrecognized stock-based compensation expense and as we grant additional stock-based awards to continue to attract and retain our employees.

Fair Value of Common Stock and Series B Preferred Stock

As previously described, we are required to estimate the fair value of our common stock underlying our stock-based awards when estimating the grant date fair value of those awards. Additionally, we were required to estimate the fair value of the Series B preferred stock issued pursuant to the right of reference and license agreement that we entered into with GSK in February 2019. As there has been no public market for our common stock or Series B preferred stock to date, the estimated fair value of our common stock and Series B preferred stock has been determined by our board of directors and management, respectively, as of the date of each equity issuance considering our most recently available third-party valuations of common stock or Series B preferred stock, and our assessment of additional objective and subjective factors. These third-party valuations were performed in accordance with the guidance outlined in the American Institute of Certified Public Accountants' Accounting and Valuation Guide, Valuation of Privately-Held-Company Equity Securities Issued as Compensation. Our common stock valuations were prepared using the guideline public company method and/or the precedent transaction method to estimate our equity value, and we utilized the option-pricing method, or OPM, or the hybrid method to allocate equity value to our common stock and preferred stock. The hybrid method is a probability-weighted expected return method, or PWERM, where the equity value in one or more of the scenarios is allocated using an OPM. The OPM treats common stock and preferred stock as call options on the total equity value of a company, with exercise prices based on the value thresholds at which the allocation among the various holders of a company's securities changes. Under this method, the common stock has value only if the funds available for distribution to stockholders exceeded the value of the preferred stock liquidation preferences at the time of the liquidity event, such as a strategic sale or a merger or an initial public offering, or IPO. The PWERM is a scenario-based method that estimates the fair value of common stock and preferred stock based upon an analysis of future values for the company, assuming various outcomes. The common stock and preferred stock value is based on the probability-weighted present value of expected future investment returns considering each of the possible outcomes available, as well as the rights of each class of stock. The future value of the common stock and preferred stock under each outcome is discounted back to the valuation date at an appropriate risk-adjusted discount rate and probability weighted to arrive at an indication of value for the common stock. In our application of the hybrid method, we considered an IPO scenario under the PWERM framework, in which the shares of convertible preferred stock are assumed to convert to common stock, and a non-IPO scenario modeled using an OPM. Our Series B preferred stock valuation was prepared using the hybrid method. The relative probability of the IPO scenario was determined based on an analysis of market conditions at the time and our expectations as to the timing and likely prospects of the IPO at each valuation date. In our application of the guideline public company method, we considered recently completed IPOs as indicators of our estimated future value in an IPO.

Based on our early stage of development and other relevant factors, our board of directors determined that the OPM was the most appropriate method for allocating our enterprise value to determine the estimated fair value of our common stock for the valuations performed as of December 31, 2016, December 31, 2017 and June 1, 2018, which resulted in our board of directors determining that the fair value of our common stock was \$2.94 per share, \$3.29 per share and \$4.83 per share, respectively. Following the issuance of the Series B preferred stock in August 2018, our board of directors determined that the hybrid method was the most appropriate method for allocating our enterprise value to determine the estimated fair value of our common stock for valuations performed as of August 24, 2018, November 30, 2018, March 15, 2019 and May 10, 2019, which resulted in our board of directors determining that the fair value of our common stock was \$7.63 per share, \$7.84 per share, \$8.33 per share and \$11.06 per share, respectively. Our board of directors determined that it was appropriate to change the methodology for determining the fair value of our common stock to the hybrid method beginning with the

August 24, 2018 valuation as greater certainty developed regarding a possible IPO upon the issuance of the Series B preferred stock. Management determined that the value of our Series B preferred stock was \$2.04 per share as of February 8, 2019.

Our board of directors and management considered various objective and subjective factors to determine the fair value of our common stock and Series B preferred stock, respectively, including:

- valuations of our common stock and Series B preferred stock performed by independent third-party valuation specialists;
- our stage of development and business strategy, including the status of research and development efforts of our product candidates;
- the analysis of IPOs and the valuation of similar publicly traded companies in the biopharmaceutical industry;
- our financial position, including our levels of available capital resources;
- the lack of an active public market for our common stock and our preferred stock;
- the prices of our convertible preferred stock sold to investors in arm's length transactions and the rights, preferences and privileges of our convertible preferred stock relative to those of our common stock;
- the likelihood and potential timing of achieving a liquidity event, such as an IPO, in light of prevailing market conditions; and
- external market conditions affecting the biotechnology industry, and trends within the biopharmaceutical industry.

The assumptions underlying these valuations represent our best estimates, which involve inherent uncertainties and the application of judgment. As a result, if factors or expected outcomes change and we use significantly different assumptions or estimates, our stock-based compensation expense or in-process research and development expense could be materially different.

Once a public trading market for our common stock has been established in connection with the completion of this offering, it will no longer be necessary for our board of directors to estimate the fair value of our common stock in connection with our accounting for granted stock options and other such awards we may grant, as the fair value of our common stock will be determined based on the quoted market price of our common stock.

Grants of Stock-Based Awards

The following table presents the grant dates, numbers of underlying shares of common stock, the per share purchase prices and exercise prices, and the fair values of the underlying common stock as of the grant dates for awards granted between January 1, 2018 and June 30, 2019, along with the fair value per award on the date of grant:

Grant Date	Type of Award	Number of Shares Subject to Awards Granted	Per Share Exercise Price or Purchase Price	Per Share Fair Value of Common Stock on Grant Date	Per Share Estimated Fair Value of Award on Grant Date ⁽¹⁾
1/23/2018	Restricted Stock	225,717	\$ 0.07	\$ 3.29(2)	\$ 3.22
2/23/2018	Restricted Stock	24,285	\$ 0.07	\$ 3.29(2)	\$ 3.22
6/20/2018	Restricted Stock	6,714	\$ 0.07	\$ 4.83	\$ 4.76
6/20/2018	Stock Options	82,700	\$ 4.83	\$ 4.83	\$ 3.43
7/11/2018	Stock Options	34,356	\$ 4.83	\$ 4.83	\$ 3.50
10/17/2018	Stock Options	71,765	\$ 7.63	\$ 7.63	\$ 5.39
12/13/2018	Stock Options	15,499	\$ 7.84	\$ 7.84	\$ 5.53
12/18/2018	Stock Options	303,571	\$ 7.84	\$ 7.84	\$ 5.53
1/22/2019	Stock Options	1,006,213	\$ 7.84	\$ 7.84	\$ 5.53
3/20/2019	Stock Options	14,283	\$ 8.33	\$ 8.33	\$ 5.88
5/21/2019	Stock Options	93,995	\$ 11.06	\$ 11.06	\$ 7.77

- (1) For restricted stock, the Per Share Estimated Fair Value of Award on Grant Date reflects the weighted average fair value of restricted stock at the date of grant, which is equal to the fair value of our common stock as of the date of grant as determined by our board of directors, less the applicable purchase price of the restricted stock. For stock options, the Per Share Estimated Fair Value of Award on Grant Date reflects the weighted average fair value of stock options as estimated at the date of grant using the Black-Scholes option-pricing model.
- (2) We undertook a retrospective valuation of the fair value of our common stock as of December 31, 2017 and this value represents our estimated fair value per common share in accordance with such retrospective valuation.

Stock Option Grants in Connection with Initial Public Offering

Our board of directors has approved, effective upon the commencement of trading of our common stock on the Nasdaq Global Market, grants of stock options to purchase an aggregate of 308,486 shares of our common stock at a purchase price per share equal to the estimated fair market value of our common stock on such date of grant, which our board of directors determined to be equal to the initial public offering price of our common stock in this offering.

Income Taxes

We account for income taxes using the asset and liability method, which requires the recognition of deferred tax assets and liabilities for the expected future tax consequences of events that have been recognized in the consolidated financial statements or in our tax returns. Under this method, deferred tax assets and liabilities are determined based on differences between the financial statement carrying amounts and the tax bases of the assets and liabilities using the enacted tax rates in effect in the years in which the differences are expected to reverse. A valuation allowance against deferred tax assets is recorded if, based on the weight of the available evidence, it is more likely than not that some or all of the deferred tax assets will not be realized. Potential for recovery of deferred tax assets is evaluated by considering several factors, including estimating the future taxable profits expected, estimating future reversals of existing taxable temporary differences, considering taxable profits in carryback periods, and considering prudent and feasible tax planning strategies.

We account for uncertain tax positions using a more-likely-than-not threshold for recognizing and resolving uncertain tax positions. The evaluation of uncertain tax positions is based on factors including, but not limited to, changes in the law, the measurement of tax positions taken or expected to be taken in tax returns, the effective settlement of matters subject to audit, new audit activity, and changes in facts or circumstances related to a tax position. As of each balance sheet date, we did not have any uncertain tax positions.

Recently Issued Accounting Pronouncements

We have reviewed all recently issued standards and have determined that, other than as disclosed in Note 2 to our annual and interim consolidated financial statements appearing at the end of this prospectus, these standards will not have a material impact on our financial statements or do not otherwise apply to our operations.

Quantitative and Qualitative Disclosures about Market Risk

Our primary exposure to market risk is interest rate sensitivity, which is affected by changes in the general level of U.S. interest rates, particularly because our cash equivalents are in the form of money market funds that are invested in U.S. Treasury securities. As of March 31, 2019, we had cash and cash equivalents of \$62.5 million. Interest income is sensitive to changes in the general level of interest rates; however, due to the nature of these investments, an immediate 10% change in interest rates would not have a material effect on the fair market value of our investment portfolio.

We are also exposed to market risk related to changes in foreign currency exchange rates. We contract with vendors that are located outside of the United States and certain invoices are denominated in foreign currencies. We are subject to fluctuations in foreign currency rates in connection with these arrangements. We do not currently hedge our foreign currency exchange rate risk. As of March 31, 2019, we had minimal or no liabilities denominated in foreign currencies.

Inflation generally affects us by increasing our cost of labor and clinical trial costs. We do not believe that inflation had a material effect on our business, financial condition or results of operations during the years ended December 31, 2017 and 2018 or the three months ended March 31, 2018 and 2019.

Emerging Growth Company Status

As an emerging growth company, or EGC, under the Jumpstart Our Business Startups Act of 2012, or JOBS Act, we may delay the adoption of certain accounting standards until such time as those standards apply to private companies. Other exemptions and reduced reporting requirements under the JOBS Act for EGCs include presentation of only two years of audited financial statements in a registration statement for an IPO, an exemption from the requirement to provide an auditor's report on internal controls over financial reporting pursuant to Section 404(b) of the Sarbanes-Oxley Act of 2002, an exemption from any requirement that may be adopted by the Public Company Accounting Oversight Board regarding mandatory audit firm rotation, and less extensive disclosure about our executive compensation arrangements. Additionally, the JOBS Act provides that an EGC can take advantage of an extended transition period for complying with new or revised accounting standards. This allows an EGC to delay the adoption of certain accounting standards until those standards would otherwise apply to private companies. We have elected to avail ourselves of this exemption and, therefore, while we are an EGC, we will not be subject to new or revised accounting standards at the same time that they become applicable to other public companies that are not EGCs. As a result, our consolidated financial statements may not be comparable to companies that comply with new or revised accounting pronouncements as of public company effective dates.

We may remain classified as an EGC until the end of the fiscal year in which the fifth anniversary of this offering occurs, although if the market value of our common stock that is held by non-affiliates exceeds \$700 million as of any June 30 before that time or if we have annual gross revenues of \$1.07 billion or more in any fiscal year, we would cease to be an EGC as of December 31 of the applicable year. We also would cease to be an EGC if we issue more than \$1 billion of non-convertible debt over a three-year period.

BUSINESS

Overview

We are a clinical-stage biopharmaceutical company focused on improving the lives of patients with genetically defined diseases in areas of high unmet medical need, with an initial focus on rare diseases. We have developed a proprietary product engine that we employ to systematically identify and validate cellular drug targets that can potentially modulate gene expression to treat the known root cause of genetically defined diseases. We are using our product engine to identify targets that can be drugged by small molecules regardless of the particular underlying mechanism of gene mis-expression. We have identified drug targets to treat the root causes of facioscapulohumeral muscular dystrophy, or FSHD, and certain hemoglobinopathies, namely sickle cell disease, or SCD, and β -thalassemia. We expect to initiate a Phase 2b clinical trial of losmapimod, our product candidate for FSHD, in mid-2019. We commenced a Phase 1 clinical trial in February 2019 to obtain safety and tolerability data for losmapimod in patients with FSHD. We plan to submit an investigational new drug application, or IND, for FTX-HbF, our product candidate for certain hemoglobinopathies, in mid-2020.

We are using our proprietary product engine to identify and validate drug targets and develop product candidates to address diseases caused by the mis-expression of certain genes. Our product engine integrates patient-derived tissue-relevant cell models and drug target screens with our pharmacologically-diverse small molecule compound library and customized CRISPR libraries. We also employ computational biology and FulcrumSeek, our proprietary relational database, to guide target selection and to generate hypotheses on other targets that might be relevant along a gene regulatory pathway.

Our first product candidate, losmapimod, is a small molecule that we are developing for the treatment of FSHD, a rare, progressive and disabling muscle wasting disorder that leads to significant physical impairments and disability. Losmapimod selectively targets p38a/b mitogen activated protein kinase, or p38a/b. We utilized our product engine to discover that inhibition of p38a/b reduced expression of the *DUX4* gene in muscle cells derived from patients with FSHD. The mis-expression of the *DUX4* gene is the known root cause of FSHD. There are no approved therapies for FSHD, one of the most common forms of muscular dystrophy, with an estimated patient population of 16,000 to 38,000 in the United States.

Following our discovery of the role of p38a/b inhibitors in the reduction of *DUX4* expression, we performed an extensive review of known compounds. As a result of our evaluation, we identified losmapimod as the preferred developmental candidate based on the substantial and attractive preclinical and clinical data. We in-licensed losmapimod from affiliates of GlaxoSmithKline, or GSK, in February 2019. GSK had previously treated nearly 3,500 subjects with losmapimod across multiple clinical trials, including one Phase 3 clinical trial. GSK did not conduct a clinical trial of losmapimod in patients with FSHD or any other muscle disorder. We have conducted extensive preclinical testing of losmapimod in patient-derived tissue-relevant cell models and have observed that losmapimod selectively reduced *DUX4*-driven gene expression and restored a healthy gene expression signature with minimal impact on healthy human muscle cells or other cell types.

We plan to conduct a randomized, double-blind placebo-controlled Phase 2b clinical trial to investigate whether treatment with losmapimod reduces *DUX4*-driven gene expression in affected skeletal muscle. In this Phase 2b clinical trial, we will also evaluate the safety and tolerability of losmapimod. We plan to concurrently conduct an open label Phase 2 clinical trial to investigate the safety and tolerability of chronic treatment with losmapimod in patients with FSHD. In this open label trial, we will also evaluate the ability of losmapimod to reduce *DUX4*-driven gene expression in affected skeletal muscle over varying treatment durations. We expect to initiate the Phase 2b clinical trial at multiple sites in the United States and Europe and the open label Phase 2 clinical trial in Europe in mid-2019. We expect to complete a Phase 1 clinical trial in healthy volunteers and patients with FSHD in 2019. We utilized data from GSK's clinical trials of losmapimod and our preclinical data to submit in May 2019 an IND, and clinical trial applications, or CTAs, in Europe and Canada, that will enable us to advance our clinical development plan

for losmapimod in FSHD, including initiating a Phase 2b clinical trial in mid-2019. The FDA accepted the IND in June 2019. The timing of the initiation of the Phase 2b clinical trial is not dependent on the completion of the Phase 1 clinical trial.

We are additionally conducting several preparatory studies to assess biomarker endpoints and clinical outcome assessments and are participating in a natural history study that will follow 150 subjects with FSHD in the United States and 70 subjects in Europe over 18 months. We expect to utilize the data generated from our preparatory studies and the natural history study to inform future clinical trial designs and discussions with regulatory agencies. We believe that these preparatory studies and the safety data from GSK's prior losmapimod clinical trials, together with safety and efficacy data generated from our Phase 1 and Phase 2 clinical trials, may enable us to apply for accelerated approval of losmapimod for the treatment of FSHD. If we observe positive results in our Phase 2b clinical trial based on our proposed biomarker efficacy endpoint of measuring DUX4-driven gene expression in muscle biopsies, we plan to discuss accelerated approval with regulatory agencies and may seek accelerated approval if such regulatory agencies agree that our biomarker endpoint is sufficiently predictive of clinical benefit. The FDA or other regulatory authorities may require us to conduct comparability assessments of GSK-manufactured tablets to tablets manufactured by us or another party.

Our second product candidate, FTX-HbF, is a small molecule designed to upregulate fetal hemoglobin in patients with SCD and b-thalassemia. SCD is a genetic blood disorder caused by a mutation in the b-subunit gene, or *HBB* gene. This mutation results in the formation of abnormal hemoglobin, which causes red blood cells, or RBCs, to change from a round shape into a sickle shape that significantly impairs their function. b-thalassemia is a rare blood disorder caused by various genetic mutations in the *HBB* gene that can significantly impair the production of RBCs.

We designed FTX-HbF to compensate for the root cause of these hemoglobinopathies by inducing the expression of the two g-globin genes, *HBG1/2*, whose expression is normally silenced shortly after birth. The *HBG1/2* genes encode for g-globin, a component of fetal hemoglobin, which is known to compensate for the presence of abnormal hemoglobin in SCD and b-thalassemia. We have observed *in vitro* and *in vivo* activation of the *HBG1/2* genes in preclinical studies with FTX-HbF. We have also observed that FTX-HbF demonstrated robust levels of fetal hemoglobin elevation with no adverse effect on important cellular health markers. We have initiated IND-enabling studies and plan to submit an IND for FTX-HbF in mid-2020.

According to the National Institutes of Health, or NIH, there are approximately 7,000 rare, genetically defined human diseases, many of which have inadequate or no approved treatments. We plan to utilize our product engine to complete four new drug target identification screens in 2019 in Duchenne muscular dystrophy, Friedreich ataxia, myotonic dystrophy 1 and a-synucleinopathies. We also expect to complete an additional six screens in 2020. Our current drug target identification and development efforts are focused on rare neuromuscular disorders, hemoglobinopathies and central nervous system, or CNS, diseases. We also anticipate utilizing our product engine to discover drug targets for genetically defined diseases in other therapeutic areas. In addition to drug targets that we prioritize for internal development, we may identify other drug targets that we would consider for development through partnerships.

Our Pipeline

We designed our proprietary product engine with potential application across a broad array of genetically defined diseases with a known root cause. The following chart summarizes key information about our lead product candidates.



Our Strategy

We are leveraging the broad applicability of our proprietary product engine to discover and develop small molecule therapies that modulate gene expression to address the known root cause of genetically defined diseases in areas of high unmet medical need, with an initial focus on rare diseases. We believe that our initial product candidates for the treatment of FSHD, SCD and b-thalassemia may have the potential to treat patients with these debilitating and, in some cases, life-threatening illnesses. The key components of our strategy include:

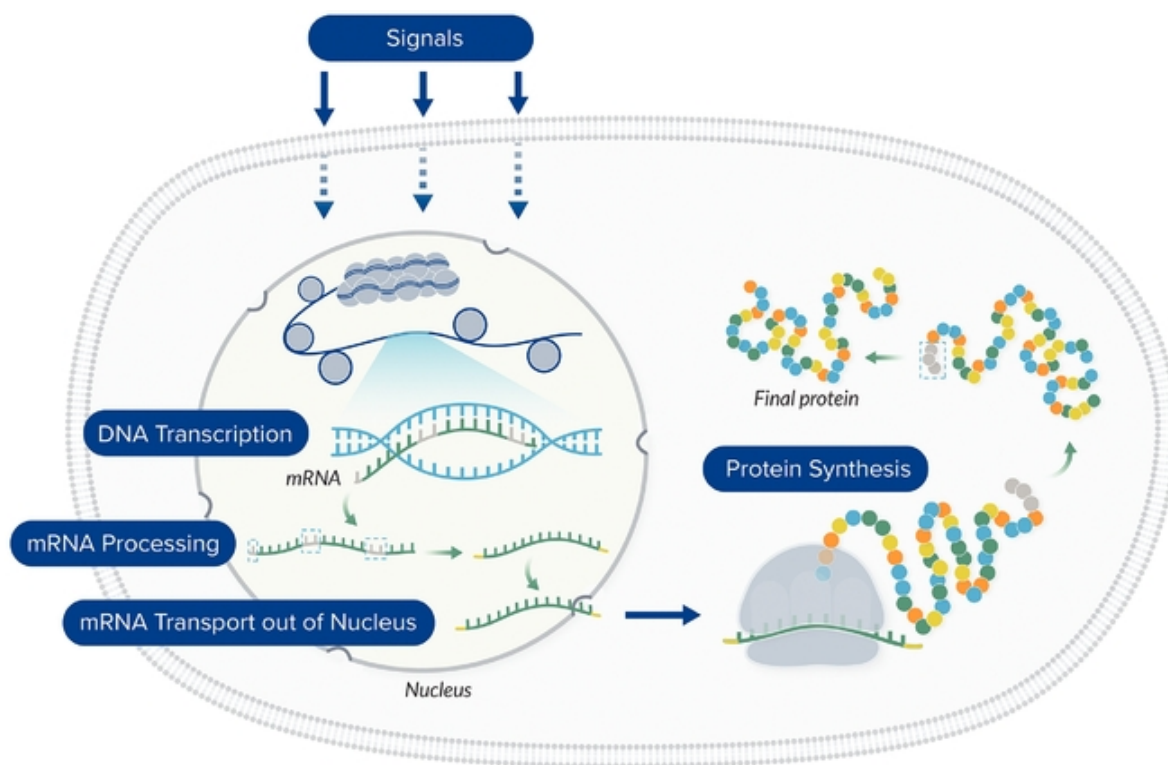
- **Rapidly develop losmapimod for the treatment of FSHD.** We aim to rapidly develop losmapimod for the treatment of FSHD through clinical development and regulatory approval. We plan to initiate a Phase 2b clinical trial of losmapimod in mid-2019 and, subject to positive results, plan to meet with regulators to discuss the potential to pursue accelerated approval given the significant unmet medical need in FSHD and the absence of approved therapies for patients.
- **Advance FTX-HbF into clinical development.** We have initiated IND-enabling studies of FTX-HbF and we aim to submit an IND in mid-2020. We intend to develop FTX-HbF for the treatment of SCD and certain types of b-thalassemia.
- **Continue to apply our proprietary product engine to grow our portfolio of product candidates for the treatment of genetically defined diseases.** We have developed a rigorous assessment and selection process to determine which of the approximately 7,000 rare, genetically defined diseases we intend to evaluate in drug target identification activities. We are applying our product engine to discover drug targets to modulate gene expression and develop product candidates for the potential treatment of the root cause of the disease. We plan to utilize our product engine to complete four new drug target identification screens in 2019 and an additional six screens in 2020, and we expect to advance the most compelling programs identified for development.
- **Further expand our product engine capabilities.** Our product engine incorporates patient-derived cell lines and/or other relevant human cell lines, our annotated small molecule compound library and customized CRISPR libraries. We intend to further expand our product engine capabilities, including FulcrumSeek, to enhance the therapeutic reach and productivity of our drug discovery process.
- **Maximize the commercial potential of our product candidates.** We have retained all rights to our lead product candidates focused on rare genetically defined diseases, and plan to commercialize any approved product using a targeted sales infrastructure. We may in the future pursue commercialization partnerships for certain product candidates and/or markets outside the United States.

- **Selectively enter into strategic partnerships to maximize the value of our product engine and pipeline.** Given the breadth of opportunities for our proprietary product engine to discover drug targets and develop product candidates for genetically defined diseases, we may enter into strategic partnerships for certain drug targets, product candidates or disease areas. Partnerships may provide an attractive avenue for expanding the impact of our proprietary product engine.

Gene Regulation

The human genome provides the blueprint, or genetic code, for life. The sequencing of the human genome has enabled significant insights into understanding the genetic underpinnings of many diseases. Genes are the fundamental units of biology, but the gene itself is rather static. The identity and function of each cell is determined by a specific set of factors that activate or repress mechanisms that regulate genes in the desired manner. There are many mechanisms that control the human genome by up or down regulating gene expression, and these regulatory mechanisms are controlled by various pathways and signals. Defects in a gene or any of these regulatory mechanisms can result in aberrant expression or silencing of a gene that may lead to disease.

The graphic below illustrates the key steps in the gene expression process in cells and how they are under the control of a variety of regulatory signals and pathways.



Our Opportunity

We have the ability to develop, scale and characterize complex cellular models of human disorders of gene mis-regulation. Our current drug target identification and development efforts are focused on rare neuromuscular disorders, hemoglobinopathies and CNS diseases. We also anticipate utilizing our product engine to discover drug targets for genetically defined diseases in other therapeutic areas. Our target identification and validation process provides a systematic way to approach the identification of unique drug targets that, when activated or inhibited, may increase or decrease gene expression in genetically

defined diseases with the aim of restoring a healthy or functional phenotype. Our product engine is designed to be agnostic to cell type, pathway and therapeutic modality. While our drug target selection process is guided by our strategy to advance small molecule therapeutics that treat the root cause of disease into clinical development, we also may identify drug targets that might be addressable by other treatment modalities, such as antisense oligonucleotides, or ASOs, small interfering RNAs, or siRNAs, or antibodies.

We are continuing to expand our proprietary relational database, FulcrumSeek, which is designed to facilitate the process by which we assess diseases and generate drug target hypotheses through our computational biology expertise. We screen our proprietary small molecule library and customized CRISPR libraries across healthy and diseased human skeletal muscle cells, cardiac muscle cells, brain cells and blood cells. The data from these screens allow us to develop a broader understanding of biology that may be relevant in disease. With the completion of each additional screening, FulcrumSeek increases in size, and our insights and knowledge are further expanded.

According to the NIH there are approximately 7,000 rare, genetically defined human diseases, many of which have inadequate or no approved treatments. We believe that our approach to selecting and modeling certain of these human diseases with patient-derived tissue-relevant cells, followed by screening with our proprietary small molecule library and customized CRISPR libraries, could be broadly applied to the identification of drug targets that have the potential to balance the expression of many genes known to drive or ameliorate disease.

Our Approach

The ability to intervene in gene regulatory pathways that control gene expression provides the basis of our product engine. Our approach is to broadly search for mechanisms that can change gene expression in the desired manner. These drug targets may be intracellular targets or extracellular targets that affect a signaling pathway. Key considerations we use to determine which genetically defined diseases are suitable to evaluate in drug target identification activities include:

- *Unmet medical need and market opportunity:* we consider the severity of disease, the number of patients who could be treated and the competitive landscape.
- *Clear mechanistic link between a root cause genetic defect and disease:* we evaluate whether there is genetic validation of the gene's role in disease and the effect of gene modulation on disease.
- *Drug discovery execution:* we consider whether relevant patient-derived tissue-specific cell models and assays are available or whether we can develop such models using our expertise.
- *Clinical feasibility:* we evaluate potential biomarker and clinical endpoints, whether there is a meaningful treatment window and whether there is an accessible patient population to undertake clinical trials in a reasonable time frame.

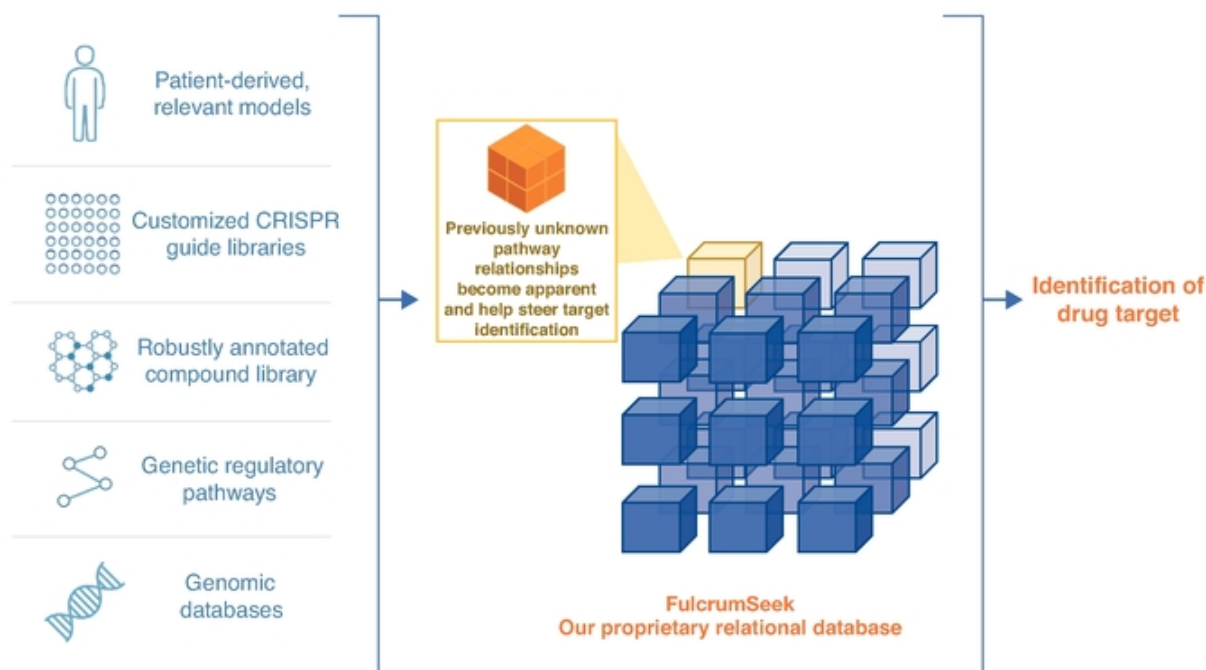
Our product engine is designed to enable us to address diseases in which genes are mis-expressed, silenced or result in mutated gene products, such as RNA or protein, due to an underlying genetic defect. There are varied approaches to treating disease by balancing gene expression including reducing the expression of a gene that causes disease (*e.g.*, *DUX4* in FSHD), increasing the expression of an under-expressed gene (*e.g.*, *FXN* in Friedreich ataxia) or expressing a compensatory gene (*e.g.*, *HBG1/2* in SCD and b-thalassemia). Our preclinical modeling of the relevant tissue is critical for success, and we believe this is best achieved using human cell systems derived from patients with the disease. We primarily seek to identify drug targets that may balance gene expression in these human cell systems and that are amenable to drugging using a small molecule. In addition to drug targets that we prioritize for internal development, we may identify other drug targets that we would consider for development through partnerships.

Overview of Our Product Engine

Our product engine is a high-throughput discovery platform that we designed to identify and validate drug targets that balance the expression of the genes known to drive or ameliorate disease. We employ a systematic methodology that starts with selecting genetically defined diseases with a known root cause. We obtain patient-derived tissue-relevant cell lines or other relevant human cell lines. We then differentiate these cell lines into those most relevant for the disease pathology, including skeletal muscle myotubes, cardiomyocytes, neurons and RBCs, which we then scale up, characterize and prepare for screening. We also generate methods to quantify the desired modulation of expression of the gene of interest in these cell lines. We apply our annotated small molecule compound library and customized CRISPR libraries to the cells to assess for the desired modulation. We confirm drug target hits with multiple modalities and undertake further validation in several patient-derived tissue-relevant cell lines. Additional studies in these cell models are conducted to understand how the modulation of the gene of interest affects cellular function. We employ computational biology using our FulcrumSeek database and other databases to guide drug target selection and generate hypotheses on other drug targets that might be related along a gene regulatory pathway.

To further optimize and increase productivity of our product engine, we have continued to invest in customized lab automation and applied technologies. We believe that these investments have increased assay throughput and robustness and have expanded the breadth of biological parameters we can effectively measure in our assay systems. We believe that we have built a robust product engine to conduct drug target screening at scale in physiologically-relevant assay systems.

We designed our discovery and development model to recapitulate this systematic approach of applying our product engine to each new disease that we evaluate with the goal of providing disease-modifying therapies to patients. The following graphic presents an overview of our drug target identification process.



Patient-Derived Tissue-Relevant Cell Models

Accurate modeling of human disease is critical for drug discovery endeavors, and we have the ability to model disease and identify drug targets that modulate gene expression in patient-derived, differentiated cells. These cells provide the appropriate context in which to understand signaling pathways that affect human gene expression and function, and have the potential to increase the translatability from preclinical studies to clinical trials. Prior to initiating screening activities, we characterize and expand the cells. We also create a cell line where the genetic defect associated with the disease has been corrected, or use a cell line from a healthy individual, in order to compare the gene regulation between diseased and normal cells. If the degree of gene activation or repression required to have a functional benefit is not known, we will undertake physiological characterization of these cell lines in order to define what threshold of gene regulation is functionally relevant.

Our process to characterize patient-derived cell models, produce cells at scale and develop suitable screens to identify drug targets typically takes between six and nine months. Depending on the disease, we may design the screen to measure effects on RNA and/or protein.

Drug Target Identification

We employ three approaches to identify drug targets that can potentially modulate gene expression to treat genetically defined diseases at the root cause—two lab-based library screening approaches as well as computational biology using our FulcrumSeek database and other databases. We then evaluate possible drug targets identified from these efforts with the goal to advance programs into lead optimization.

Small Molecule Probe Library Screening

Our small molecule probe library is annotated, which means it consists of known, well-characterized molecules that interact with biochemical mechanisms and that have cellular activity. The purpose of our small molecule probe library is to identify and interrogate mechanisms that regulate the expression of the gene of interest. We designed our library with the intent to optimize biological diversity, in contrast with other small molecule screening approaches that optimize chemical diversity. The library was developed by our medicinal chemists who reviewed primary and patent literature to identify probe molecules that interact with known biochemical targets. They selected chemical probes based on their cellular activity, potency and selectivity. In order to expand our library beyond commercially-available small molecules, we undertook a custom synthesis campaign to generate compounds that were not available from commercial sources. Our library currently includes more than 4,000 small molecules relating to approximately 2,000 biochemical targets covering a wide breadth of pharmacology, including chromatin modifiers, transcription regulation and RNA processing, kinases and metabolic enzymes. Our library will continue to expand as we identify and acquire new mechanistic probes.

CRISPR Screening

We may also use a customized CRISPR library screening, which is an approach to interrogate the genome by selectively knocking out, reducing or increasing gene expression, for target identification. We have chosen to use CRISPR libraries as complementary or additional screening tools for drug target identification alongside our small molecule screening approach. We use both an array-based CRISPR library and our pooled, custom-designed CRISPR library. Pooled CRISPR screening is an approach to target identification in which we combine cells and reagents in a single tube to simplify the experimental procedures. Pooled CRISPR screening is not suitable for all cell types, and we use array-based CRISPR screening where appropriate. Specific targets that modulate the gene of interest can be identified via CRISPR library screening, and these targets can then be validated for our drug discovery endeavors. If small molecules that interact with these targets are identified from the literature, they are then obtained for further pharmacological validation. If no known chemical matter is available, we may establish a screen

to identify chemical matter that interacts with the drug target. This chemical matter would serve as a starting point for medicinal chemistry work. Alternatively, we may seek partnerships for development using other modalities.

FulcrumSeek and Computational Biology

The primary role of FulcrumSeek and our computational biology capabilities is to generate drug target and biomarker hypotheses using externally generated patient data and internal screening data. Our approach is to leverage our network biology capabilities and expertise to determine how pathways interact with each other in a cell, to develop a network map of regulatory interactions that control gene expression and cellular function and propose targets that potentially could be pursued to address the root cause of diseases of interest. In each case, we explore these hypotheses through biological experimentation designed to validate predicted drug targets and biomarkers. We use confirmatory studies to aid in the refinement of our computational models in an iterative manner.

Drug Target Validation

Our initial focus on drug target validation is to establish a robust link between the drug target that we identified through our screening approaches and modulation of the expression of the root cause gene of interest. Our validation work seeks to evaluate identified drug targets in a manner that allows us to prioritize targets where we may be able to deliver safe and effective therapies to patients. We conduct our validation tests using a diverse set of pharmacological tools and multiple genetic reagents to profile their effect on orthogonal read-outs of gene expression (RNA and protein) and the subsequent effects on physiological function.

The important elements of our systematic approach to drug target validation include:

- *Evaluation of different treatment modalities to interact with the drug target:* we evaluate whether small molecules and genomic modulation approaches similarly affect expression of the gene of interest.
- *Efficacy:* we attempt to establish a link between the identified drug target and the level of the expression of the gene of interest.
- *Safety:* we evaluate whether modulation of the target and the resulting changes in gene expression cause undesired effects, including an assessment of cell health markers to ensure there is minimal cellular toxicity.
- *Profiling cell lines from multiple patients:* we analyze the modulation of the drug target to determine whether the original cell line used to screen targets is representative of disease in other patients.
- *Verification:* we conduct studies designed to ensure that the modulation of the drug target and the resulting change in gene expression leads to a desired functional effect.
- *Prioritization:* we prioritize drug targets based on our assessment of our ability to deliver a candidate for clinical development based on that target.

Development Candidate Discovery and Characterization

Following target identification and target validation, we initiate medicinal chemistry and drug discovery activities to advance a development candidate that is suitable for testing in clinical trials. This work optimizes characteristics that are important for an orally available small molecule, including potency, selectivity, pharmacokinetic, or PK, and safety parameters. There is an opportunity to bypass or considerably accelerate discovery and characterization activities if we identify and validate an attractive drug target that has been pursued previously by others in different indications. For example, available chemical matter and support from the scientific literature regarding p38a/b enabled us to rapidly identify our product candidate for the treatment of FSHD.

A key element of our preclinical compound profiling approach is to investigate a development candidate across many patient-derived tissue-relevant cells. We choose these cells based on our assessment of the patient heterogeneity that may be encountered in clinical trials. The purpose of this analysis is to enable us to understand if the activity of the molecule differs among cells with different genetic subtypes, or if a patient stratification strategy is appropriate for clinical trials.

Many genetically defined diseases are not well modeled with animal models because such models do not have appropriate predictive validity. In these cases, we seek to develop an engraftment model where patient-derived human cells are engrafted into the relevant tissue of a host, immunodeficient mouse to produce a chimeric mouse. We may use these chimeric mice to assess gene regulation in the engrafted human cells, and for the efficient development of PK-pharmacodynamic, or PK/PD, relationships that will be the basis of therapeutic index calculations and human dose projections.

Advantages of a Small Molecule Approach

We believe that our approach to the treatment of genetically defined diseases using orally available, small molecule therapeutics may offer significant advantages over other treatment modalities due to:

- **Biodistribution:** small molecules can achieve broad distribution in the body. The ability to access tissues broadly is particularly relevant in neuromuscular disorders where multiple muscles are affected by disease, or in CNS diseases where brain permeability may be limited with other treatment modalities.
- **Tolerability:** small molecules have a limited risk of immunogenicity and lack procedural risk relative to administering other treatment modalities, such as ASOs and gene therapies.
- **Manufacturing and quality:** the production and quality control of drug supplies for clinical development are well understood. Specialized facilities are generally not required, and many vendors offer services for manufacturing. We believe small molecule manufacturing may provide cost advantages relative to other modalities.
- **Patient access:** small molecule, oral medicines can be administered by the patient and do not require complicated in-patient procedures that are sometimes only available in a limited number of treatment centers.

Our Lead Product Candidates

We have used our proprietary product engine and screening efforts to identify drug targets for our lead product candidates. We in-licensed our first product candidate, losmapimod, after we discovered that it could reduce aberrant expression of the *DUX4* gene, which is the known root cause of FSHD. We expect to initiate a randomized Phase 2b clinical trial in mid-2019. We designed our second product candidate, FTX-HbF, to upregulate fetal hemoglobin, which we believe would compensate for abnormal hemoglobin in SCD and certain types of β -thalassemia. We aim to submit an IND for FTX-HbF in mid-2020. The following chart summarizes key information about our lead product candidates.



Our Product Candidate for Facioscapulohumeral Muscular Dystrophy

Overview of Facioscapulohumeral Muscular Dystrophy

Facioscapulohumeral muscular dystrophy is a rare, progressive and disabling disease for which there are no approved treatments. FSHD is one of the most common forms of muscular dystrophy and affects both sexes equally, with onset typically in teens and young adults. FSHD is characterized by progressive skeletal muscle loss that initially causes weakness in muscles in the face, shoulders, arms and trunk and progresses to weakness in muscles in lower extremities and the pelvic girdle. Skeletal muscle weakness results in significant physical limitations, including progressive loss of facial muscles that can cause an inability to smile or communicate, difficulty using arms for activities of daily living and difficulty getting out of bed, with many patients ultimately becoming dependent upon the use of a wheelchair for daily mobility activities. The majority of patients with FSHD also report experiencing chronic pain, anxiety and depression. The diagnosis and treatment of patients with FSHD is typically performed by neurologists.

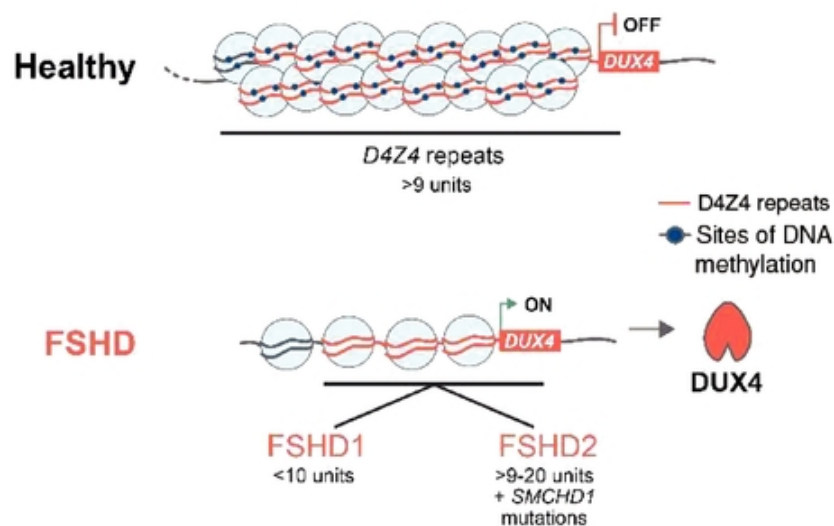
The FSH Society estimated that the prevalence of FSHD in the United States is approximately 1 in 20,000 people. A recent study conducted in the Netherlands reported a more frequent prevalence of 1 in 8,333. Based on these estimates and a U.S. population of 320 million, we estimate that the patient population is between 16,000 to 38,000 in the United States. We believe that there may be additional patients who are not formally diagnosed due to a perceived difficulty of obtaining a diagnosis and the fact that there are no approved treatments. Approximately two-thirds of cases are familial-inherited in an autosomal dominant fashion and one-third of cases are sporadic. FSHD affects all ethnic groups with similar incidence and prevalence.

FSHD Biology

FSHD is caused by aberrant expression of *DUX4* in skeletal muscle resulting in the inappropriate presence of DUX4 protein, a transcription factor causing the expression of other genes. Normally DUX4-driven gene expression is limited to early embryonic development, after which time the *DUX4* gene is silenced. In patients with FSHD, aberrant production of DUX4 protein in skeletal muscle regulates other genes encoding proteins, some of which are toxic to the muscle. Evidence of aberrant DUX4-driven gene expression is the major molecular signature that distinguishes muscle tissue affected by FSHD from healthy muscle. The result of aberrant *DUX4* expression in FSHD is death of muscle and its replacement by fat, resulting in skeletal muscle weakness and progressive disability. We believe that reducing expression of the *DUX4* gene and its downstream transcriptional program could provide a disease-modifying therapeutic approach for the treatment of FSHD at its root cause.

In all patients with FSHD, the *DUX4* gene is unsilenced, or de-repressed, as a result of one of two different types of genetic alterations, leading to FSHD1 or FSHD2. Approximately 95% of patients have FSHD1 and approximately 5% of patients have FSHD2. FSHD1 is caused by the contraction of an array of DNA, known as a D4Z4 repeat, from greater than ten repeat units to nine or fewer units. This contraction causes de-repression of *DUX4*. Patients with FSHD2 do not have meaningful D4Z4 repeat contraction, but have mutations in a regulatory gene, known as the *SMCHD1* gene, that normally contributes to the repression of the *DUX4* gene via DNA methylation.

The figure below illustrates how genetic mutations in the D4Z4 repeat array (FSHD1) or the *SMCHD1* gene (FSHD2) result in aberrant expression of *DUX4* in skeletal muscle.



Our Product Engine Identified the Drug Target for FSHD

We utilized patient-derived FSHD1 muscle cells, known as myotubes, and screened them with our small molecule probe library to identify drug targets that reduced *DUX4* expression. We identified several potential drug targets, however the modulation of the majority of the targets adversely affected the health or differentiation of muscle cells. One drug target that we identified from our screening efforts for which we did not observe adverse cell health issues was p38a/b, which had been studied extensively in other diseases, but had not been reported to be linked to *DUX4* expression or FSHD until we conducted our screening efforts. We evaluated multiple small molecule p38a/b inhibitors and observed a consistent reduction of both *DUX4* expression and *DUX4*-driven gene transcripts with each p38a/b inhibitor. We conducted further validation experiments to confirm that inhibition of p38a using genetic approaches such as siRNA and CRISPR single-guide RNAs, also led to a reduction in *DUX4* expression.

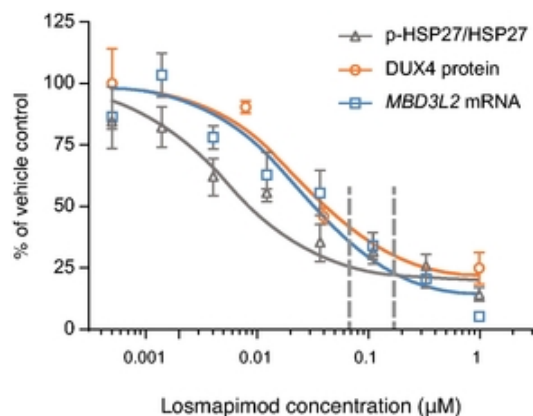
Losmapimod

After identifying p38a/b as a potential drug target, we evaluated multiple small molecule inhibitors of p38a/b. Each of these inhibitors had previously been evaluated in clinical trials for the treatment of various diseases but never in muscle disorders. As a result of our evaluation and relative to other p38a/b inhibitors, we identified losmapimod as the preferred development candidate based on substantial and attractive preclinical and clinical data regarding safety, PK and target inhibition, and its advanced stage of development. Losmapimod was originally evaluated by GSK in nearly 3,500 subjects in clinical trials across multiple indications and in multiple countries. GSK did not evaluate losmapimod in FSHD or in any other muscle disorder. Although GSK did not pursue regulatory approval in the indications evaluated, losmapimod demonstrated an attractive PK, PD, safety and tolerability profile, including in chronic dosing.

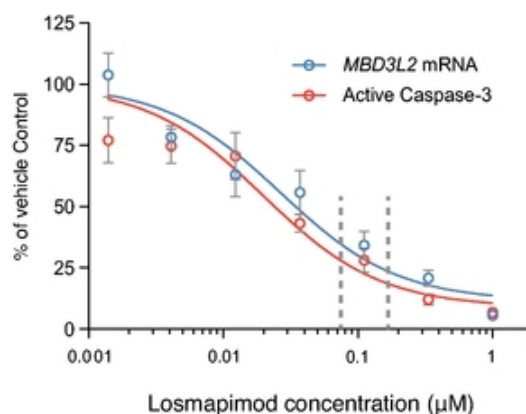
As shown in the figure on the left below, we observed in preclinical studies using losmapimod that inhibition of the p38a/b pathway reduced *DUX4* expression and downstream gene expression, as measured by the mRNA transcribed by *MBD3L2*, a gene that is only expressed following *DUX4* activation. In the study, we demonstrated that *MBD3L2* was representative of broader *DUX4*-driven gene expression changes in myotubes. We assessed the ability of losmapimod to inhibit p38a/b by measuring the effect on the phosphorylation of a downstream protein called heat shock protein 27, or HSP27. The level of phosphorylation of HSP27 has been used in previous clinical trials, including by GSK, as a biomarker to

measure the degree of p38a/b inhibition. As shown in the figure on the right below, we also observed reduced cell death, or apoptosis, in FSHD myotubes, as measured by active caspase-3. We used active caspase-3 to quantify cell death because it is a protein that has been shown to be an important regulator of the apoptosis pathway in myotubes.

Losmapimod reduced DUX4 protein levels and DUX4-driven gene expression



Losmapimod reduced apoptosis in FSHD myotubes



The dotted lines in each graphic above indicate the Cmin (left) and Cmax (right) observed in a clinical trial conducted by GSK that used a 15 mg twice per day dose of losmapimod. Cmin represents the minimum concentration in plasma prior to administration of a subsequent dose and Cmax represents the highest concentration in plasma after administration of a dose.

After identifying losmapimod, we in-licensed the molecule from GSK because we believed that its safety and pharmacology history would significantly expedite our development plan and enhance our future regulatory submissions. In February 2019, we obtained an exclusive worldwide license from GSK to the losmapimod patents and preclinical and clinical data for all indications, subject to certain conditions. This license includes a letter of reference for the U.S. Food and Drug Administration, or FDA, providing us the right to reference all the previous INDs that had been filed by GSK for losmapimod, as well as a license to their losmapimod data, including the original preclinical study and clinical trial reports. We also received active pharmaceutical ingredient, or API, and losmapimod tablets that had been manufactured by GSK. We plan to use the API and tablets to support our clinical development of losmapimod in FSHD, including our planned Phase 2 clinical trials. We utilized the GSK data and our preclinical data to submit an IND in the United States and CTAs in Europe and Canada in May 2019 that will enable us to advance our clinical development plan for losmapimod in FSHD, including initiating a Phase 2b clinical trial. The IND was accepted by the FDA in June 2019.

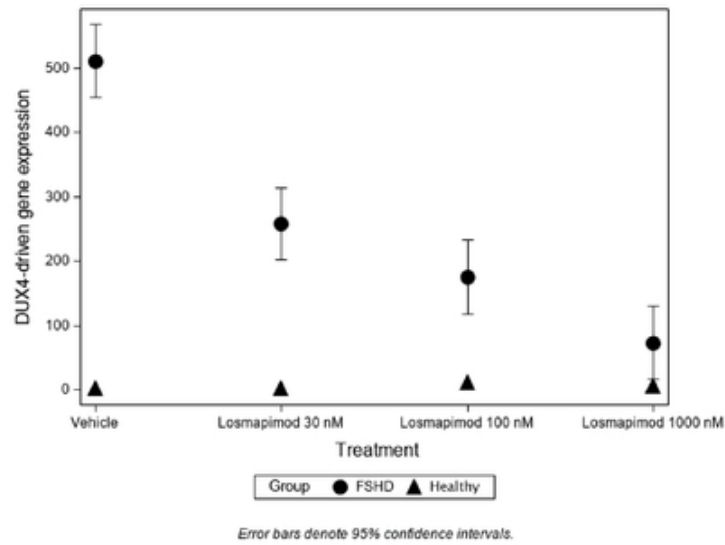
Preclinical Development

We conducted several preclinical studies designed to evaluate the ability of losmapimod to reduce DUX4-driven gene expression. In a preclinical study of losmapimod, we treated myotubes from primary cell lines of eight FSHD1 and three FSHD2 patients for four days with different concentrations of losmapimod or vehicle as a negative control. To model the effect of losmapimod treatment on DUX4-driven gene expression across diverse disease-causing genotypes, we measured *MBD3L2* transcript levels relative to the transcript levels of *POLR2A*, a gene whose expression is not regulated by DUX4 protein. We observed that clinically achievable concentrations of losmapimod (30 to 100 nM) decreased DUX4-driven expression by 50% to 65%, as measured by quantitative polymerase chain reaction amplification of the *MBD3L2* transcripts. The observed treatment effect was similar in all cells tested.

regardless of genotype. We believe that this data suggests that losmapimod has the potential to treat FSHD patients across all genotypes.

The graphic below shows the least square mean estimates for DUX4-driven gene expression from 11 FSHD primary cells and healthy cells treated with losmapimod presented as mean and 95% confidence intervals, which demonstrates that losmapimod reduced DUX4-driven gene expression, as measured by MBD3L2 and POLR2A transcript levels in a concentration-dependent manner.

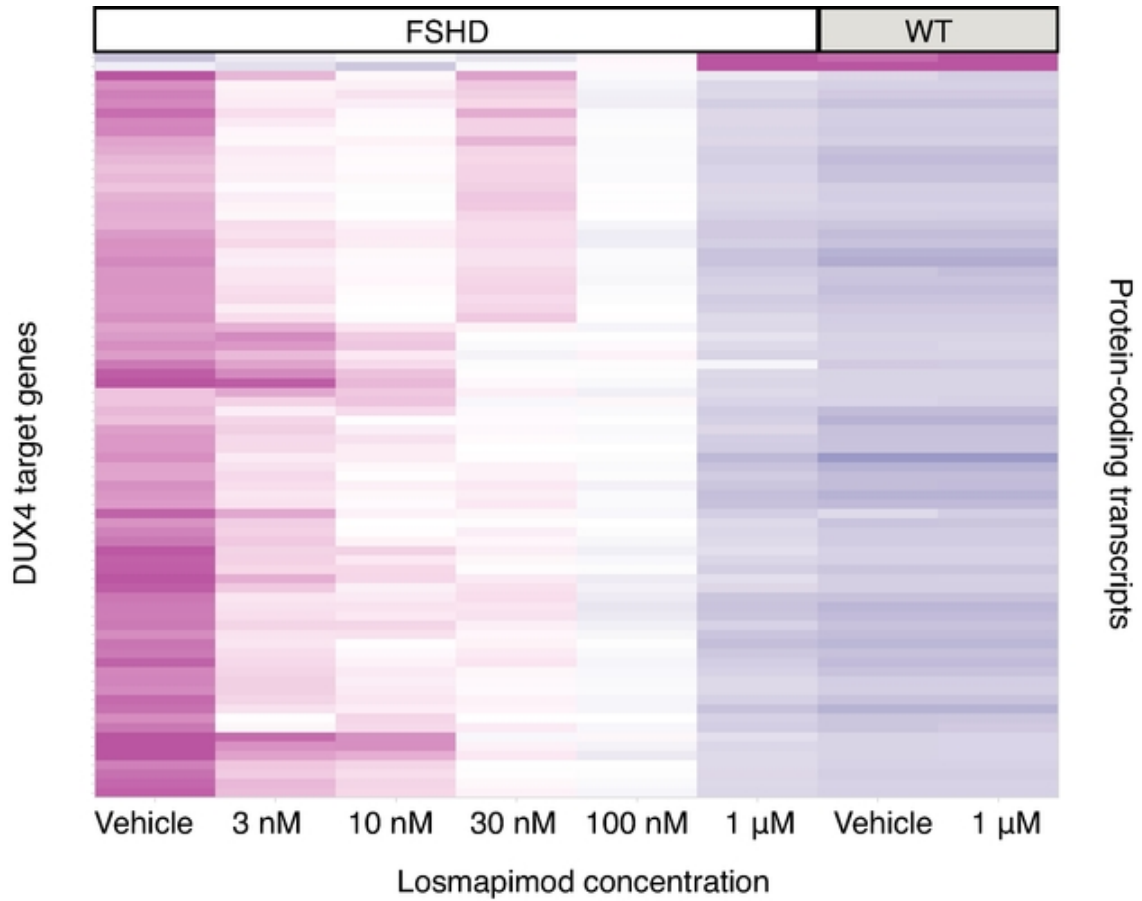
Reduction of DUX4-driven gene expression at increasing concentrations of losmapimod



In our preclinical studies, we have also observed that treatment of FSHD patient-derived myotubes with losmapimod is highly specific for DUX4-driven gene expression. We conducted a study in which we measured the FSHD gene expression signature and observed a minimal impact on myogenesis when healthy human myotubes were treated with losmapimod. We treated FSHD cells with losmapimod for five days and a subsequent RNA-seq analysis revealed that only 89 transcripts (0.45%) out of approximately 20,000 protein coding genes were differentially expressed more than four-fold. Of these 89 differentially expressed transcripts, 90% were transcripts directly regulated by DUX4. We believe that this is strong evidence that the effects of losmapimod in affected skeletal muscle are highly specific for the treatment of the root cause of FSHD. Importantly, we did not observe changes in levels of myogenin, a transcriptional activator that promotes transcription of muscle-specific genes and plays a role in muscle differentiation, cell cycle exit and muscle atrophy, and observed minimal impact on other myogenic factors during myoblast differentiation into myotubes.

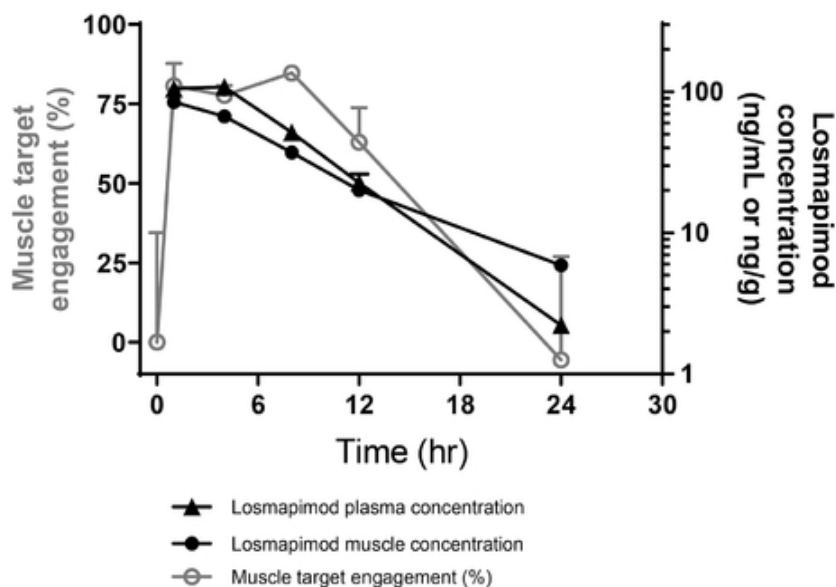
The graphic below depicts the gene expression signature in FSHD at increasing concentrations of losmapimod as compared to a high concentration of losmapimod in healthy wild type, or WT, myotubes. In

the graphic, darker pink tones indicate more gene expression and darker blue tones indicate less gene expression.



GSK observed concentrations of losmapimod in human plasma of 28.4 ng/mL to 74.1 ng/mL with an average of 50.5 ng/mL at a 15 mg twice per day dose in its clinical trials. In preclinical studies in animal models, we observed that losmapimod reached muscle tissue and engaged the p38a/b target in the muscle tissue. As shown below, we detected similar concentrations of losmapimod in rat plasma and muscle, and significant target engagement is observed at concentrations that we expect to achieve in clinical trials using a 15 mg twice per day dose.

p38a/b target engagement over time



We obtained further evidence that losmapimod distributed to muscle from a preclinical study in which GSK profiled distribution of losmapimod to all tissues in rats. Our review of this data similarly confirmed that muscles were well exposed to losmapimod.

Clinical Development Overview

We began dosing in a Phase 1 clinical trial of losmapimod in healthy volunteers and patients with FSHD in Europe in February 2019 following the filing of a CTA in December 2018. We plan to conduct a randomized, double-blind placebo-controlled Phase 2b clinical trial with approximately 66 patients with FSHD to investigate whether oral administration of 15 mg of losmapimod twice per day reduces expression of DUX4-driven genes in affected skeletal muscle. We also plan to concurrently conduct an open label Phase 2 clinical trial in 16 patients with FSHD to investigate the safety and tolerability of 15 mg losmapimod twice per day for chronic use and to evaluate the ability of losmapimod to reduce expression of DUX4-driven genes in affected skeletal muscle over varying durations of treatment. We are planning an open label extension trial to enable patients in our Phase 2b clinical trial who are treated with losmapimod to continue receiving treatment after the 24-week treatment period and to enable patients given placebo in our Phase 2b clinical trial to be treated with losmapimod.

We believe that a 15 mg twice per day dose of losmapimod is an appropriate dose for the treatment of patients with FSHD based on previous clinical data and p38a/b target engagement data generated by GSK and p38a/b target engagement data from our preclinical studies.

We submitted a CTA in Europe for the open label Phase 2 clinical trial in April 2019 and submitted CTAs in Europe and Canada for the Phase 2b clinical trial in May 2019. The FDA accepted the IND in June 2019. We expect to initiate the randomized Phase 2b clinical trial and the open label Phase 2 clinical trial in mid-2019.

We are also conducting several preparatory non-drug studies to assess biomarker endpoints and clinical outcome assessments. In addition, we are participating in a natural history study that will follow 150 subjects with FSHD in the United States and 70 subjects in Europe over 18 months. We expect to utilize the data generated from our non-drug studies and the natural history study to inform discussions with regulatory agencies and future clinical trial design.

We believe that the safety data from GSK's prior losmapimod clinical trials, together with safety and efficacy data from our Phase 1 and Phase 2 clinical trials, may enable us to apply for accelerated approval. We believe a treatment for FSHD may be eligible for accelerated approval because FSHD is a rare, slowly progressive and disabling disease with no approved treatments. We plan to discuss accelerated approval with regulatory agencies if we observe positive results in our Phase 2b clinical trial based on biomarker endpoints that we believe are likely to predict clinical benefit. We also plan to apply for orphan drug designation for FSHD in the United States and Europe in 2019.

Prior Clinical Development of Losmapimod by GSK

GSK conducted multiple Phase 1 and Phase 2 clinical trials and one Phase 3 clinical trial of losmapimod, including in patients with chronic obstructive pulmonary disease, or COPD, acute coronary syndrome and other cardiovascular diseases, neuropathic pain, major depression disorder, focal segmental glomerulosclerosis, and rheumatoid arthritis. Nearly 3,500 subjects in 24 trials were given losmapimod with single doses as high as 60 mg and repeated oral doses as high as 15 mg twice per day for up to 52 weeks. We plan to use a dose of 15 mg twice per day in our clinical trials of losmapimod in FSHD. GSK did not conduct a clinical trial of losmapimod in patients with FSHD or any other muscle disorder.

In clinical trials of losmapimod conducted by GSK, no significant differences were observed in the frequency of adverse events, or AEs, in subjects given losmapimod and subjects given placebo. GSK generally observed a similar frequency of serious adverse events, or SAEs, and deaths between patients given losmapimod and patients given placebo. These trials included extensive evaluation of the cardiovascular risk profile of losmapimod, including completion of an evaluation of the potential to prolong corrected QT. GSK reported that there was no clinically relevant difference with regard to the occurrence of electrocardiogram abnormalities post-baseline or vital signs with losmapimod as compared to placebo. GSK did not identify a safety signal attributed to losmapimod in any of these trials. There were no SAEs reported in 14 of these 24 clinical trials of losmapimod.

The table below presents safety data from the largest placebo-controlled clinical trial of losmapimod, which was a Phase 3 clinical trial for the treatment of acute coronary syndrome following a heart attack, in which over 1,700 patients were given 7.5 mg of losmapimod or placebo twice per day for 12 weeks and were followed for an additional 12 weeks. In this trial, GSK observed a similar proportion of AEs in the placebo group as compared to the losmapimod group. The data in the table below presents the SAEs reported by more than 0.5% of patients in any group in the trial through 24 weeks.

Safety data from GSK's Phase 3 clinical trial of losmapimod in patients with acute coronary syndrome		
	Placebo	Losmapimod
	N = 1,752	N = 1,724
	n (%)	n (%)
Any SAE	323 (18.4)	363 (21.1)
Cardiac disorders	114 (6.5)	138 (8.0)
Infections and infestations	54 (3.1)	55 (3.2)
Respiratory, thoracic and mediastinal disorders	24 (1.4)	41 (2.4)
General disorders and administration site conditions	35 (2.0)	26 (1.5)
Renal and urinary disorders	18 (1.0)	31 (1.8)
Investigations	28 (1.6)	18 (1.0)
Musculoskeletal and connective tissue disorders	14 (0.8)	25 (1.5)

There were also ten fatal SAEs in the placebo group and 13 fatal SAEs in the losmapimod group. In the placebo group, the fatal SAEs were infections and infestations (two), general disorders and administrative site conditions (two), respiratory, thoracic and mediastinal disorders (three), cardiac disorder (one), gastrointestinal disorder (one) and neoplasm (one). In the losmapimod group, the fatal SAEs were infections and infestations (four), general disorders and administrative site conditions (three),

respiratory, thoracic and mediastinal disorders (two), cardiac disorder (one), injury poisoning and procedural complications (one), gastrointestinal disorder (one) and neoplasm (one).

The following table presents SAEs reported during treatment from a total of 11 Phase 1 and Phase 2 placebo-controlled clinical trials of losmapimod with repeat dosing for which GSK reported integrated data. The 11 trials presented include three of the 14 trials in which no SAEs were reported.

Safety data from 11 clinical trials of losmapimod conducted by GSK		
	Placebo	Losmapimod
	N = 735	N = 1,327
	n (%)	n (%)
Any SAE	47 (6)	120 (9)
Cardiac disorders	17 (2)	41 (3)
Respiratory, thoracic and mediastinal disorders	11 (1)	26 (2)
Infections and infestations	7 (<1)	14 (1)
General disorders and administrative site conditions	7 (<1)	13 (<1)
Nervous system disorders	5 (<1)	10 (<1)
Injury, poisoning and procedural complications	1 (<1)	11 (<1)
Gastrointestinal disorders	1 (<1)	7 (<1)
Vascular disorders	1 (<1)	5 (<1)
Renal and urinary disorders	2 (<1)	4 (<1)
Musculoskeletal and connective tissue disorders	2 (<1)	4 (<1)
Skin and subcutaneous tissue disorders	2 (<1)	4 (<1)
Hepatobiliary disorders	0	4 (<1)
Psychiatric disorders	2 (<1)	3 (<1)
Neoplasms (benign, malignant and unspecified)	1 (<1)	3 (<1)
Blood and lymphatic system disorders	0	1 (<1)
Immune system disorders	0	1 (<1)
Metabolism and nutrition disorders	0	1 (<1)

This table includes safety data from the second largest clinical trial of losmapimod, which was a placebo-controlled Phase 2 clinical trial of losmapimod in patients with COPD, in which 602 adult patients were given 2.5 mg, 7.5 mg or 15 mg of losmapimod or placebo twice per day for 24 weeks and were followed for an additional week. In this trial, GSK observed a similar proportion of AEs in the placebo group as compared to the losmapimod group. Additionally, in this trial there were three fatal SAEs in the placebo group due to severe exacerbation of COPD, acute myocardial infarction and pulmonary embolism, one fatal SAE in the losmapimod 7.5 mg group due to acute myocardial infarction and associated pulmonary edema and two fatal SAEs in the 15 mg group due to respiratory failure and bilateral purulent pleuritis and mediastinitis. The most common SAE observed in the trial was exacerbation of COPD, which was experienced by eight subjects in the placebo group, six subjects in the losmapimod 2.5 mg group, two subjects in the losmapimod 7.5 mg group and three subjects in the losmapimod 15 mg group. Other SAEs in the placebo group included a liver event, eczema, leukoplakia, sinobronchitis and anxiety. Other SAEs in the losmapimod groups included two subjects with liver events, one subject with eczema and leukoplakia, one subject with pyrexia and one subject with pemphigoid.

In addition to the trials and data summarized above, GSK also conducted a placebo-controlled Phase 2 clinical trial in which 184 adult patients with frequently exacerbating COPD were given 15 mg of losmapimod or placebo twice per day for up to 52 weeks. In this trial, the proportion of subjects with AEs and SAEs was higher in the losmapimod group than in the placebo group; there was one fatal SAE in the

placebo group and three fatal SAEs in the losmapimod group, none of which was considered related to losmapimod. The data in the table below presents the SAEs reported in the trial.

Safety data from GSK's Phase 2 clinical trial of losmapimod in patients with COPD		
	Placebo	Losmapimod
	N = 94	N = 90
	n (%)	n (%)
Any SAE	8 (9%)	18 (20%)
Respiratory, thoracic and mediastinal disorders	2 (2)	7 (8)
Cardiac disorders	3 (3)	4 (4)
Infections and infestations	1 (1)	6 (7)
Injury, poisoning and procedural complications	1 (1)	2 (2)
Neoplasms (benign, malignant and unspecified)	2 (2)	1 (1)

In addition to the 24 trials conducted by GSK, another sponsor conducted a placebo-controlled Phase 2 clinical trial of losmapimod in which 73 subjects with COPD with cardiovascular manifestations were given 7.5 mg of losmapimod or placebo for 16 weeks. There were 36 subjects in the losmapimod group and 37 in the placebo group. In this trial, there were a total of six (17%) SAEs in the losmapimod group, consisting of exacerbations of COPD and pneumonia, and there was one (3%) SAE in the placebo group.

In prior studies, GSK observed that the p38a/b target inhibition in humans was approximately 10%, 30% and 50% at trough and 40%, 60% and 70% at peak following twice per day doses of 2.5 mg, 7.5 mg and 15 mg, respectively. In addition, based on *in vitro* data from our studies in FSHD myotubes with losmapimod, we believe that the muscle exposures that we have achieved in rodents, which are similar to concentrations in human blood from the 15 mg twice per day dose, will result in robust p38a/b target engagement and will reduce DUX4-driven gene expression in FSHD skeletal muscle by more than 50%. We believe that this data supports our determination that 15 mg of losmapimod twice per day is an appropriate dose for the treatment of patients with FSHD.

Preparatory Studies

There are currently four ongoing preparatory studies designed to inform molecular biomarker and clinical development efficacy endpoints for planned clinical trials of losmapimod in patients with FSHD.

Study	Subjects (Planned)	Description / Endpoints
Biomarker Preparatory Study (Fulcrum SRA 002-2018)	18	DUX4-driven gene expression in skeletal muscle and whole-body skeletal muscle MRI
Optimized Time Up and Go Test Preparatory Study (Fulcrum SRA 003-2018)	22	Optimized time up and go test for FSHD, or FSHD-TUG
Direct Patient Input (Fulcrum SRA 004-2018)	100	Direct patient input into the Phase 2b clinical trial
ReSOLVE Natural History Study (NIH) and Reachable Work Space (Fulcrum SRA 003-2017)	150	Natural history study Reachable work space
EU Natural History Study and Reachable Work Space (SRA 003-2017)	70	Natural history study Reachable work space

Biomarker Preparatory Study (Fulcrum SRA 002-2018)

We designed this preparatory study to investigate, inform and optimize the DUX4-driven gene expression and MRI efficacy biomarker endpoints that we intend to use in clinical trials of losmapimod. We are evaluating 18 subjects at seven clinical sites. We completed enrollment in May 2019 and will use the data to inform our planned Phase 2 trials of losmapimod for the treatment of FSHD.

This preparatory study is designed to measure aberrant DUX4-driven gene expression in affected skeletal muscle via a subset of DUX4-driven gene transcripts in order to develop a molecular muscle endpoint designed to track the root cause of disease. We are using MRI to inform affected leg muscles selected for biopsy. We believe that the measurement could be a primary endpoint in a clinical trial to support accelerated approval of losmapimod for FSHD. We are also using whole-body MRI scans one to three months apart to evaluate changes in skeletal muscle health (lean muscle tissue volume and muscle tissue replaced by fat).

The subjects have clinical severity scores of two to four on the Ricci scale, which is the clinical impairment disability scale for patients with FSHD, where a zero indicates that a subject has no disability and five indicates that a subject is permanently dependent upon the use of a wheelchair for daily mobility activities.

We also plan to use other MRI-based measures as exploratory endpoints in our planned Phase 2 clinical trials. We believe that inflammation in muscles of patients with FSHD is predictive of muscle degradation and subsequent fat replacement. We intend to utilize MRI-based endpoints to identify the level of inflammation and the overall fat content in muscles. MRI imaging sequences, which are settings of pulses and gradients, have been developed that enable an increased contrast between tissues of interest. We use a T2 MRI sequence to observe and quantify areas of high muscle water content, or muscle edema, which is a marker of inflammation. These areas will have a higher T2 value than the background tissue. T2

provides information about the muscle's physiological status, however it is not specific for inflammation and may indicate other abnormal physiological conditions in muscle tissue. We plan to use the Dixon MRI sequence, or the Dixon method, to quantify the fat content of muscles, which is a marker for muscle degradation. The Dixon method separates the signals from water and fat and the separated fat signal can then be utilized to determine the fat fraction within the muscle. We intend to utilize these MRI-based approaches as exploratory endpoints in our Phase 2 and Phase 2b clinical trials to identify muscles with higher levels of inflammation, as evidenced by a higher signal in the T2 sequence, and muscle degradation, as evidenced by the muscle fat fraction determined using the Dixon method.

A third-party study found that these MRI techniques, when applied to skeletal muscles, were able to quantify the increase in inflammation, as measured by T2 signal, and fat fraction, as determined using the Dixon method, over a 20-month period. In particular, skeletal muscles with severe inflammation, as determined by elevated T2 signal, demonstrated worsening of fat fraction over this period. This effect was observed as early as six months. Skeletal muscles in patients with FSHD that had low inflammation, based on a low T2 signal, demonstrated both lower levels of fat fraction and slower fat fraction progression. We believe that these data suggest that fat fraction progression is higher in muscles with a higher level of inflammation and support the usage of these MRI-based exploratory endpoints in clinical trials.

Optimized Time Up and Go Test Preparatory Study (Fulcrum SRA 003-2018)

We are evaluating a modified version of the classic time up and go, or classic TUG, test that we are optimizing as a clinical outcome assessment of mobility and ambulation, which we refer to as the FSHD-TUG test. The classic TUG test requires patients to get up from a chair, walk three meters, turn around, walk back to the chair and sit down. It was originally developed for clinical practice to assess mobility, balance, walking ability and fall risk in older adults prior to discharge from hospitalization and was used recently as a key secondary efficacy endpoint in a registration trial in multiple sclerosis in Europe. The classic TUG test is also one of the clinical outcome assessments in the ReSOLVE natural history study discussed below.

While we believe that the classic TUG test is a valid, reliable and objective test to quantify functional mobility in all age groups, we believe that a minor modification, asking patients to get up from a standardized bed, will be more appropriate for FSHD patients. We believe that the FSHD-TUG test may be more sensitive to measure treatment effects in patients with FSHD. Patients with FSHD generally have a difficult time rising from a chair and even more so from a recumbent position and this difficulty progresses over time. Patients with FSHD report that limitations in mobility and in the use of the shoulders and upper arms are the two most important areas of concern. The FSHD-TUG test may be a useful clinical outcome assessment endpoint for measurement of treatment effects of losmapimod on mobility.

We are currently testing the FSHD-TUG test in comparison to the classic TUG test in a group of 22 subjects with FSHD and in 20 healthy volunteers who are age and gender matched. The subjects will have clinical severity scores of one to four on the Ricci scale. We are evaluating the subjects in five visits over approximately 12 months.

Direct Patient Input (Fulcrum SRA 004-2018)

We are also seeking to obtain direct patient input into the design and feasibility of our planned Phase 2b clinical trial by having approximately 100 patients with FSHD complete a survey based on their review of the proposed schedule of clinical outcome assessments for the trial. The patients will provide their views on their willingness to participate and any potential barriers to their participation in our planned Phase 2b clinical trial. We conduct these surveys during a face-to-face interview in clinics in the United States and France, via an internet survey for members of an FSHD registry in the United Kingdom and through in-person groups in Canada. We have the ability to refine the protocol for our Phase 2b clinical trial to reflect the feedback from patients.

ReSOLVE Natural History Study

The Clinical Trial Readiness to Solve Barriers to Drug Development in FSHD, or ReSOLVE study, is an ongoing natural history study funded by the NIH to help identify the patient population, efficacy biomarker and clinical outcome assessments for future FSHD drug trials. The study is being coordinated by the University of Rochester and University of Kansas Medical Center and enrolled the first subject in April 2018. The study will follow approximately 150 subjects for 18 months across a network of eight U.S. clinical centers and will evaluate multiple biomarkers and clinical outcome assessments that may be suitable for clinical trials and will evaluate patient selection criteria based on genetic, demographic or clinical characteristics. Three sites in the European Union have joined the ReSOLVE protocol and will follow approximately 70 subjects for 18 months. As of June 2019, over 140 subjects have been enrolled. We believe that the results of this natural history study will inform the design and implementation of clinical trials and will inform discussions with regulatory agencies. We also believe that this study may provide valuable insights into the timeline for disease progression and functional changes in FSHD in the absence of treatment.

In connection with the ReSOLVE study, we have funded the addition of a clinical outcome assessment, which we refer to as reachable work space, or RWS. RWS is an objective assessment of upper arm function in a quantitative manner by measuring arm and shoulder mobility with and without weights. A hallmark of FSHD progression is weakness in the shoulder muscles and upper arms that eventually leads to an inability of patients to lift their arms above their shoulders. The RWS assessments are analyzed by a central reader. We have provided standardized hardware, software, and testing conditions to evaluate RWS at eight sites that are part of the ReSOLVE study in the United States and at three European sites. To date, we have collected over 300 RWS assessments in the study.

A recent third-party study assessed changes in RWS for 18 subjects with FSHD for up to five years. The study concluded that the RWS measure is able to detect slow declines in upper extremity function in subjects with FSHD. The study also found that the most notable declines in RWS were in above-the-shoulder level quadrants with no significant changes in lower quadrants and that RWS declined more significantly if the subjects were challenged with 500-gram weights.

Phase 1 Clinical Trial

We are conducting a randomized Phase 1 clinical trial of losmapimod in healthy adult volunteers and patients with FSHD in Europe under a CTA that we filed in December 2018. We expect that this trial will be completed in 2019. We intend to present data in the fourth quarter of 2019 at a scientific conference.

In this trial, we have dosed eight healthy volunteers with 7.5 mg of losmapimod capsules, followed by a washout period, and subsequently dosed the same volunteers with a 15 mg dose of losmapimod capsules. As part of this trial, we have also dosed two healthy volunteers with placebo capsules in both periods. Consistent with the extensive data that we in-licensed from GSK, losmapimod has been well tolerated in this trial.

Following the completion of the healthy volunteer cohort, we began dosing patients with FSHD in April 2019. We plan to enroll up to 20 patients in this trial. This trial is designed to obtain safety and tolerability of losmapimod in patients with FSHD. Patients are being randomized across three arms of 7.5 mg or 15 mg of losmapimod capsules or placebo twice per day for 14 days. We also intend to compare p38a/b target engagement in skeletal muscle of patients treated with a dose of 7.5 mg and 15 mg of losmapimod twice per day relative to that of patients on placebo. We aim to confirm that 15 mg twice per day is the appropriate dose for our Phase 2 trials based on higher muscle exposures and target engagement than the 7.5 mg twice per day dose. We will measure target engagement and other biomarkers in muscle needle biopsies before and after two weeks of treatment.

We manufactured the losmapimod capsules for this trial prior to our license agreement with GSK. For our Phase 2 clinical trials, we will use losmapimod tablets that were manufactured by GSK. We confirmed that the PK of the losmapimod capsules were consistent with published data on the PK of the losmapimod

tablets manufactured by GSK. In this trial, we are also confirming that the p38a/b target engagement in blood from our losmapimod capsules is consistent with the previous data on target engagement of the losmapimod tablets manufactured by GSK.

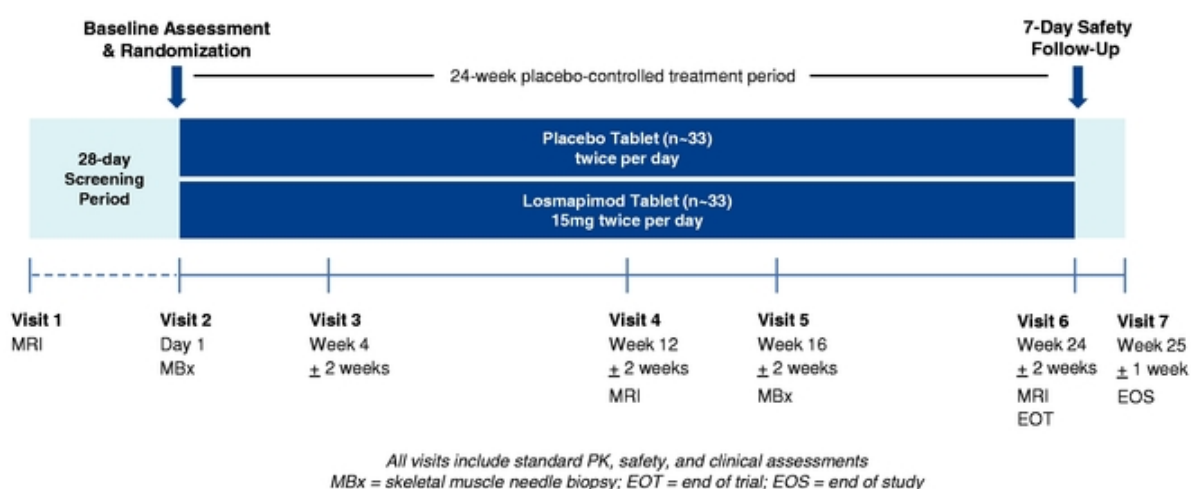
Phase 2b Clinical Trial

We plan to initiate a randomized, double-blind, placebo-controlled Phase 2b clinical trial in approximately 66 patients with FSHD1 and clinical severity scores of two to four on the Ricci scale. In this trial, we will evaluate treatment with 15 mg of losmapimod or placebo tablets twice per day over a 24-week period. Patients will be randomized 1:1 between the treatment and placebo arms. The FDA accepted the IND for losmapimod in June 2019, and we also submitted CTAs in May 2019 to conduct the trial at sites in Europe and Canada and expect to initiate this trial in mid-2019.

The primary endpoint will be the reduction of DUX4-driven gene expression in affected skeletal muscle biopsies before treatment and after approximately 16 weeks of treatment. We selected the number of patients to enroll in this trial based on the magnitude of reduction of DUX4-driven gene expression that we have observed in our preclinical studies using losmapimod concentrations similar to those measured when dosing with 15 mg twice per day in clinical trials completed by GSK.

Secondary endpoints of the trial will include evaluation of safety and tolerability in FSHD patients, PK in blood, losmapimod concentration in skeletal muscle biopsies, and p38a/b target engagement in blood and in muscle biopsies. This trial will also include evaluation of exploratory efficacy endpoints including MRI biomarkers and clinical outcome assessments. The clinical outcome assessments include centrally read RWS, FSHD-TUG test and patient-reported outcomes and muscle strength measured by quantitative dynamometry and motor function ability measurements obtained by physical therapists.

The graphic below presents the design of the Phase 2b clinical trial.



Phase 2 Open Label Clinical Trial

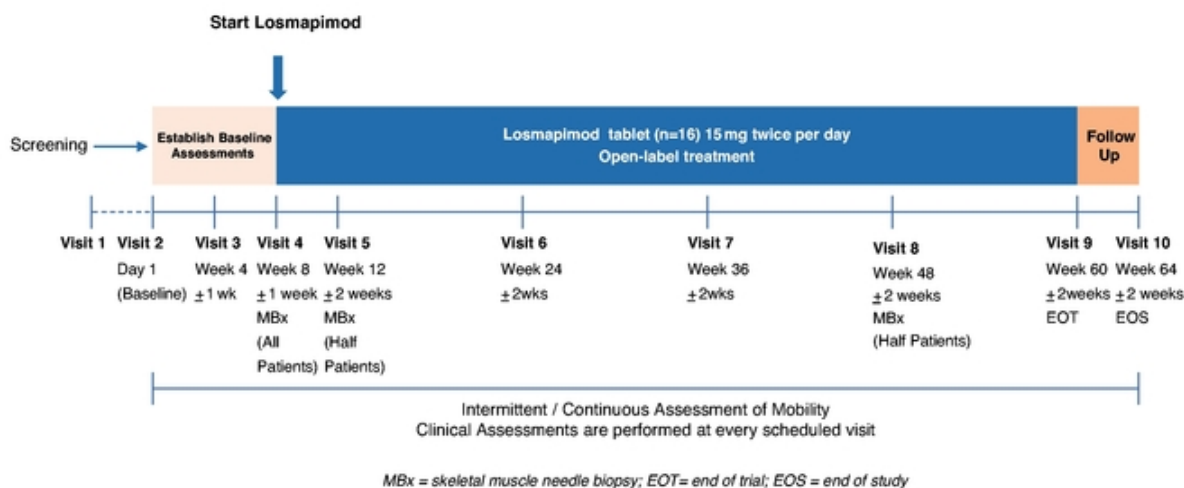
In parallel with the Phase 2b clinical trial, we also plan to initiate enrollment in mid-2019 for an open label, single site Phase 2 clinical trial of losmapimod in 16 patients with FSHD1 and clinical severity scores of two to four on the Ricci scale. Patients will receive tablets containing 15 mg of losmapimod twice per day for up to 52 weeks. The treatment period will be preceded by eight weeks of pre-treatment assessments to establish a baseline for musculoskeletal MRI biomarkers and clinical outcome assessments. We filed a CTA for this trial in April 2019 and plan to conduct the trial at one site in the Netherlands.

The primary objective is to investigate the safety and tolerability of losmapimod for chronic dosing in FSHD patients. The primary endpoints are to assess safety and tolerability over the 52-week period. The secondary endpoints are the change from baseline in pHSP27 and the ratio of pHSP27 to total HSP27 in blood and muscle for assessment of the inhibition of p38a/b during the dosing period. This trial is also designed to provide initial data regarding changes in DUX4-driven gene expression, MRI biomarkers, objective clinical outcome assessments and patient-reported outcomes that may occur at various times following initiation of treatment with losmapimod relative to the pre-treatment period. We intend to use this data to further guide our clinical development strategy for losmapimod in FSHD.

We will measure DUX4-driven gene expression before and during treatment using muscle needle biopsies in affected muscles. All patients will have a pre-treatment biopsy and we will obtain a second muscle needle biopsy from each patient, with half of the patients undergoing a biopsy after four weeks of treatment and the remaining half after approximately 40 weeks of treatment.

We will measure potential losmapimod treatment effects on shoulder and upper arm function and mobility/ambulation, as well as on muscle strength and function and quality of life and activities of daily living, similar to the assessments in the Phase 2b clinical trial. The clinical outcome assessments will be RWS, FSHD-TUG, muscle strength, motor function ability and generic and FSHD-specific patient reports of quality of life and activities of daily living. There will also be an assessment of day-to-day mobility using wearable sensors.

The graphic below presents the design of the Phase 2 open label trial.



Market Research

We engaged Clarion Healthcare, LLC to conduct market research with physicians and payors to better understand the commercial landscape and to assist in our commercial planning. A total of 14 physicians in the United States, European Union and Asia and nine payors and payor experts in the United States and European Union were surveyed. Both groups acknowledged the severity of the disease and lack of any existing therapies for patients. Physicians were asked their views on potentially prescribing a small molecule product candidate that effectively repressed DUX4 gene expression in skeletal muscle and resulted in the preservation of muscle function. Based on an April 2018 report prepared by Clarion, we believe that physicians would be receptive to prescribing a product with these qualities, subject to the efficacy and safety of the product, due to the chronic nature of the disease.

Our Product Candidate for Hemoglobinopathies

Hemoglobinopathies are a category of genetic disorders affecting RBCs. We intend to develop FTX-HbF to elevate the level of fetal hemoglobin for the treatment of patients with certain hemoglobinopathies, namely sickle cell disease and for certain types of β -thalassemia.

Overview of Sickle Cell Disease

Sickle cell disease is a genetic disorder of RBCs. SCD patients typically suffer from serious clinical consequences, which may include vaso-occlusive crises, anemia, pain, infections, stroke, heart disease, pulmonary hypertension, kidney failure, liver disease and reduced life expectancy. According to a study published by the American Medical Association, approximately 32.5% of adult patients with SCD were hospitalized three or more times per year due to pain crises. SCD is reported to shorten patient life expectancy by approximately 20 to 30 years. Patients with SCD are primarily treated by hematologists.

In the United States, where newborn screening for SCD is mandatory, the estimated prevalence is approximately 100,000 individuals. In Europe, the estimated prevalence is approximately 134,000 individuals according to the European Medicines Agency, or EMA. According to the World Health Organization, the global incidence is estimated to be approximately 300,000 births annually. SCD is most prevalent in Africa and the Middle East.

Approved drug treatments for SCD focus primarily on the management and reduction of pain episodes. The two drug treatments approved in the United States are hydroxyurea and L-glutamine. Hydroxyurea is approved for the treatment of anemia related to SCD to reduce the frequency of painful crises and the need for blood transfusions. Hydroxyurea has a black box warning for myelosuppression and malignancy. In general, it is limited by its adverse side effects, inconsistent patient responses and concerns regarding the cytotoxic effect of the drug. L-glutamine is approved to reduce severe complications associated with the disorder. While treatment with L-glutamine decreases the mean number of pain crises, side effects include nausea, noncardiac chest pain, fatigue, and musculoskeletal pain.

Blood transfusions can be utilized to decrease the sickling of RBCs. While blood transfusions can be critical to manage SCD, there are a number of limitations associated with this therapeutic approach, including limited patient access and serious complications such as iron overload. The only potentially curative treatment currently approved for severe SCD is bone marrow transplantation. However, this treatment option is not commonly used due to the difficulties of finding a suitable matching donor and the risks associated with the treatment, which include an approximately 5% mortality rate. Bone marrow transplantation is more commonly offered to pediatric patients with available sibling-matched donors.

While multiple experimental approaches to treat SCD are being explored in clinical trials, the majority are focused on symptomatic relief or gene therapy approaches. Symptomatic approaches under investigation aim to affect issues associated with cell adhesion, sickling, thrombosis and iron homeostasis. We anticipate that a novel orally available therapy that affects the root cause of SCD may be used in combination with symptomatic therapeutics. Novartis AG, or Novartis, Global Blood Therapeutics, Inc. and GlycoMimetics Inc. in collaboration with Pfizer, Inc. are conducting late stage clinical trials aiming to provide symptomatic relief for patients with SCD. Several gene therapy approaches to treat SCD are focused on elevating fetal hemoglobin, however no gene therapy approaches have been approved for SCD and the efficacy, safety and durability of gene therapy approaches have yet to be established. Gene therapies need to be administered in an in-patient procedure through a bone marrow transplant, which is also referred to as a stem cell transplant or hematopoietic stem cell transplant. As part of the transplant process, the patient receives myeloablative chemotherapy which kills cells in the bone marrow in order to support the gene therapy. Despite ongoing efforts to develop gene therapies for SCD, we believe there is still a high unmet need that could be better addressed by a small molecule, oral therapy to treat the disease by increasing fetal hemoglobin.

SCD Biology

SCD is caused by a mutation in the *HBB* gene. This gene encodes a protein that is a key component of hemoglobin, a protein complex whose function is to transport oxygen in the body. Hemoglobin in adults is a complex of four proteins, two hemoglobin β -subunits and two hemoglobin α -subunits. In patients with SCD, hemoglobin is composed of two mutant β -subunits and two α -subunits and the result is the formation of abnormal hemoglobin. The result of the mutation is less efficient oxygen transport and the formation of RBCs that have a sickle shape. These sickle shaped cells are much less flexible than healthy cells and can block blood vessels (vaso-occlusion) or rupture cells (lysis), leading to pain, anemia, irreversible organ damage or even death.

During fetal development, the major form of hemoglobin is fetal hemoglobin. Similar to hemoglobin in adults, fetal hemoglobin is also a complex of four proteins, two α -subunits and two γ -subunits. Shortly after birth, the genes encoding the γ -subunits, the *HBG1* and *HBG2* genes, are silenced and the *HBB* gene is activated. As described above, SCD is caused by a mutation in the *HBB* gene that gives rise to mutated β -subunits.

A small subset of individuals with the sickle cell mutation continue to produce high levels of fetal hemoglobin due to inheritance of additional genetic mutations, which is called Hereditary Persistence of Fetal Hemoglobin, or HPFH. The production of fetal hemoglobin in these individuals allows them to maintain at least 30% fetal hemoglobin. Patients with elevated fetal hemoglobin exhibit few, if any, clinical manifestations of SCD. Further, an increase of fetal hemoglobin as low as 3% over baseline in patients without HPFH, due to either therapeutic intervention or the inheritance of other genetic traits, can result in reduced clinical manifestations of the disease.

Our Approach to Address the Root Cause of SCD

Our strategy to address the root cause of SCD was to identify a drug mechanism that induces expression of fetal hemoglobin. We believe that FTX-HbF may address the root cause of SCD through this mechanism of action.

Overview of β -Thalassemia

β -thalassemia is a rare blood disorder associated with the absence or reduced production of β -globin, which is one of the two proteins that comprise adult hemoglobin. This results in an abnormally low level of hemoglobin as well as an excess of α -globin chains that cause destruction of RBCs. The severity of the phenotype is related to the degree of imbalance between α - and non- α -globin chain synthesis. The absence of β -globin due to *HBB* gene deletions is referred to as β^0 thalassemia. Other *HBB* gene alterations allow some β -globin to be produced but in reduced amounts. A reduced amount of β -globin is called β^+ thalassemia. Many patients with β -thalassemia require chronic blood transfusions due to severe anemia that results from low hemoglobin levels, which are referred to as transfusion-dependent patients. It is estimated that 40,000 babies are born worldwide with β -thalassemia per year of whom 25,000 require blood transfusions. Patients with β -thalassemia are primarily treated by hematologists.

β -thalassemia has been clinically characterized into three forms, depending on disease severity: major, intermedia and minor. The most severe form, β -thalassemia major (also known as Cooley's anemia), is generally diagnosed shortly after birth and patients have life-threatening anemia. Pediatric patients do not grow and gain weight at the typical rates, and often have liver, heart and bone problems. Many β -thalassemia major patients require frequent blood transfusions to prevent severe anemia, a treatment that itself can cause long-term problems due to a build-up of iron in the body. β -thalassemia intermedia is a less severe form of the disease that results in mild to moderate anemia. These patients sometimes require blood transfusions depending on the severity of the symptoms. Patients with β -thalassemia minor suffer from very mild anemia and generally do not require treatment. Having either β^0 or β^+ thalassemia does not necessarily predict clinical disease severity as people with both types have been diagnosed with

thalassemia major and thalassemia intermedia. Any increase in fetal hemoglobin has the potential to ameliorate the disease.

The current standard of care for many patients with b-thalassemia is frequent blood transfusions to manage anemia. The only potentially curative therapy for b-thalassemia is allogeneic hematopoietic stem cell transplant, which is associated with risks of complications, including mortality, and is limited to patients with a suitable donor. The European Commission granted conditional marketing authorization for ZYNTÉGLO, a gene therapy developed by bluebird bio, Inc., or bluebird, for the treatment of adult and adolescent patients with transfusion-dependent b-thalassemia and with certain genotypes, in Europe in June 2019. bluebird announced that it plans to file a biologics license application, or BLA, in the United States in 2019. Acceleron Pharma, Inc., or Acceleron, in collaboration with Celgene Corp., or Celgene, is conducting Phase 3 clinical trials of luspatercept (ACE-536), an erythroid maturation agent. Celgene submitted a BLA for luspatercept for the treatment of adult patients with anemia associated with b-thalassemia and who require frequent transfusions. Celgene and Acceleron submitted a marketing authorization application to the EMA in the second quarter of 2019. There are also multiple other experimental approaches to treat b-thalassemia being explored in clinical trials, including approaches that use small molecule, gene therapy and gene editing approaches. Despite ongoing efforts to develop new therapies for b-thalassemia, we believe there is still a high unmet need that could be addressed by a small molecule, oral therapy to treatment the disease by increasing fetal hemoglobin.

Biology of b-Thalassemia

b-thalassemia is caused by genetic mutations in the *HBB* gene. The mutations interfere with the production of b-globin. Some mutations result in no b-globin being produced, while other mutations result in a decreased amount of b-globin being produced.

Our Approach to Address the Root Cause of b-Thalassemia

We believe that some types of b-thalassemia may be treated by a therapy that upregulates fetal hemoglobin. Babies born with b-thalassemia major generally do not have any symptoms shortly after birth because they have fetal hemoglobin in their blood. As the fetal hemoglobin levels decrease after birth and the b-globin fails to increase, anemia appears and the babies with b-thalassemia begin to exhibit symptoms of the disease. Patients with b-thalassemia intermedia that have higher levels of fetal hemoglobin have fewer symptoms than patients with low levels of fetal hemoglobin. We believe that FTX-HbF may be suitable for clinical development for the treatment of patients who are not b⁰ but who are transfusion dependent.

Our Product Engine Identified the Drug Target for SCD and b-Thalassemia

Applying our product engine, we conducted target identification and validation activities using human umbilical cord blood-derived erythroid progenitor 2, or HUDEP2, cells as a model to study fetal hemoglobin reactivation. HUDEP2 cells are immature RBCs. By screening our small molecule probe library and a CRISPR library, we identified several potential drug targets that activated the *HBG1/2* genes and resulted in fetal hemoglobin elevation. Each screening approach identified the same protein complex which we believe plays an important role in the expression of genes responsible for the production of fetal hemoglobin. We conducted additional validation experiments in which we observed that inhibition of several components of this complex resulted in the desired elevation of fetal hemoglobin. We also observed that inhibition of these components did not adversely affect important cell health markers.

We selected a member of this protein complex for drug discovery activities following an assessment of its tractability as a drug target, which we refer to as the HbF drug target. The normal physiological role of the HbF drug target is to facilitate a post-translational protein modification, and the goal of our medicinal chemistry program was to optimize inhibitors of the HbF drug target. We developed *in vitro* and *in vivo*

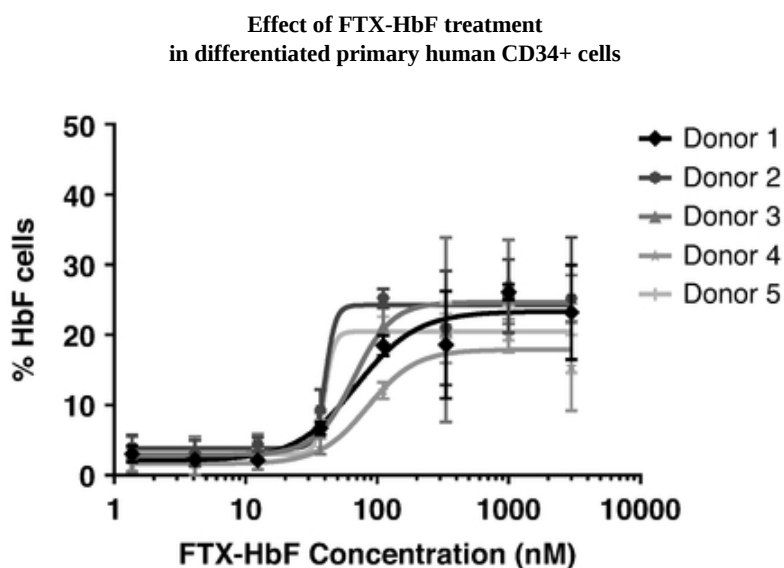
target engagement assays, as well as enabled X-ray crystallography, to discover and develop FTX-HbF, a novel small molecule inhibitor of the HbF drug target.

FTX-HbF

FTX-HbF, our novel small molecule that we designed to inhibit the HbF drug target and thereby elevate fetal hemoglobin, possesses properties that we believe are well aligned with preferred parameters for oral drug delivery. We studied the cellular potency and the PK data of FTX-HbF in preclinical animal models and observed that its profile would be predictive of once or twice daily oral administration. We have not observed any off-target concerns in our *in vitro* profiling studies, and we are conducting *in vivo* toxicology studies to evaluate FTX-HbF. We have initiated IND-enabling activities and we aim to submit an IND in mid-2020.

Preclinical Studies

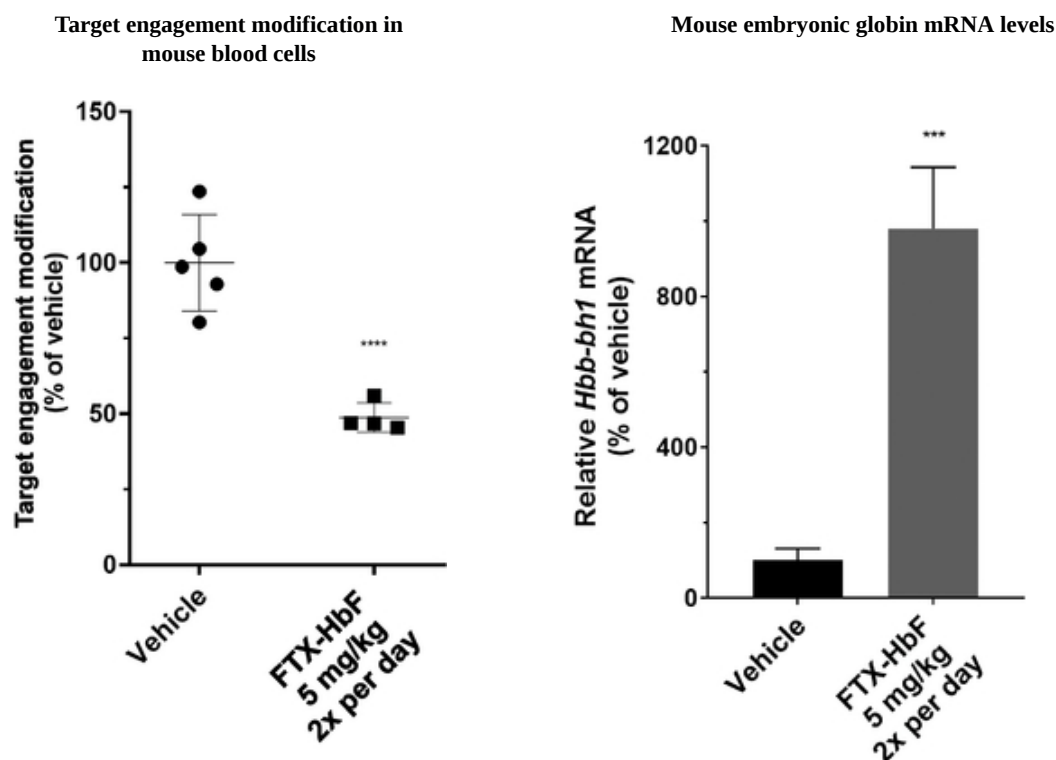
We have observed *in vitro* and *in vivo* activation of the *HBG1/2* genes in preclinical studies with FTX-HbF. We observed that FTX-HbF elevated levels of fetal hemoglobin with minimal adverse effect on important cellular health markers. As depicted in the graphic below, we also observed *in vitro* upregulation of fetal hemoglobin in primary human CD34+ cells differentiated into RBCs from five different human donors after five days of drug treatment. FTX-HbF showed a significant elevation of fetal hemoglobin over baseline in each of these five cell lines.



Additionally, we compared the effect of FTX-HbF in CD34+ derived cells relative to that of hydroxyurea. We observed that hydroxyurea had a minimal impact on fetal hemoglobin elevation, whereas we observed that FTX-HbF significantly elevated fetal hemoglobin. In cells treated with the combination of FTX-HbF and hydroxyurea, we observed an increased effect relative to either compound alone.

In preclinical PK/PD studies in mice, we observed that blood cells had dose-dependent drug target engagement after 4.5 days of oral treatment. We believe our drug target is conserved between species, which is supported by our observation of a concomitant upregulation of the mouse embryonic globin gene under conditions where we observed drug target engagement. Since mice do not have the *HBG1/2* genes found in humans, we used the mouse embryonic globin gene *hbb-bh1* as a surrogate for the human *HBG1/2* genes. We measured the target engagement in the mouse from whole blood. We concluded from the data

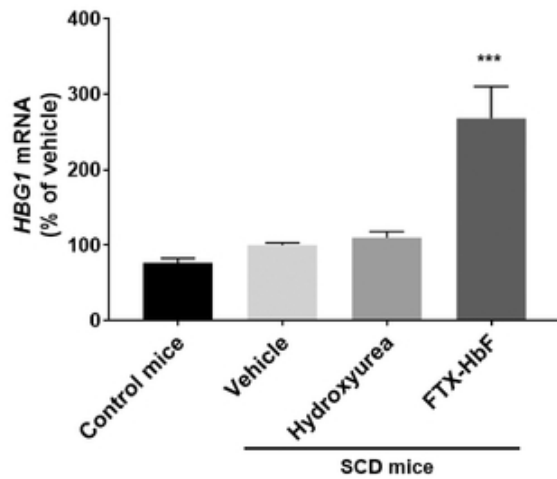
that FTX-HbF engaged the drug target *in vivo* and modulated the endogenous mouse globin gene expression program. The results of this study are depicted below.



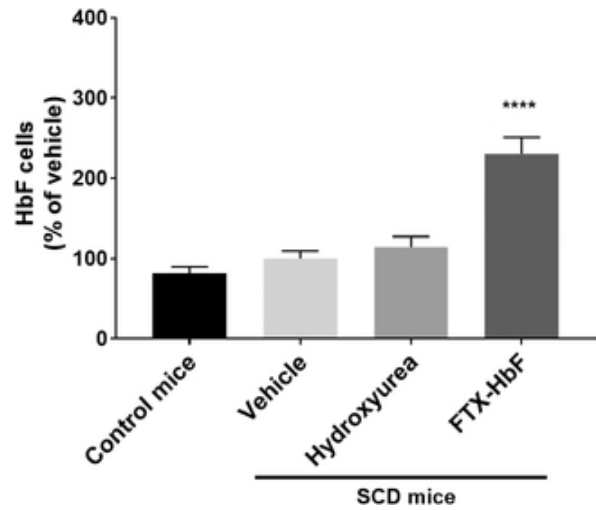
In the graphic on the left, we measured the amount of drug target engagement modification in mouse blood cells after five days of treatment. In the vehicle-treated mice, we observed maximum levels of protein modification, whereas in the FTX-HbF treated mice, we observed significantly lower levels of modification, which indicates significant target engagement. Each point represents the value for a different mouse, shown as a percent of the average vehicle-treated value. In the graphic on the right, we determined the level of mouse embryonic globin mRNA levels in mouse blood after five days of treatment. The data is from an average of four or five mice per treatment. In these studies, we used a conventional method of assessing statistical significance known as a two-tailed test. The p-value for each of the studies depicted above was 0.0005. A p-value is a conventional statistical method for measuring the statistical significance of experimental results. A p-value of less than 0.05 is generally considered to represent statistical significance, meaning that there is a less than five percent likelihood that the observed results occurred by chance.

Additionally, we studied FTX-HbF in a mouse model of SCD, known as the Townes mouse model. In this model, mouse globin genes have been replaced with human globin genes, thereby allowing investigations of mechanisms that may regulate human hemoglobin gene expression. The Townes mouse model has been widely used to study potential treatments for SCD. As shown in the figures below, we observed that FTX-HbF resulted in a significant increase in *HBG1* gene expression and HbF protein after 28 days of dosing at 5 mg/kg twice per day. Hydroxyurea did not result in a significant elevation of *HBG1* gene expression.

HBG1 mRNA levels in Townes mouse treated with FTX-HbF



HbF protein levels in Townes mouse treated with FTX-HbF



In the graphic on the left, we determined the level of human HBG1 mRNA for the four treatment conditions from mouse blood, shown as a percentage of vehicle-alone-treated SCD mice. In the graphic on the right, we determined the level of human HbF protein for the four treatment conditions, shown as a percentage of vehicle-alone-treated SCD mice. Each value represents the mean value from five or six mice per treatment after 28 days of treatment. In these studies, we used a conventional method of assessing statistical significance known as a one-way analysis of variance, or ANOVA. The p-value for the study depicted on the left was less than 0.0001 and the p-value for the study depicted on the right was less than 0.001.

Our Development Plan for FTX-HbF

We are currently conducting IND-enabling studies and intend to submit an IND for FTX-HbF in mid-2020. We intend to initiate a Phase 1 clinical trial of FTX-HbF in healthy volunteers in late 2020. The Phase 1 trial will be designed to investigate the safety and tolerability of single and multiple ascending doses of FTX-HbF and to define the relationship between PK and target engagement in blood.

Following completion of the Phase 1 trial, we would consider a parallel development path in SCD and b-thalassemia. We expect that our target SCD patient population will be adult SCD patients with inadequate disease control and that concomitant use of hydroxyurea and/or L-glutamine will be allowed when available. We expect that our target b-thalassemia patient population will be adult b-thalassemia patients who are not b⁰ but are transfusion-dependent.

Discovery Screening Programs

We have leveraged our proprietary product engine to discover targets that we are pursuing with small molecules for FSHD and SCD and b-thalassemia. We are leveraging the broad applicability of our product engine to discover drug targets for other rare, genetically defined diseases across neuromuscular and CNS diseases. We plan to complete four additional screens in 2019. These four diseases and our approach to identifying targets to address the root cause of each disease are further described below.

DISCOVERY SCREENING INDICATIONS	DIRECTION OF GENE MODULATION	DISCOVERY	PRECLINICAL	PHASE 1	PHASE 2	PHASE 3	STATUS
Duchenne Muscular Dystrophy	UTRN ↑	▶					Target ID / Validation
Friedreich Ataxia	FXN ↑	▶					Target ID / Validation
Myotonic Dystrophy 1	DMPK ↓	▶					Target ID / Validation
α-Synucleinopathies	SNCA ↓	▶					Target ID / Validation

We currently plan to conduct six additional screens in 2020, and we are undergoing a rigorous disease assessment and selection process. Although we believe our product engine and screening efforts are robust and have a high likelihood of identifying drug targets for each new screen area, we intend to focus on advancing the most attractive targets and development candidates identified from our screening efforts for development. We may also selectively consider external partnerships for those areas that may be more appropriate for a partner to advance.

Duchenne Muscular Dystrophy

Duchenne muscular dystrophy, or DMD, is the most common childhood-onset muscular dystrophy with a prevalence of approximately one out of every 3,500 male births. Patients usually are diagnosed before five years of age and typically require the use of wheelchairs before their teens. Life-threatening cardiac and respiratory complications result in a life expectancy of 20-30 years without any treatment. Currently, management of these complications by standard of care treatment (*e.g.*, corticosteroids) can extend life expectancy, however, there are no approved disease-modifying therapies. This X-chromosome linked disease is caused by mutations in the *DMD* gene resulting in the loss of expression or function of the protein dystrophin. Dystrophin is an integral component of a large multiprotein complex that functions by linking the sarcolemma (the plasma membrane in muscle fibers) with the cytoskeleton and other motor machinery. In the absence of dystrophin, progressive muscle fiber degeneration results in loss of function and clinical manifestation of the disease.

Our goal is to apply our product engine to identify drug targets to increase the expression of utrophin, a dystrophin-related protein, that can replace the function of dystrophin in the membrane and address the dysfunction due to damaged muscle fibers. Utrophin is normally expressed in other tissues and studies have shown that higher levels of this protein result in functional improvements in animal models of the disease.

Friedreich Ataxia

Friedreich ataxia, or FA, a neuromuscular disorder affecting about one out of every 40,000 people, is the most common hereditary ataxia, with a typical age of onset between 10 and 15 years. The progressive impaired muscle coordination, ataxia, is caused by the degeneration of neurons in the cerebellum and dorsal root ganglia in the spinal cord. FA patients also commonly suffer from life-threatening heart conditions such as hypertrophic cardiomyopathy, myocardial fibrosis and heart failure. There are no approved disease-modifying therapies. The genetic root cause of FA is an expansion of a sequence in the frataxin gene, *FXN*, which causes its downregulation. Loss of function of frataxin, an important protein involved in iron metabolism, results in oxidative stress and mitochondrial dysfunction.

Our goal is to apply our product engine to identify drug targets that can upregulate the levels of frataxin protein to levels that will impact and restore function to prevent neuronal and cardiac cell degeneration.

Myotonic Dystrophy 1

Myotonic dystrophy 1, or DM1, is the most common adult-onset muscular dystrophy affecting about one out of every 8,000 people, with a typical age of onset between 20 and 40 years. It is characterized by muscle weakness and myotonia. Cardiopulmonary complications when present can be life-threatening and current treatments are directed toward managing these complications. There are no approved disease-modifying therapies. DM1 is caused by expansion of a triple nucleotide repeat present in the non-coding region of the *DMPK* gene and are part of its mature transcript. More than 50 cytosine-thymine-guanine repeats are usually associated with pathology and disease severity is proportional to the number of repeats, which can expand to over 4,000. The accumulation of *DMPK* gene transcripts containing long repeats result in the sequestration of proteins important for the correct splicing of important transcripts participating in the function of skeletal and cardiac muscle and other tissues.

Our goal is to apply our product engine to identify drug targets that may lead to downregulation of the expression of the *DMPK* gene in order to reduce the levels of the pathological repeats and improve muscle function. Reduction of *DMPK* gene expression in DM1 models has been shown to reduce aberrant splicing and to be well tolerated.

***α*-Synucleinopathies**

In rare cases, α-Synucleinopathies result from point mutations and multiplications in the *SNCA* gene that encodes the protein α-synuclein. Familial forms of Parkinson's disease can result from these mutations and multiplications in the *SNCA* gene. Parkinson's disease is a common progressive neurodegenerative disease characterized by movement disorders such as bradykinesia, rigidity and tremor. Genome wide association studies have linked single nucleotide polymorphisms in *SNCA* with increased risk of Parkinson's disease. These mutations have been shown to increase levels of pathological, aggregated α-synuclein, leading to the loss of midbrain dopaminergic neurons important for motor control. Abnormal deposits of α-synuclein protein, or Lewy bodies, are the characteristic histological signature of Parkinson's disease at autopsy. According to the Parkinson's Foundation, nearly one million people will be living with Parkinson's disease in the United States by 2020.

Our goal is to use our product engine to identify drug targets for genetically defined α-synucleinopathies that may lead to reduction in α-synuclein levels in the most relevant cell type for Parkinson's disease—dopaminergic neurons. Our goal is to lower the overall α-synuclein load in the brain of patients with sporadic or genetic α-synucleinopathies by starting treatment early in their disease course to prevent further α-synuclein-dependent neurodegeneration, thus representing a potential disease-modifying approach across all α-synucleinopathies.

Right of Reference and License Agreement with GlaxoSmithKline

In February 2019, we entered into a right of reference and license agreement with affiliates of GSK, pursuant to which GSK granted us a right of reference to certain INDs filed with the FDA and controlled by GSK or its affiliates relating to losmapimod and an exclusive worldwide license under certain patent rights related to losmapimod. The agreement also provides us with an exclusive worldwide license to certain of GSK's preclinical and clinical data with respect to losmapimod. As partial consideration for the right of reference and licenses granted under the agreement, we issued 12,500,000 shares of our Series B preferred stock to GSK at the time we entered into the reference and license agreement. The agreement obligates us to use commercially reasonable efforts to develop and commercialize a licensed product for the treatment of FSHD.

The agreement grants us an exclusive, sublicensable license under the licensed patent rights and data rights to research, develop and commercialize losmapimod or any product containing losmapimod as an API, which we refer to as a licensed product, to treat disease in humans. GSK retained the right, without the right to grant sublicenses, to conduct nonclinical research under the licensed patents and data rights and, with our consent, GSK may engage in certain developmental activities relating to the use of a licensed product in connection with a specified prophylactic use. GSK also agreed to and has since transferred to us its existing manufactured supply of losmapimod.

Under the agreement, we will be obligated to make milestone payments to GSK aggregating up to \$37.5 million upon the achievement of specified clinical and regulatory milestones with respect to the first licensed product to achieve such milestones, and up to \$60.0 million upon the achievement of one-time aggregate annual worldwide net sales milestones. We will also be obligated to pay royalties ranging from a mid single-digit percentage to a low double-digit, but less than teens, percentage to GSK based on our, and any of our affiliates' and sublicensees', annual net sales of licensed products. The royalties are payable on a product-by-product and country-by-country basis, and may be reduced in specified circumstances.

Our obligation to make royalty payments extends with respect to a licensed product in a country until the earlier of the approval of a generic version of such licensed product by the applicable regulatory agency

in such country or the tenth anniversary of the first commercial sale of such licensed product in such country, which we refer to as the royalty term. Following the expiration of any exclusive marketing rights or data exclusivity rights granted by a regulatory authority, other than patent rights, for any licensed product on a country-by-country basis, the applicable royalty rate will be reduced. Additionally, if we or our affiliates or sublicensees determine that it is necessary to obtain a license from a third party under any patent rights to exploit a licensed product in a country, then we may deduct a certain percentage of the license fees under such third party license payable by us to the third party from the royalty payment that would otherwise be due to GSK in such country.

If, prior to our completion of the first Phase 2 clinical trial for a licensed product, we wish to sublicense any of the licensed patent or data rights granted to us under the agreement to any third party outside of the United States, we must notify GSK of the terms on which we propose to grant such sublicense. GSK has the right to enter into negotiations with us for such sublicense, and if GSK so elects, then we must negotiate in good faith with GSK for a prescribed period. If we and GSK do not agree to a sublicense of the relevant rights, we may sublicense the relevant rights to the third party on terms no less favorable than any terms offered to us by GSK.

The agreement continues on a country-by-country and licensed product-by-licensed product basis until the expiration of the royalty term in each country, at which time the agreement expires with respect to such licensed product in such country and we shall have a fully-paid up, royalty-free and perpetual license to the licensed patent rights and data with respect to such licensed product in such country. Either party has the right to terminate the agreement if the other party has materially breached in the performance of its obligations under the agreement and such breach has not been cured within the applicable cure period.

We also agreed to provide GSK the opportunity to purchase shares of common stock in this offering or in a concurrent private placement equal to the proportion that the shares of common stock held by GSK (assuming conversion of all preferred stock into common stock upon consummation of this offering) bear to the total number of shares of common stock immediately prior to the closing of this offering (assuming conversion of all preferred stock into common stock upon consummation of this offering and all outstanding options).

Intellectual Property

We strive to protect and enhance the proprietary technology, inventions and improvements that are commercially important to the development of our business, including by seeking, maintaining and defending patent rights, whether developed internally or licensed from third parties. We also rely on trade secrets, know-how, continuing technological innovation and in-licensing opportunities to develop, strengthen and maintain our proprietary position in our field.

Our future commercial success depends, in part, on our ability to: obtain and maintain patent and other proprietary protection for commercially important technology, inventions and know-how related to our business; defend and enforce in our intellectual property rights, in particular our patents rights; preserve the confidentiality of our trade secrets; and operate without infringing, misappropriating or violating the valid and enforceable patents and proprietary rights of third parties. Our ability to stop third parties from making, using, selling, offering to sell or importing our products may depend on the extent to which we have rights under valid and enforceable patents or trade secrets that cover these activities.

The patent positions of biotechnology and pharmaceutical companies like ours are generally uncertain and can involve complex legal, scientific and factual issues. We cannot predict whether the patent applications we are currently pursuing will issue as patents in any particular jurisdiction or whether the claims of any issued patents will provide sufficient proprietary protection from competitors. We also cannot ensure that patents will issue with respect to any patent applications that we or our licensors may file in the future, nor can we ensure that any of our owned or licensed patents or future patents will be commercially useful in protecting our product candidates and methods of manufacturing the same. In addition, the coverage claimed in a patent application may be significantly reduced before a patent is

issued, and its scope can be reinterpreted and even challenged after issuance. As a result, we cannot guarantee that any of our products will be protected or remain protectable by enforceable patents. Moreover, any patents that we hold may be challenged, circumvented or invalidated by third parties. See "Risk Factors—Risks Related to Our Intellectual Property" for a more comprehensive description of risks related to our intellectual property.

We generally file patent applications directed to our key programs in an effort to secure our intellectual property positions vis-a-vis these programs. As of June 30, 2019, we owned one allowed U.S. patent application, one U.S. pending non-provisional patent application, four foreign pending patent applications, three pending Patent Cooperation Treaty, or PCT, applications and four U.S. provisional patent applications.

The intellectual property portfolio for our most advanced programs as of June 30, 2019, is summarized below. Prosecution is a lengthy process, during which the scope of the claims initially submitted for examination by the U.S. Patent and Trademark Office may be significantly narrowed before issuance, if issued at all. We expect this may be the case with respect to some of our pending patent applications referred to below.

Losmapimod and Derivatives

The patent portfolio for losmapimod is based upon Fulcrum-owned patent applications and in-licensed patents directed to new methods of using losmapimod and other p38 inhibitors to treat FSHD, pharmaceutical compositions generically and specifically covering p38 inhibitors, and methods for identifying novel compositions to treat FSHD. As of June 30, 2019, we owned one allowed U.S. patent application, one U.S. pending non-provisional patent application, four foreign patent applications filed in Taiwan, Uruguay, Venezuela and Argentina and three pending PCT applications relating to our p38a/b program, primarily relating to methods of using losmapimod and certain other p38 inhibitors for the treatment of FSHD. On June 19, 2019, we were notified by the USPTO that a patent covering the use of losmapimod for the treatment of patients with FSHD will issue to us on July 9, 2019. We own the patent application relating to this patent and, once issued, we will own the patent. While we believe that the specific and generic claims contained in our allowed U.S. patent application provide protection for the method of using losmapimod for the treatment of FSHD, and is not implicated by invalidating prior art, third parties may nevertheless challenge such claims. If any such claims are invalidated or rendered unenforceable for any reason, we will lose valuable intellectual property rights and our ability to prevent others from competing with us would be impaired. Any U.S. or ex-U.S. patents that may issue from pending applications that we own, if any, for our p38a/b program are projected to have a statutory expiration date in 2038, excluding any additional term for patent term adjustments or patent term extension, if applicable.

Losmapimod is currently protected by patents owned by GSK (as a composition of matter and certain uses which do not include FSHD) and certain of these patents are licensed to us. As soon as the patents covering the composition of matter expire on February 10, 2023, or are no longer in-force, the GSK-licensed patents will no longer be a barrier to entry for any unclaimed new uses, including FSHD. Even during the term of these composition of matter patents, losmapimod can still be developed in the meantime in certain geographies, including in the United States, under safe harbor regulations.

FTX-HbF

As of June 30, 2019, the intellectual property portfolio for our FTX-HbF program includes one U.S. provisional patent application directed to pharmaceutical compositions generically and specifically covering inhibitors of a certain protein or protein complex that regulate fetal hemoglobin, as well as to methods for using and making these compositions. In order to continue to pursue protection based on this provisional patent application, we will need to file a PCT, foreign applications, and/or U.S. non-provisional patent application prior to the applicable deadline. If we do continue to pursue protection, any patents that

may issue from the non-provisional patent applications would be projected to have statutory expiration dates in 2039, excluding any additional term for patent term adjustments or patent term extension, if applicable. While we believe that the specific and generic claims, contained in our U.S. provisional patent application, if filed as U.S. non-provisional application, PCT application and/or foreign application(s), provide protection for the claimed pharmaceutical compositions and methods of use and are not implicated by invalidating prior art, third parties may nevertheless challenge such claims. If any such claims are invalidated or rendered unenforceable for any reason, we will lose valuable intellectual property rights and our ability to prevent others from competing with us would be impaired.

The term of individual patents depends upon the legal term of the patents in the countries in which they are obtained. In most countries in which we file, the patent term is 20 years from the earliest date of filing a non-provisional patent application.

In the United States, the term of a patent covering an FDA-approved drug may, in certain cases, be eligible for a patent term extension under the Drug Price Competition and Patent Term Restoration Act of 1984 as compensation for the loss of patent term during the FDA regulatory review process. The period of extension may be up to five years, but cannot extend the remaining term of a patent beyond a total of 14 years from the date of product approval. Only one patent among those eligible for an extension and only those claims covering the approved drug, a method for using it, or a method for manufacturing it may be extended. Similar provisions are available in Europe and in certain other jurisdictions to extend the term of a patent that covers an approved drug. It is possible that issued U.S. patents covering the use of losmapimod and products from our intellectual property may be entitled to patent term extensions. If our use of drug candidates or the drug candidate itself receive FDA approval, we intend to apply for patent term extensions, if available, to extend the term of patents that cover the approved use or drug candidate. We also intend to seek patent term extensions in any jurisdictions where available, however, there is no guarantee that the applicable authorities, including the FDA, will agree with our assessment of whether such extensions should be granted, and even if granted, the length of such extensions.

In addition to patent protection, we rely upon unpatented trade secrets and confidential know-how and continuing technological innovation to develop and maintain our competitive position. However, trade secrets and confidential know-how are difficult to protect. We seek to protect our proprietary information, in part, using confidentiality agreements with any collaborators, scientific advisors, employees and consultants and invention assignment agreements with our employees. We also have agreements requiring assignment of inventions with selected consultants, scientific advisors and collaborators. These agreements may not provide meaningful protection. These agreements may also be breached, and we may not have an adequate remedy for any such breach. In addition, our trade secrets and/or confidential know-how may become known or be independently developed by a third party, or misused by any collaborator to whom we disclose such information. Despite any measures taken to protect our intellectual property, unauthorized parties may attempt to copy aspects of our products or to obtain or use information that we regard as proprietary. Although we take steps to protect our proprietary information, third parties may independently develop the same or similar proprietary information or may otherwise gain access to our proprietary information. As a result, we may be unable to meaningfully protect our trade secrets and proprietary information. See "Risk Factors—Risks Related to our Intellectual Property" for a more comprehensive description of risks related to our intellectual property.

Manufacturing

We do not have any manufacturing facilities. We obtained sufficient losmapimod tablets, or drug product, from GSK to complete our planned Phase 2 clinical trials. We obtained losmapimod API from GSK and plan to engage a contract manufacturing organization to convert the API into losmapimod tablets. We believe that the quantity of API will be sufficient to complete further clinical trials in FSHD. We believe that we have all the necessary information from GSK to enable the required technology transfers to contract manufacturing organizations. We also intend to identify and engage contract

manufacturing organizations to prepare our own API and to manufacture tablets to support potential commercialization.

We expect to rely on third parties for the manufacture of FTX-HbF and any future product candidates for preclinical and clinical testing, as well as for commercial manufacture if our product candidates receive marketing approval. Our lead product candidates are small molecules and can be manufactured in reliable and reproducible synthetic processes from readily available starting materials. We expect to continue to develop product candidates that can be produced cost-effectively at contract manufacturing facilities.

Competition

The biotechnology and pharmaceutical industries are characterized by rapidly advancing technologies, intense competition and a strong emphasis on proprietary products. While we believe that our technologies, knowledge, experience and scientific resources provide us with competitive advantages, we face competition from many different sources, including major pharmaceutical, specialty pharmaceutical and biotechnology companies, academic institutions and governmental agencies and public and private research institutions. Any product candidates that we successfully develop and commercialize will compete with existing therapies and new therapies that may become available in the future.

Many of the companies against which we are competing or against which we may compete in the future have significantly greater financial resources and expertise in research and development, manufacturing, preclinical testing, conducting clinical trials, obtaining regulatory approvals and marketing approved products than we do. Mergers and acquisitions in the pharmaceutical and biotechnology industry may result in even more resources being concentrated among a smaller number of our competitors. Smaller or early stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies. These competitors also compete with us in recruiting and retaining qualified scientific and management personnel and establishing clinical trial sites and patient registration for clinical trials, as well as in acquiring technologies complementary to, or necessary for, our programs.

The key competitive factors affecting the success of all of our therapeutic product candidates, if approved, are likely to be their efficacy, safety, convenience, price, the effectiveness of companion diagnostics in guiding the use of related therapeutics, the level of generic competition and the availability of reimbursement from government and other third-party payors.

Our commercial opportunity could be reduced or eliminated if our competitors develop and commercialize products that are safer, more effective, have fewer or less severe side effects, are more convenient or are less expensive than any products that we may develop. Our competitors also may obtain FDA or other regulatory approval for their products more rapidly than we may obtain approval for ours, which could result in our competitors establishing a strong market position before we are able to enter the market. In addition, our ability to compete may be affected in many cases by insurers or other third-party payors seeking to encourage the use of generic products. If our product candidates achieve marketing approval, we expect that they will be priced at a significant premium over competitive generic products.

If our lead product candidates are approved for the indications for which we are currently undertaking clinical trials, they will compete with the therapies and currently marketed drugs discussed below.

FSHD

There are no approved therapies for the treatment of FSHD. Controlled trials of albuterol, corticosteroids and a myostatin inhibitor all failed to demonstrate a clinical benefit to patients with FSHD. Low-intensity aerobic exercise tailored to the patient's distribution of weakness may provide some limited beneficial effect. Limited range of motion in the shoulder girdle can stem from periscapular muscle weakness, and in such cases surgical scapular fixation can result in some functional improvement for

certain patients. There is also no standard practice regarding the use of physical or occupational therapy across countries and sites.

We are not aware of any product candidate currently in clinical development for FSHD with the same mechanism of action as losmapimod or that is designed to treat the root cause of FSHD. We are aware of ACE-083, a locally injected myostatin inhibitor for intermittent treatment of weakness for ankle dorsiflexion (foot drop) and elbow flexion, which is currently in Phase 2a clinical development for FSHD by Acceleron. aTyr Pharma, Inc., or aTyr, conducted a Phase 1/2 clinical trial of resolaris, a physiocrine immune modulation protein. aTyr discontinued development of resolaris in FSHD. aTyr publicly disclosed that they do not intend to further develop resolaris without a partner.

SCD

Approved drug treatments for SCD focus primarily on the management and reduction of pain episodes. The two drug treatments approved in the United States are hydroxyurea and L-glutamine. Hydroxyurea, marketed by Bristol-Myers Squibb Company, is approved for the treatment of anemia related to SCD, to reduce the frequency of painful crises and the need for blood transfusions. L-glutamine, marketed by Emmaus Life Sciences, Inc., is approved to reduce severe complications associated with the disorder.

Blood transfusions can be utilized to decrease the sickling of RBCs. While blood transfusions can be critically important to the management of SCD, there are a number of limitations associated with this therapeutic approach, including limited patient access and serious complications such as iron overload. The only potentially curative treatment currently approved for severe SCD is bone marrow transplantation. However, this treatment option is not commonly used given the difficulties of finding a suitable matched donor and the risks associated with the treatment, which include an approximately 5% mortality rate. Bone marrow transplantation is more commonly offered to pediatric patients with available sibling-matched donors.

FTX-HbF could face competition from a number of different therapeutic approaches in development for patients with SCD. Novartis is conducting Phase 3 clinical trials of crizanlizumab, an anti-P-selectin monoclonal antibody, for the prevention of vaso-occlusive crises in patients with SCD. In January 2019, Novartis announced that crizanlizumab was granted breakthrough therapy designation by the FDA, and that Novartis expected to file a BLA for crizanlizumab in the first half of 2019. Global Blood Therapeutics, Inc. is conducting a Phase 3 clinical trial of voxelotor (GBT440), a hemoglobin modifier, to prevent the sickling of RBCs. GlycoMimetics Inc. and Pfizer, Inc. are conducting a Phase 3 clinical trial of rivipansel (GMI-1070), a pan-selectin inhibitor. bluebird has been granted conditional marketing authorization by the European Commission for ZYNTEGLO, a gene therapy, as a one-time treatment for SCD that aims to treat SCD by inserting a functional human b-globin gene into the patient's own hematopoietic stem cells *ex vivo* and then transplanting the modified stem cell into the patient's bloodstream. EpiDestiny, Inc., or EpiDestiny, in collaboration with Novo Nordisk A/S, is evaluating EPI01, a small molecule designed to increase production of fetal hemoglobin, in Phase 2 clinical trials. Imara, Inc. is evaluating IMR-687, a PDE9 inhibitor, in a Phase 2a clinical trial in patients with sickle cell anemia. Aruvant Sciences, Inc. is evaluating RVT-1801, a gene therapy, in a Phase 1/2 trial. Sangamo Therapeutics Inc., or Sangamo, in collaboration with Bioverativ Inc., or Bioverativ, is developing BIVV-003, a gene editing cell therapy that modifies cells to produce functional RBCs using fetal hemoglobin. There are also several other gene editing approaches being evaluated by Intellia Therapeutics, Inc. (in collaboration with Novartis), Editas Medicine, Inc. and CRISPR Therapeutics AG (in collaboration with Vertex Pharmaceuticals Incorporated, or Vertex). Pfizer conducted a Phase 1b clinical trial with PF-04447943, a PDE9 inhibitor, in patients with SCD.

b-thalassemia

The current standard of care for many patients with b-thalassemia is frequent blood transfusions to manage anemia. The only potentially curative therapy for b-thalassemia is allogeneic hematopoietic stem cell transplant, which is associated with serious risk and is limited to patients with a suitable donor. The European Commission granted conditional marketing authorization for ZYNTEGLO, a gene therapy developed by bluebird for the treatment of adult and adolescent patients with transfusion-dependent b-thalassemia and with certain genotypes, in Europe in June 2019. bluebird announced that it plans to file a BLA in the United States in 2019.

FTX-HbF could face competition from a number of different therapeutic approaches are in development as a therapeutic option for patients with transfusion-dependent b-thalassemia. Acceleron, in collaboration with Celgene, is conducting Phase 3 clinical trials of luspatercept (ACE-536), an erythroid maturation agent. Celgene submitted a BLA for luspatercept for the treatment of adult patients with anemia associated with b-thalassemia and who require frequent transfusions. Celgene and Acceleron submitted a marketing authorization application, or MAA, to the EMA in the second quarter of 2019.

Bellicum Pharmaceuticals, Inc. is conducting a Phase 1/2 clinical trial to evaluate a modified donor T cell therapy to be used in conjunction with hematopoietic stem cell transplant. Kiadis Pharma is conducting Phase 2 and Phase 3 clinical trials of an adjunctive T cell immunotherapy treatment in conjunction with hematopoietic stem cell transplant. EpiDestiny, in collaboration with Novo Nordisk A/S, is evaluating EPI01, a small molecule designed to increase production of fetal hemoglobin, in Phase 2 clinical trials. Orchard Therapeutics plc is conducting Phase 2 clinical trials of OTL-300, an autologous *ex vivo* gene therapy for the treatment of transfusion-dependent b-thalassemia. Sangamo, in collaboration with Bioverativ, is conducting a Phase 1/2 clinical trial of ST-400, which uses a genome-edited cell therapy approach designed to produce functional RBCs using fetal hemoglobin. CRISPR Therapeutics AG, in collaboration with Vertex, is conducting a Phase 1/2 clinical trial of CTX001, which uses a gene editing approach to upregulate the expression of fetal hemoglobin, in patients with transfusion-dependent b-thalassemia.

Government Regulation and Product Approvals

Government authorities in the United States at the federal, state and local level, and in other countries and jurisdictions, including the European Union, extensively regulate, among other things, the research, development, testing, manufacture, pricing, reimbursement, quality control, approval, packaging, storage, recordkeeping, labeling, advertising, promotion, distribution, marketing, post-approval monitoring and reporting, and import and export of biopharmaceutical products. The processes for obtaining marketing approvals in the United States and in foreign countries and jurisdictions, along with compliance with applicable statutes and regulations and other regulatory authorities, require the expenditure of substantial time and financial resources.

Approval and Regulation of Drugs in the United States

In the United States, drug products are regulated under the Federal Food, Drug and Cosmetic Act, or FDCA, and applicable implementing regulations and guidance. The failure of an applicant to comply with the applicable regulatory requirements at any time during the product development process, including non-clinical testing, clinical testing, the approval process or post-approval process, may result in delays to the conduct of a study, regulatory review and approval and/or administrative or judicial sanctions. These sanctions may include, but are not limited to, the FDA's refusal to allow an applicant to proceed with clinical trials, refusal to approve pending applications, license suspension or revocation, withdrawal of an approval, imposition of a clinical hold, issuance of warning letters and other types of letters, adverse publicity, product recalls, product seizures, total or partial suspension of production or distribution, injunctions, fines, refusals of government contracts, restitution, disgorgement of profits or civil or criminal investigations and penalties brought by the FDA or Department of Justice, or DOJ, or other government entities, including state agencies.

An applicant seeking approval to market and distribute a new drug in the United States generally must satisfactorily complete each of the following steps before the product candidate will be approved by the FDA:

- preclinical testing including laboratory tests, animal studies and formulation studies, which must be performed in accordance with the FDA's good laboratory practice, or GLP, regulations and standards;
- submission to the FDA of an IND for human clinical testing, which must become effective before human clinical trials may begin;
- approval by an independent institutional review board, or IRB, representing each clinical site before each clinical trial may be initiated;
- performance of adequate and well-controlled human clinical trials to establish the safety, potency and purity of the product candidate for each proposed indication, in accordance with current good clinical practices, or GCP;
- preparation and submission to the FDA of a new drug application, or NDA, for a drug product which includes not only the results of the clinical trials, but also, detailed information on the chemistry, manufacture and quality controls for the product candidate and proposed labelling for one or more proposed indication(s);
- review of the product candidate by an FDA advisory committee, where appropriate or if applicable;
- satisfactory completion of an FDA inspection of the manufacturing facility or facilities, including those of third parties, at which the product candidate or components thereof are manufactured to assess compliance with current good manufacturing practices, or cGMP, requirements and to assure that the facilities, methods and controls are adequate to preserve the product's identity, strength, quality and purity;
- satisfactory completion of any FDA audits of the non-clinical and clinical trial sites to assure compliance with GCP and the integrity of clinical data in support of the NDA;
- payment of user fees and securing FDA approval of the NDA to allow marketing of the new drug product; and
- compliance with any post-approval requirements, including the potential requirement to implement a Risk Evaluation and Mitigation Strategy, or REMS, and the potential requirement to conduct any post-approval studies required by the FDA.

Preclinical Studies

Before an applicant begins testing a product candidate with potential therapeutic value in humans, the product candidate enters the preclinical testing stage, including *in vitro* and animal studies to assess the safety and activity of the drug for initial testing in humans and to establish a rationale for therapeutic use. Preclinical tests include laboratory evaluations of product chemistry, formulation and stability, as well as other studies to evaluate, among other things, the toxicity of the product candidate. The conduct of the preclinical tests and formulation of the compounds for testing must comply with federal regulations and requirements, including GLP regulations and standards. The results of the preclinical tests, together with manufacturing information, analytical data, any available clinical data or literature and plans for clinical trials, among other things, are submitted to the FDA as part of an IND. Some long-term preclinical testing, such as animal tests of reproductive adverse events and carcinogenicity and long-term toxicity studies may continue after the IND is submitted.

The IND and IRB Processes

Clinical trials involve the administration of the investigational product to human subjects under the supervision of qualified investigators in accordance with GCP requirements, which include, among other

things, the requirement that all research subjects provide their voluntary informed consent in writing before their participation in any clinical trial. Clinical trials are conducted under written study protocols detailing, among other things, the inclusion and exclusion criteria, the objectives of the study, the parameters to be used in monitoring safety and the effectiveness criteria to be evaluated. A protocol for each clinical trial and any subsequent protocol amendments must be submitted to the FDA as part of the IND.

An IND is an exemption from the FDCA that allows an unapproved product candidate to be shipped in interstate commerce for use in an investigational clinical trial and a request for FDA authorization to administer such investigational product to humans. Such authorization must be secured prior to interstate shipment and administration of any product candidate that is not the subject of an approved NDA. In support of a request for an IND, applicants must submit a protocol for each clinical trial, and any subsequent protocol amendments must be submitted to the FDA as part of the IND. In addition, the results of the preclinical tests, together with manufacturing information, analytical data, any available clinical data or literature and plans for clinical trials, among other things, must be submitted to the FDA as part of an IND. The FDA requires a 30-day waiting period after the filing of each IND before clinical trials may begin. This waiting period is designed to allow the FDA to review the IND to determine whether human research subjects will be exposed to unreasonable health risks. At any time during this 30-day period or thereafter, the FDA may raise concerns or questions about the conduct of the trials as outlined in the IND and impose a clinical hold or partial clinical hold. In these cases, the IND sponsor and the FDA must resolve any outstanding concerns before clinical trials can begin.

Following commencement of a clinical trial under an IND, the FDA may also place a clinical hold or partial clinical hold on that trial. Clinical holds are imposed by the FDA whenever there is concern for patient safety and may be a result of new data, findings, or developments in clinical, nonclinical, and/or chemistry, manufacturing, and controls. A clinical hold is an order issued by the FDA to the sponsor to delay a proposed clinical investigation or to suspend an ongoing investigation. A partial clinical hold is a delay or suspension of only part of the clinical work requested under the IND. For example, a specific protocol or part of a protocol may not be allowed to proceed, while other protocols may be allowed. No more than 30 days after imposition of a clinical hold or partial clinical hold, the FDA will provide the sponsor a written explanation of the basis for the hold. Following issuance of a clinical hold or partial clinical hold, a clinical trial may only resume after the FDA has so notified the sponsor. The FDA will base that determination on information provided by the sponsor correcting the deficiencies previously cited or otherwise satisfying the FDA that the clinical trial can proceed.

A sponsor may choose, but is not required, to conduct a foreign clinical study under an IND. When a foreign clinical study is conducted under an IND, all FDA IND requirements must be met unless waived. When a foreign clinical study is not conducted under an IND, the sponsor must ensure that the study complies with certain regulatory requirements of the FDA in order to use the study as support for an IND or application for marketing approval. Specifically, on April 28, 2008, the FDA amended its regulations governing the acceptance of foreign clinical studies not conducted under an investigational new drug application as support for an IND or a new drug application. The final rule provides that such studies must be conducted in accordance with GCP, including review and approval by an independent ethics committee, or IEC, and informed consent from subjects. The GCP requirements in the final rule encompass both ethical and data integrity standards for clinical studies. The FDA's regulations are intended to help ensure the protection of human subjects enrolled in non-IND foreign clinical studies, as well as the quality and integrity of the resulting data. They further help ensure that non-IND foreign studies are conducted in a manner comparable to that required for IND studies.

In addition to the foregoing IND requirements, an IRB representing each institution participating in the clinical trial must review and approve the plan for any clinical trial before it commences at that institution, and the IRB must conduct continuing review and reapprove the study at least annually. The IRB must review and approve, among other things, the study protocol and informed consent information to be provided to study subjects. An IRB must operate in compliance with FDA regulations. An IRB can

suspend or terminate approval of a clinical trial at its institution, or an institution it represents, if the clinical trial is not being conducted in accordance with the IRB's requirements or if the product candidate has been associated with unexpected serious harm to patients.

Additionally, some trials are overseen by an independent group of qualified experts organized by the trial sponsor, known as a data safety monitoring board or committee. This group provides authorization as to whether or not a trial may move forward at designated check points based on access that only the group maintains to available data from the study. Suspension or termination of development during any phase of clinical trials can occur if it is determined that the participants or patients are being exposed to an unacceptable health risk. Other reasons for suspension or termination may be made by us based on evolving business objectives and/or the competitive environment.

Information about clinical trials must be submitted within specific timeframes to the NIH for public dissemination on its ClinicalTrials.gov website.

Expanded Access to an Investigational Drug for Treatment Use

Expanded access, sometimes called "compassionate use," is the use of investigational new drug products outside of clinical trials to treat patients with serious or immediately life-threatening diseases or conditions when there are no comparable or satisfactory alternative treatment options. The rules and regulations related to expanded access are intended to improve access to investigational drugs for patients who may benefit from investigational therapies. FDA regulations allow access to investigational drugs under an IND by the company or the treating physician for treatment purposes on a case-by-case basis for: individual patients (single-patient IND applications for treatment in emergency settings and non-emergency settings); intermediate-size patient populations; and larger populations for use of the drug under a treatment protocol or Treatment IND Application.

When considering an IND application for expanded access to an investigational product with the purpose of treating a patient or a group of patients, the sponsor and treating physicians or investigators will determine suitability when all of the following criteria apply: patient(s) have a serious or immediately life-threatening disease or condition, and there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the disease or condition; the potential patient benefit justifies the potential risks of the treatment and the potential risks are not unreasonable in the context or condition to be treated; and the expanded use of the investigational drug for the requested treatment will not interfere with the initiation, conduct, or completion of clinical investigations that could support marketing approval of the product or otherwise compromise the potential development of the product.

On December 13, 2016, the 21st Century Cures Act, or the Cures Act, established (and the 2017 Food and Drug Administration Reauthorization Act later amended) a requirement that sponsors of one or more investigational drugs for the treatment of a serious disease(s) or condition(s) make publicly available their policy for evaluating and responding to requests for expanded access for individual patients. Although these requirements were rolled out over time, they have now come into full effect. This provision requires drug and biologic companies to make publicly available their policies for expanded access for individual patient access to products intended for serious diseases. Sponsors are required to make such policies publicly available upon the earlier of initiation of a Phase 2 or Phase 3 study; or 15 days after the drug or biologic receives designation as a breakthrough therapy, fast track product, or regenerative medicine advanced therapy.

In addition, on May 30, 2018, the Right to Try Act, was signed into law. The law, among other things, provides a federal framework for certain patients to access certain investigational new drug products that have completed a Phase I clinical trial and that are undergoing investigation for FDA approval. Under certain circumstances, eligible patients can seek treatment without enrolling in clinical trials and without obtaining FDA permission under the FDA expanded access program. There is no obligation for a drug manufacturer to make its drug products available to eligible patients as a result of the Right to Try Act, but the manufacturer must develop an internal policy and respond to patient requests according to that policy.

Human Clinical Trials in Support of an NDA

Clinical trials involve the administration of the investigational product candidate to human subjects under the supervision of a qualified investigator in accordance with GCP requirements, which include, among other things, the requirement that all research subjects provide their informed consent in writing before their participation in any clinical trial. Clinical trials are conducted under written clinical trial protocols detailing, among other things, the objectives of the study, inclusion and exclusion criteria, the parameters to be used in monitoring safety and the effectiveness criteria to be evaluated.

Human clinical trials are typically conducted in three sequential phases, but the phases may overlap or be combined. Additional studies may also be required after approval.

Phase 1 clinical trials are initially conducted in a limited population to test the product candidate for safety, including adverse effects, dose tolerance, absorption, metabolism, distribution, excretion and pharmacodynamics in healthy humans or in patients. During Phase 1 clinical trials, information about the investigational drug product's pharmacokinetics and pharmacological effects may be obtained to permit the design of well-controlled and scientifically valid Phase 2 clinical trials.

Phase 2 clinical trials are generally conducted in a limited patient population to identify possible adverse effects and safety risks, evaluate the efficacy of the product candidate for specific targeted indications and determine dose tolerance and optimal dosage. Multiple Phase 2 clinical trials may be conducted by the sponsor to obtain information prior to beginning larger and more costly Phase 3 clinical trials. Phase 2 clinical trials are well controlled, closely monitored and conducted in a limited patient population.

Phase 3 clinical trials proceed if the Phase 2 clinical trials demonstrate that a dose range of the product candidate is potentially effective and has an acceptable safety profile. Phase 3 clinical trials are undertaken within an expanded patient population to further evaluate dosage, provide substantial evidence of clinical efficacy and further test for safety in an expanded and diverse patient population at multiple, geographically dispersed clinical trial sites. A well-controlled, statistically robust Phase 3 clinical trial may be designed to deliver the data that regulatory authorities will use to decide whether or not to approve, and, if approved, how to appropriately label a drug. Such Phase 3 studies are referred to as "pivotal."

In some cases, the FDA may approve an NDA for a product candidate but require the sponsor to conduct additional clinical trials to further assess the product candidate's safety and effectiveness after approval. Such post-approval trials are typically referred to as Phase 4 clinical trials. These studies are used to gain additional experience from the treatment of a larger number of patients in the intended treatment group and to further document a clinical benefit in the case of drugs approved under accelerated approval regulations. Failure to exhibit due diligence with regard to conducting Phase 4 clinical trials could result in withdrawal of approval for products.

Progress reports detailing the results of the clinical trials must be submitted at least annually to the FDA and more frequently if serious adverse events occur. In addition, IND safety reports must be submitted to the FDA for any of the following: serious and unexpected suspected adverse reactions; findings from other studies or animal or *in vitro* testing that suggest a significant risk in humans exposed to the product; and any clinically important increase in the case of a serious suspected adverse reaction over that listed in the protocol or investigator brochure. Phase 1, Phase 2 and Phase 3 clinical trials may not be completed successfully within any specified period, or at all. Furthermore, the FDA or the sponsor may suspend or terminate a clinical trial at any time on various grounds, including a finding that the research subjects are being exposed to an unacceptable health risk. Similarly, an IRB can suspend or terminate approval of a clinical trial at its institution, or an institution it represents, if the clinical trial is not being conducted in accordance with the IRB's requirements or if the product has been associated with unexpected serious harm to patients. The FDA will typically inspect one or more clinical sites to assure compliance with GCP and the integrity of the clinical data submitted.

Concurrent with clinical trials, companies often complete additional animal studies. They must also develop additional information about the chemistry and physical characteristics of the drug as well as finalize a process for manufacturing the product in commercial quantities in accordance with cGMP requirements. The manufacturing process must be capable of consistently producing quality batches of the drug candidate and, among other things, must develop methods for testing the identity, strength, quality, purity, and potency of the final drug. Additionally, appropriate packaging must be selected and tested and stability studies must be conducted to demonstrate that the drug candidate does not undergo unacceptable deterioration over its shelf life.

Pediatric Studies

Under the Pediatric Research Equity Act of 2003, an NDA or supplement thereto must contain data that are adequate to assess the safety and effectiveness of the product for the claimed indications in all relevant pediatric subpopulations and to support dosing and administration for each pediatric subpopulation for which the product is safe and effective. Sponsors must also submit pediatric study plans prior to the assessment data. Those plans must contain an outline of the proposed pediatric study or studies the applicant plans to conduct, including study objectives and design, any deferral or waiver requests and other information required by regulation. The applicant, the FDA, and the FDA's internal review committee must then review the information submitted, consult with each other and agree upon a final plan. The FDA or the applicant may request an amendment to the plan at any time.

For drugs intended to treat a serious or life-threatening disease or condition, the FDA must, upon the request of an applicant, meet to discuss preparation of the initial pediatric study plan or to discuss deferral or waiver of pediatric assessments. In addition, the FDA will meet early in the development process to discuss pediatric study plans with sponsors, and the FDA must meet with sponsors by no later than the end-of-phase 1 meeting for serious or life-threatening diseases and by no later than ninety (90) days after the FDA's receipt of the study plan.

The FDA may, on its own initiative or at the request of the applicant, grant deferrals for submission of some or all pediatric data until after approval of the product for use in adults, or full or partial waivers from the pediatric data requirements. Additional requirements and procedures relating to deferral requests and requests for extension of deferrals are contained in the Food and Drug Administration Safety and Innovation Act in 2012. Unless otherwise required by regulation, the pediatric data requirements do not apply to products with orphan designation.

Review and Approval of an NDA

In order to obtain approval to market a drug product in the United States, a marketing application must be submitted to the FDA that provides sufficient data establishing the safety, purity and potency of the proposed drug product for its intended indication. The application includes all relevant data available from pertinent preclinical and clinical trials, including negative or ambiguous results as well as positive findings, together with detailed information relating to the product's chemistry, manufacturing, controls and proposed labeling, among other things. Data can come from company-sponsored clinical trials intended to test the safety and effectiveness of a use of a product, or from a number of alternative sources, including studies initiated by independent investigators. To support marketing approval, the data submitted must be sufficient in quality and quantity to establish the safety, purity and potency of the drug product to the satisfaction of the FDA.

The NDA is a vehicle through which applicants formally propose that the FDA approve a new product for marketing and sale in the United States for one or more indications. Every new non-biologic drug product candidate must be the subject of an approved NDA before it may be commercialized in the United States. BLAs are submitted for approval of biologic products. Under federal law, the submission of most NDAs is subject to an application user fee, which for federal fiscal year 2019 is \$2,588,478 for an application requiring clinical data. The sponsor of an approved NDA is also subject to an annual program fee, which for fiscal year 2019 is \$309,915. Certain exceptions and waivers are available for some of these

fees, such as an exception from the application fee for products with orphan designation, an exception from the program fee when the program does not engage in manufacturing the drug during a particular fiscal year and a waiver for certain small businesses.

The FDA conducts a preliminary review of the application, generally within 60 calendar days of its receipt, and strives to inform the sponsor within 74 days whether the application is sufficiently complete to permit substantive review. The FDA may request additional information rather than accept the application for filing. In this event, the application must be resubmitted with the additional information. The resubmitted application is also subject to review before the FDA accepts it for filing. Once the submission is accepted for filing, the FDA begins an in-depth substantive review. The FDA has agreed to specified performance goals in the review process of NDAs. Under that agreement, 90% of applications seeking approval of New Molecular Entities, or NMEs, are meant to be reviewed within ten months from the date on which the FDA accepts the application for filing, and 90% of applications for NMEs that have been designated for Priority Review are meant to be reviewed within six months of the filing date. For applications seeking approval of products that are not NMEs, the ten-month and six-month review periods run from the date that the FDA receives the application. The review process and the Prescription Drug User Fee Act, or PDUFA, goal date may be extended by the FDA for three additional months to consider new information or clarification provided by the applicant to address an outstanding deficiency identified by the FDA following the original submission.

Before approving an application, the FDA typically will inspect the facility or facilities where the product is being or will be manufactured. These pre-approval inspections may cover all facilities associated with an NDA submission, including component manufacturing, finished product manufacturing and control testing laboratories. The FDA will not approve an application unless it determines that the manufacturing processes and facilities are in compliance with cGMP requirements and adequate to assure consistent production of the product within required specifications. Additionally, before approving an NDA, the FDA will typically inspect one or more clinical sites to assure compliance with GCP. Under the FDA Reauthorization Act of 2017, the FDA must implement a protocol to expedite review of responses to inspection reports pertaining to certain applications, including applications for products in shortage or those for which approval is dependent on remediation of conditions identified in the inspection report.

In addition, as a condition of approval, the FDA may require an applicant to develop a REMS. A REMS uses risk-minimization strategies beyond the professional labeling to ensure that the benefits of the product outweigh the potential risks. To determine whether a REMS is needed, the FDA will consider the size of the population likely to use the product, the seriousness of the disease, the expected benefit of the product, the expected duration of treatment, the seriousness of known or potential adverse events and whether the product is a new molecular entity.

The FDA may refer an application for a novel product to an advisory committee or explain why such referral was not made. Typically, an advisory committee is a panel of independent experts, including clinicians and other scientific experts, that review, evaluate and provide a recommendation as to whether the application should be approved and under what conditions. The FDA is not bound by the recommendations of an advisory committee, but the FDA considers such recommendations carefully when making decisions.

Fast Track, Breakthrough Therapy, Priority Review and Regenerative Advanced Therapy Designations

The FDA is authorized to designate certain products for expedited review if they are intended to address an unmet medical need in the treatment of a serious or life-threatening disease or condition. These programs are referred to as Fast Track designation, Breakthrough Therapy designation, Priority Review designation and Regenerative Advanced Therapy designation.

Specifically, the FDA may designate a product for Fast Track review if it is intended, whether alone or in combination with one or more other products, for the treatment of a serious or life-threatening disease or condition and it demonstrates the potential to address unmet medical needs for such a disease or

condition. For Fast Track products, sponsors may have greater interaction with the FDA, and the FDA may initiate review of sections of a Fast Track product's application before the application is complete. This rolling review may be available if the FDA determines, after preliminary evaluation of clinical data submitted by the sponsor, that a Fast Track product may be effective. The sponsor must also provide, and the FDA must approve, a schedule for the submission of the remaining information, and the sponsor must pay applicable user fees. However, the FDA's time-period goal for reviewing a Fast Track application does not begin until the last section of the application is submitted. In addition, the Fast Track designation may be withdrawn by the FDA if the FDA believes that the designation is no longer supported by data emerging in the clinical trial process.

Second, a product may be designated as a Breakthrough Therapy if it is intended, either alone or in combination with one or more other products, to treat a serious or life-threatening disease or condition and preliminary clinical evidence indicates that the product may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. The FDA may take certain actions with respect to Breakthrough Therapies, including holding meetings with the sponsor throughout the development process; providing timely advice to the product sponsor regarding development and approval; involving more senior staff in the review process; assigning a cross-disciplinary project lead for the review team and taking other steps to design the clinical trials in an efficient manner.

Third, the FDA may designate a product for Priority Review if it treats a serious condition and, if approved, would provide a significant improvement in safety or effectiveness. The FDA determines, on a case-by-case basis, whether the proposed product represents a significant improvement when compared with other available therapies. Significant improvement may be illustrated by evidence of increased effectiveness in the treatment of a condition, elimination or substantial reduction of a treatment-limiting product reaction, documented enhancement of patient compliance that may lead to improvement in serious outcomes, and evidence of safety and effectiveness in a new subpopulation. A Priority Review designation is intended to direct overall attention and resources to the evaluation of such applications and to shorten the FDA's goal for taking action on a marketing application from ten months to six months.

With passage of the Cures Act in December 2016, Congress authorized the FDA to accelerate review and approval of products designated as Regenerative Advanced Therapies. A product is eligible for this designation if it is a regenerative medicine therapy that is intended to treat, modify, reverse or cure a serious or life-threatening disease or condition and if preliminary clinical evidence indicates that the product has the potential to address unmet medical needs for such disease or condition. The benefits of a Regenerative Advanced Therapy designation include early interactions with the FDA to expedite development and review, benefits available to breakthrough therapies, potential eligibility for Priority Review and accelerated approval based on surrogate or intermediate endpoints.

Accelerated Approval Pathway

The FDA may grant accelerated approval to a product for a serious or life-threatening condition that provides meaningful therapeutic advantage to patients over existing treatments based upon a determination that the product has an effect on a surrogate endpoint that is reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit. The FDA may also grant accelerated approval for such a condition when the product has an effect on an intermediate clinical endpoint that can be measured earlier than an effect on irreversible morbidity or mortality, or IMM, and that is reasonably likely to predict an effect on IMM or other clinical benefit, taking into account the severity, rarity or prevalence of the condition and the availability or lack of alternative treatments. Products granted accelerated approval must meet the same statutory standards for safety and effectiveness as those granted traditional approval.

For the purposes of accelerated approval, a surrogate endpoint is a marker, such as a laboratory measurement, radiographic image, physical sign, efficacy biomarker or other measure that is thought to

predict clinical benefit but is not itself a measure of clinical benefit. Surrogate endpoints can often be measured more easily or more rapidly than clinical endpoints. An intermediate clinical endpoint is a measurement of a therapeutic effect that is considered reasonably likely to predict the clinical benefit of a drug, such as an effect on IMM. The FDA has limited experience with accelerated approvals based on intermediate clinical endpoints but has indicated that such endpoints generally may support accelerated approval where the therapeutic effect measured by the endpoint is not itself a clinical benefit and basis for traditional approval, if there is a basis for concluding that the therapeutic effect is reasonably likely to predict the ultimate clinical benefit of a product.

The accelerated approval pathway is most often used in settings in which the course of a disease is long and an extended period of time is required to measure the intended clinical benefit of a product, even if the effect on the surrogate or intermediate clinical endpoint occurs rapidly. The benefit of accelerated approval derives from the potential to receive approval based on surrogate endpoints sooner than possible for trials with clinical or survival endpoints, rather than deriving from any explicit shortening of the FDA approval timeline, as is the case with Priority Review.

The accelerated approval pathway is usually contingent on a sponsor's agreement to conduct, in a diligent manner, additional post-approval confirmatory studies to verify and describe the product's clinical benefit. As a result, a product candidate approved on this basis is subject to rigorous post-marketing compliance requirements, including the completion of Phase 4 or post-approval clinical trials to confirm the effect on the clinical endpoint. Failure to conduct required post-approval studies, or to confirm a clinical benefit during post-marketing studies, would allow the FDA to initiate expedited proceedings to withdraw approval of the product. All promotional materials for product candidates approved under accelerated regulations are subject to prior review by the FDA.

The FDA's Decision on an NDA

On the basis of the FDA's evaluation of the application and accompanying information, including the results of the inspection of the manufacturing facilities, the FDA may issue an approval letter or a complete response letter. An approval letter authorizes commercial marketing of the product with specific prescribing information for specific indications. A complete response letter generally outlines the deficiencies in the submission and may require substantial additional testing or information in order for the FDA to reconsider the application. If and when those deficiencies have been addressed to the FDA's satisfaction in a resubmission of the NDA, the FDA will issue an approval letter. The FDA has committed to reviewing such resubmissions in two or six months depending on the type of information included. Even with submission of this additional information, the FDA ultimately may decide that the application does not satisfy the regulatory criteria for approval.

If the FDA approves a new product, it may limit the approved indications for use of the product, require that contraindications, warnings or precautions be included in the product labeling, or require that post-approval studies, including Phase 4 clinical trials, be conducted to further assess the drug's safety after approval. The agency may also require testing and surveillance programs to monitor the product after commercialization, or impose other conditions, including distribution restrictions or other risk management mechanisms, including a REMS, to help ensure that the benefits of the product outweigh the potential risks. REMS programs can include medication guides, communication plans for health care professionals, and elements to assure safe use, or ETASU. ETASU can include, but are not limited to, special training or certification for prescribing or dispensing, dispensing only under certain circumstances, special monitoring and the use of patent registries. The FDA may prevent or limit further marketing of a product based on the results of post-market studies or surveillance programs. The FDA may require a REMS before or after approval if it becomes aware of a serious risk associated with use of the product. The requirement for a REMS can materially affect the potential market and profitability of a product. After approval, many types of changes to the approved product, such as adding new indications, changing manufacturing processes and adding labeling claims, are subject to further testing requirements and FDA review and approval.

Post-Approval Regulation

If regulatory approval for marketing of a product or new indication for an existing product is obtained, the sponsor will be required to comply with all regular post-approval regulatory requirements as well as any post-approval requirements that the FDA may have imposed as part of the approval process. The sponsor will be required to report, among other things, certain adverse reactions and manufacturing problems to the FDA, provide updated safety and efficacy information and comply with requirements concerning advertising and promotional labeling requirements. Manufacturers and certain of their subcontractors are required to register their establishments with the FDA and certain state agencies and are subject to periodic unannounced inspections by the FDA and certain state agencies for compliance with ongoing regulatory requirements, including cGMP regulations, which impose certain procedural and documentation requirements upon manufacturers. Changes to the manufacturing process are strictly regulated and often require prior FDA approval before being implemented. Accordingly, the sponsor and its third-party manufacturers must continue to expend time, money and effort in the areas of production and quality control to maintain compliance with cGMP regulations and other regulatory requirements.

A product may also be subject to official lot release, meaning that the manufacturer is required to perform certain tests on each lot of the product before it is released for distribution. If the product is subject to official release, the manufacturer must submit to the FDA samples of each lot, together with a release protocol showing a summary of the history of manufacture of the lot and the results of all of the manufacturer's tests performed on the lot. The FDA may also perform certain confirmatory tests on lots of some products before releasing the lots for distribution. Finally, the FDA will conduct laboratory research related to the safety, purity, potency and effectiveness of pharmaceutical products.

Once an approval is granted, the FDA may withdraw the approval if compliance with regulatory requirements is not maintained or if problems occur after the product reaches the market. Later discovery of previously unknown problems with a product, including adverse events of unanticipated severity or frequency, or with manufacturing processes, or failure to comply with regulatory requirements, may result in revisions to the approved labeling to add new safety information; imposition of post-market studies or clinical trials to assess safety risks; or imposition of distribution or other restrictions under a REMS program. Other potential consequences include, among other things:

- restrictions on the marketing or manufacturing of the product, complete withdrawal of the product from the market or product recalls;
- fines, warning letters or holds on post-approval clinical trials;
- refusal of the FDA to approve pending applications or supplements to approved applications, or suspension or revocation of product license approvals;
- product seizure or detention, or refusal to permit the import or export of products; or
- injunctions or the imposition of civil or criminal penalties.

The FDA strictly regulates the marketing, labeling, advertising and promotion of prescription drug products placed on the market. This regulation includes, among other things, standards and regulations for direct-to-consumer advertising, communications regarding unapproved uses, industry-sponsored scientific and educational activities, and promotional activities involving the Internet and social media. Promotional claims about a drug's safety or effectiveness are prohibited before the drug is approved. After approval, a drug product generally may not be promoted for uses that are not approved by the FDA, as reflected in the product's prescribing information. In the United States, health care professionals are generally permitted to prescribe drugs for such uses not described in the drug's labeling, known as off-label uses, because the FDA does not regulate the practice of medicine. However, FDA regulations impose rigorous restrictions on manufacturers' communications, prohibiting the promotion of off-label uses. It may be permissible, under very specific, narrow conditions, for a manufacturer to engage in nonpromotional, non-misleading

communication regarding off-label information, such as distributing scientific or medical journal information.

If a company is found to have promoted off-label uses, it may become subject to adverse public relations and administrative and judicial enforcement by the FDA, the DOJ, or the Office of the Inspector General of the Department of Health and Human Services, as well as state authorities. This could subject a company to a range of penalties that could have a significant commercial impact, including civil and criminal fines and agreements that materially restrict the manner in which a company promotes or distributes drug products. The federal government has levied large civil and criminal fines against companies for alleged improper promotion, and has also requested that companies enter into consent decrees or permanent injunctions under which specified promotional conduct is changed or curtailed.

In addition, the distribution of prescription pharmaceutical products is subject to the Prescription Drug Marketing Act, or PDMA, and its implementing regulations, as well as the Drug Supply Chain Security Act, or DSCA, which regulate the distribution and tracing of prescription drug samples at the federal level, and set minimum standards for the regulation of distributors by the states. The PDMA, its implementing regulations and state laws limit the distribution of prescription pharmaceutical product samples, and the DSCA imposes requirements to ensure accountability in distribution and to identify and remove counterfeit and other illegitimate products from the market.

Section 505(b)(2) NDAs

NDAs for most new drug products are based on two full clinical studies which must contain substantial evidence of the safety and efficacy of the proposed new product for the proposed use. These applications are submitted under Section 505(b)(1) of the FDCA. The FDA is, however, authorized to approve an alternative type of NDA under Section 505(b)(2) of the FDCA. This type of application allows the applicant to rely, in part, on the FDA's previous findings of safety and efficacy for a similar product, or published literature. Specifically, Section 505(b)(2) applies to NDAs for a drug for which the investigations made to show whether or not the drug is safe for use and effective in use and relied upon by the applicant for approval of the application "were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted."

Thus, Section 505(b)(2) authorizes the FDA to approve an NDA based on safety and effectiveness data that were not developed by the applicant. NDAs filed under Section 505(b)(2) may provide an alternate and potentially more expeditious pathway to FDA approval for new or improved formulations or new uses of previously approved products. If the 505(b)(2) applicant can establish that reliance on the FDA's previous approval is scientifically appropriate, the applicant may eliminate the need to conduct certain preclinical or clinical studies of the new product. The FDA may also require companies to perform additional studies or measurements to support the change from the approved product. The FDA may then approve the new drug candidate for all or some of the label indications for which the referenced product has been approved, as well as for any new indication sought by the Section 505(b)(2) applicant.

Abbreviated New Drug Applications for Generic Drugs

In 1984, with passage of the Hatch-Waxman Amendments to the FDCA, Congress established an abbreviated regulatory scheme authorizing the FDA to approve generic drugs that are shown to contain the same active ingredients as, and to be bioequivalent to, drugs previously approved by the FDA pursuant to NDAs. To obtain approval of a generic drug, an applicant must submit an Abbreviated New Drug Application, or ANDA, to the agency. An ANDA is a comprehensive submission that contains, among other things, data and information pertaining to the active pharmaceutical ingredient, bioequivalence, drug product formulation, specifications and stability of the generic drug, as well as analytical methods, manufacturing process validation data and quality control procedures. ANDAs are abbreviated because

they generally do not include preclinical and clinical data to demonstrate safety and effectiveness. Instead, in support of such applications, a generic manufacturer may rely on the preclinical and clinical testing previously conducted for a drug product previously approved under an NDA, known as the reference-listed drug, or RLD.

Specifically, in order for an ANDA to be approved, the FDA must find that the generic version is identical to the RLD with respect to the active ingredients, route of administration, dosage form, strength and conditions of use of the drug. At the same time, the FDA must also determine that the generic drug is bioequivalent to the innovator drug. Under the statute, a generic drug is bioequivalent to a RLD if "the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug." Upon approval of an ANDA, the FDA indicates whether the generic product is "therapeutically equivalent" to the RLD in its publication "Approved Drug Products with Therapeutic Equivalence Evaluations," also referred to as the "Orange Book." Physicians and pharmacists consider a therapeutic equivalent generic drug to be fully substitutable for the RLD. In addition, by operation of certain state laws and numerous health insurance programs, the FDA's designation of therapeutic equivalence often results in substitution of the generic drug without the knowledge or consent of either the prescribing physician or the patient.

Under the Hatch-Waxman Amendments, the FDA may not approve an ANDA until any applicable period of non-patent exclusivity for the RLD has expired. The FDCA provides a period of five years of non-patent data exclusivity for a new drug containing a new chemical entity. For the purposes of this provision, a new chemical entity, or NCE, is a drug that contains no active moiety that has previously been approved by the FDA in any other NDA. An active moiety is the molecule or ion responsible for the physiological or pharmacological action of the drug substance. In cases where such NCE exclusivity has been granted, an ANDA may not be filed with the FDA until the expiration of five years unless the submission is accompanied by a Paragraph IV certification, in which case the applicant may submit its application four years following the original product approval.

The FDCA also provides for a period of three years of exclusivity if the NDA includes reports of one or more new clinical investigations, other than bioavailability or bioequivalence studies, that were conducted by or for the applicant and are essential to the approval of the application. This three-year exclusivity period often protects changes to a previously approved drug product, such as a new dosage form, route of administration, combination or indication. Three-year exclusivity would be available for a drug product that contains a previously approved active moiety, provided the statutory requirement for a new clinical investigation is satisfied. Unlike five-year NCE exclusivity, an award of three-year exclusivity does not block the FDA from accepting ANDAs seeking approval for generic versions of the drug as of the date of approval of the original drug product. The FDA typically makes decisions about awards of data exclusivity shortly before a product is approved.

The FDA must establish a Priority Review track for certain generic drugs, requiring the FDA to review a drug application within eight months for a drug that has three or fewer approved drugs listed in the Orange Book and is no longer protected by any patent or regulatory exclusivities, or is on the FDA's drug shortage list. The FDA is also authorized to expedite review of "competitor generic therapies" or drugs with inadequate generic competition, including holding meetings with or providing advice to the drug sponsor prior to submission of the application.

Hatch-Waxman Patent Certification and the 30-Month Stay

Upon approval of an NDA or a supplement thereto, NDA sponsors are required to list with the FDA each patent with claims that cover the applicant's product or an approved method of using the product. Each of the patents listed by the NDA sponsor is published in the Orange Book. When an ANDA applicant files its application with the FDA, the applicant is required to certify to the FDA concerning any patents listed for the reference product in the Orange Book, except for patents covering methods of use for

which the ANDA applicant is not seeking approval. To the extent that the Section 505(b)(2) applicant is relying on studies conducted for an already approved product, the applicant is required to certify to the FDA concerning any patents listed for the approved product in the Orange Book to the same extent that an ANDA applicant would.

Specifically, the applicant must certify with respect to each patent that:

- the required patent information has not been filed;
- the listed patent has expired;
- the listed patent has not expired, but will expire on a particular date and approval is sought after patent expiration; or
- the listed patent is invalid, unenforceable or will not be infringed by the new product.

A certification that the new product will not infringe the already approved product's listed patents or that such patents are invalid or unenforceable is called a Paragraph IV certification. If the applicant does not challenge the listed patents or indicates that it is not seeking approval of a patented method of use, the application will not be approved until all the listed patents claiming the referenced product have expired (other than method of use patents involving indications for which the applicant is not seeking approval).

If the ANDA applicant has provided a Paragraph IV certification to the FDA, the applicant must also send notice of the Paragraph IV certification to the NDA and patent holders once the ANDA has been accepted for filing by the FDA. The NDA and patent holders may then initiate a patent infringement lawsuit in response to the notice of the Paragraph IV certification. The filing of a patent infringement lawsuit within 45 days after the receipt of a Paragraph IV certification automatically prevents the FDA from approving the ANDA until the earlier of 30 months after the receipt of the Paragraph IV notice, the expiration of the patent, or a decision in the infringement case that is favorable to the ANDA applicant.

To the extent that the Section 505(b)(2) applicant is relying on studies conducted for an already approved product, the applicant is required to certify to the FDA concerning any patents listed for the approved product in the Orange Book to the same extent that an ANDA applicant would. As a result, approval of a Section 505(b)(2) NDA can be stalled until all the listed patents claiming the referenced product have expired, until any non-patent exclusivity, such as exclusivity for obtaining approval of a new chemical entity, listed in the Orange Book for the referenced product has expired, and, in the case of a Paragraph IV certification and subsequent patent infringement suit, until the earlier of 30 months, settlement of the lawsuit or a decision in the infringement case that is favorable to the Section 505(b)(2) applicant.

Pediatric Exclusivity

Pediatric exclusivity is another type of non-patent marketing exclusivity in the United States and, if granted, provides for the attachment of an additional six months of marketing protection to the term of any existing regulatory exclusivity, including the non-patent and orphan exclusivity. This six-month exclusivity may be granted if an NDA sponsor submits pediatric data that fairly respond to a written request from the FDA for such data. The data do not need to show the product to be effective in the pediatric population studied; rather, if the clinical trial is deemed to fairly respond to the FDA's request, the additional protection is granted. If reports of requested pediatric studies are submitted to and accepted by the FDA within the statutory time limits, whatever statutory or regulatory periods of exclusivity or patent protection cover the product are extended by six months. This is not a patent term extension, but it effectively extends the regulatory period during which the FDA cannot approve another application.

Orphan Drug Designation and Exclusivity

Under the Orphan Drug Act, the FDA may designate a drug product as an "orphan drug" if it is intended to treat a rare disease or condition, generally meaning that it affects fewer than 200,000 individuals in the United States, or more in cases in which there is no reasonable expectation that the cost of developing and making a product available in the United States for treatment of the disease or condition will be recovered from sales of the product. A company must seek orphan drug designation before submitting an NDA for the candidate product. If the request is granted, the FDA will disclose the identity of the therapeutic agent and its potential use. Orphan drug designation does not shorten the PDUFA goal dates for the regulatory review and approval process, although it does convey certain advantages such as tax benefits and exemption from the PDUFA application fee.

If a product with orphan designation receives the first FDA approval for the disease or condition for which it has such designation or for a select indication or use within the rare disease or condition for which it was designated, the product generally will receive orphan drug exclusivity. Orphan drug exclusivity means that the FDA may not approve another sponsor's marketing application for the same drug for the same condition for seven years, except in certain limited circumstances. Orphan exclusivity does not block the approval of a different product for the same rare disease or condition, nor does it block the approval of the same product for different conditions. If a drug designated as an orphan drug ultimately receives marketing approval for an indication broader than what was designated in its orphan drug application, it may not be entitled to exclusivity.

Orphan drug exclusivity will not bar approval of another product under certain circumstances, including if a subsequent product with the same drug for the same condition is shown to be clinically superior to the approved product on the basis of greater efficacy or safety, or providing a major contribution to patient care, or if the company with orphan drug exclusivity is not able to meet market demand. This is the case despite an earlier court opinion holding that the Orphan Drug Act unambiguously required the FDA to recognize orphan exclusivity regardless of a showing of clinical superiority.

Patent Term Restoration and Extension

A patent claiming a new drug product may be eligible for a limited patent term extension under the Hatch-Waxman Act, which permits a patent restoration of up to five years for patent term lost during the FDA regulatory review. The restoration period granted on a patent covering a product is typically one-half the time between the effective date of a clinical investigation involving human beings is begun and the submission date of an application, plus the time between the submission date of an application and the ultimate approval date. Patent term restoration cannot be used to extend the remaining term of a patent past a total of 14 years from the product's approval date. Only one patent applicable to an approved product is eligible for the extension, and only those claims covering the approved product, a method for using it, or a method for manufacturing it may be extended. Additionally, the application for the extension must be submitted prior to the expiration of the patent in question. A patent that covers multiple products for which approval is sought can only be extended in connection with one of the approvals. The United States Patent and Trademark Office reviews and approves the application for any patent term extension or restoration in consultation with the FDA.

Health Care Law and Regulation

Health care providers and third-party payors play a primary role in the recommendation and prescription of drug products that are granted marketing approval. Arrangements with providers, consultants, third-party payors and customers are subject to broadly applicable fraud and abuse, anti-kickback, false claims laws, patient privacy laws and regulations and other health care laws and

regulations that may constrain business and/or financial arrangements. Restrictions under applicable federal and state health care laws and regulations, include the following:

- the federal Anti-Kickback Statute, which prohibits, among other things, persons and entities from knowingly and willfully soliciting, offering, paying, receiving or providing remuneration, directly or indirectly, in cash or in kind, to induce or reward either the referral of an individual for, or the purchase, order or recommendation of, any good or service, for which payment may be made, in whole or in part, under a federal health care program such as Medicare and Medicaid;
- the federal civil and criminal false claims laws, including the civil False Claims Act, and civil monetary penalties laws, which prohibit individuals or entities from, among other things, knowingly presenting, or causing to be presented, to the federal government, claims for payment that are false, fictitious or fraudulent or knowingly making, using or causing to made or used a false record or statement to avoid, decrease or conceal an obligation to pay money to the federal government;
- the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, which created additional federal criminal laws that prohibit, among other things, knowingly and willfully executing, or attempting to execute, a scheme to defraud any health care benefit program or making false statements relating to health care matters;
- HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act, and their respective implementing regulations, including the Final Omnibus Rule published in January 2013, which impose obligations, including mandatory contractual terms, with respect to safeguarding the privacy, security and transmission of individually identifiable health information;
- the federal false statements statute, which prohibits knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false statement in connection with the delivery of or payment for health care benefits, items or services;
- the Foreign Corrupt Practices Act, or FCPA, which prohibits companies and their intermediaries from making, or offering or promising to make improper payments to non-U.S. officials for the purpose of obtaining or retaining business or otherwise seeking favorable treatment;
- the federal transparency requirements known as the federal Physician Payments Sunshine Act, under the Patient Protection and Affordable Care Act, as amended by the Health Care Education Reconciliation Act, or the ACA, which requires certain manufacturers of drugs, devices, biologics and medical supplies to report annually to the Centers for Medicare & Medicaid Services, or CMS, within the United States Department of Health and Human Services, information related to payments and other transfers of value made by that entity to physicians and teaching hospitals, as well as ownership and investment interests held by physicians and their immediate family members; and
- analogous state and foreign laws and regulations, such as state anti-kickback and false claims laws, which may apply to health care items or services that are reimbursed by non-government third-party payors, including private insurers.

Further, some state laws require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government in addition to requiring manufacturers to report information related to payments to physicians and other health care providers or marketing expenditures. Additionally, some state and local laws require the registration of pharmaceutical sales representatives in the jurisdiction. State and foreign laws also govern the privacy and security of health information in some circumstances, many of which differ from each other in significant ways and often are not preempted by HIPAA, thus complicating compliance efforts.

Pharmaceutical Insurance Coverage and Health Care Reform

In the United States and markets in other countries, patients who are prescribed treatments for their conditions and providers performing the prescribed services generally rely on third-party payors to reimburse all or part of the associated health care costs. Significant uncertainty exists as to the coverage and reimbursement status of products approved by the FDA and other government authorities. Thus, even if a product candidate is approved, sales of the product will depend, in part, on the extent to which third-party payors, including government health programs in the United States such as Medicare and Medicaid, commercial health insurers and managed care organizations, provide coverage and establish adequate reimbursement levels for, the product. The process for determining whether a payor will provide coverage for a product may be separate from the process for setting the price or reimbursement rate that the payor will pay for the product once coverage is approved. Third-party payors are increasingly challenging the prices charged, examining the medical necessity and reviewing the cost-effectiveness of medical products and services and imposing controls to manage costs. Third-party payors may limit coverage to specific products on an approved list, also known as a formulary, which might not include all of the approved products for a particular indication.

In order to secure coverage and reimbursement for any product that might be approved for sale, a company may need to conduct expensive pharmacoeconomic studies in order to demonstrate the medical necessity and cost-effectiveness of the product, in addition to the costs required to obtain FDA or other comparable marketing approvals. Nonetheless, product candidates may not be considered medically necessary or cost effective. A decision by a third-party payor not to cover a product could reduce physician utilization once the product is approved and have a material adverse effect on sales, results of operations and financial condition. Additionally, a payor's decision to provide coverage for a product does not imply that an adequate reimbursement rate will be approved. Further, one payor's determination to provide coverage for a product does not assure that other payors will also provide coverage and reimbursement for the product, and the level of coverage and reimbursement can differ significantly from payor to payor.

The containment of health care costs also has become a priority of federal, state and foreign governments and the prices of products have been a focus in this effort. Governments have shown significant interest in implementing cost-containment programs, including price controls, restrictions on reimbursement and requirements for substitution of generic products. Adoption of price controls and cost-containment measures, and adoption of more restrictive policies in jurisdictions with existing controls and measures, could further limit a company's revenue generated from the sale of any approved products. Coverage policies and third-party reimbursement rates may change at any time. Even if favorable coverage and reimbursement status is attained for one or more products for which a company or its collaborators receive marketing approval, less favorable coverage policies and reimbursement rates may be implemented in the future.

There have been a number of federal and state proposals during the last few years regarding the pricing of pharmaceutical and biopharmaceutical products, limiting coverage and reimbursement for drugs and biologics and other medical products, government control and other changes to the health care system in the United States.

In March 2010, the United States Congress enacted the ACA, which, among other things, includes changes to the coverage and payment for drug products under government health care programs. Among the provisions of the ACA of importance to our potential product candidates are:

- an annual, nondeductible fee on any entity that manufactures or imports specified branded prescription drugs and biologic agents, apportioned among these entities according to their market share in certain government healthcare programs;

- expansion of eligibility criteria for Medicaid programs by, among other things, allowing states to offer Medicaid coverage to certain individuals with income at or below 133% of the federal poverty level, thereby potentially increasing a manufacturer's Medicaid rebate liability;
- expanded manufacturers' rebate liability under the Medicaid Drug Rebate Program by increasing the minimum rebate for both branded and generic drugs and revising the definition of "average manufacturer price" for calculating and reporting Medicaid drug rebates on outpatient prescription drug prices;
- addressed a new methodology by which rebates owed by manufacturers under the Medicaid Drug Rebate Program are calculated for drugs that are inhaled, infused, instilled, implanted or injected;
- expanded the types of entities eligible for the 340B drug discount program;
- established the Medicare Part D coverage gap discount program by requiring manufacturers to provide a 70% point-of-sale-discount off the negotiated price of applicable brand drugs to eligible beneficiaries during their coverage gap period as a condition for the manufacturers' outpatient drugs to be covered under Medicare Part D; and
- a new Patient-Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research.

Other legislative changes have been proposed and adopted in the United States since the ACA was enacted. In August 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, which went into effect in April 2013 and, due to subsequent legislative amendments, will remain in effect through 2027 unless additional Congressional action is taken. In January 2013, President Obama signed into law the American Taxpayer Relief Act of 2012, which, among other things, further reduced Medicare payments to several providers, including hospitals, imaging centers, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years.

Since enactment of the ACA, there have been numerous legal challenges and Congressional actions to repeal and replace provisions of the law. For example, with enactment of the Tax Cuts and Jobs Act of 2017, which was signed by President Trump on December 22, 2017, Congress repealed the "individual mandate." The repeal of this provision, which requires most Americans to carry a minimal level of health insurance, is effective as of 2019. According to the Congressional Budget Office, the repeal of the individual mandate will cause 13 million fewer Americans to be insured in 2027 and premiums in insurance markets may rise. Additionally, on January 22, 2018, President Trump signed a continuing resolution on appropriations for fiscal year 2018 that delayed the implementation of certain ACA-mandated fees, including the so-called "Cadillac" tax on certain high cost employer-sponsored insurance plans, the annual fee imposed on certain health insurance providers based on market share, and the medical device excise tax on non-exempt medical devices. Further, the Bipartisan Budget Act of 2018, among other things, amends the ACA, effective January 1, 2019, to increase from 50 percent to 70 percent the point-of-sale discount that is owed by pharmaceutical manufacturers who participate in Medicare Part D and to close the coverage gap in most Medicare drug plans, commonly referred to as the "donut hole". The Congress will likely consider other legislation to replace elements of the ACA during the next Congressional session.

In addition, on December 14, 2018, a U.S. District Court judge in the Northern District of Texas ruled that the individual mandate portion of the ACA is an essential and inseparable feature of the ACA, and therefore because the mandate was repealed as part of the Tax Cuts and Jobs Act, the remaining provisions of the ACA are invalid as well. The Trump administration and CMS have both stated that the ruling will have no immediate effect, and on December 30, 2018 the same judge issued an order staying the judgment pending appeal. The Trump Administration has recently represented to the Court of Appeals considering this judgment that it does not oppose the lower court's ruling. It is unclear how this decision and any subsequent appeals and other efforts to repeal and replace the ACA will impact the ACA and our business. Litigation and legislation over the ACA are likely to continue, with unpredictable and uncertain results.

The Trump Administration has also taken executive actions to undermine or delay implementation of the ACA. Since January 2017, President Trump has signed two Executive Orders designed to delay the implementation of certain provisions of the ACA or otherwise circumvent some of the requirements for health insurance mandated by the ACA. One Executive Order directs federal agencies with authorities and responsibilities under the ACA to waive, defer, grant exemptions from, or delay the implementation of any provision of the ACA that would impose a fiscal or regulatory burden on states, individuals, healthcare providers, health insurers, or manufacturers of pharmaceuticals or medical devices. The second Executive Order terminates the cost-sharing subsidies that reimburse insurers under the ACA. Several state Attorneys General filed suit to stop the administration from terminating the subsidies, but their request for a restraining order was denied by a federal judge in California on October 25, 2017. In addition, CMS has recently proposed regulations that would give states greater flexibility in setting benchmarks for insurers in the individual and small group marketplaces, which may have the effect of relaxing the essential health benefits required under the ACA for plans sold through such marketplaces. Further, on June 14, 2018, U.S. Court of Appeals for the Federal Circuit ruled that the federal government was not required to pay more than \$12 billion in ACA risk corridor payments to third-party payors who argued were owed to them. The effects of this gap in reimbursement on third-party payors, the viability of the ACA marketplace, providers, and potentially our business, are not yet known.

Further, there have been several recent U.S. congressional inquiries and proposed federal and proposed and enacted state legislation designed to, among other things, bring more transparency to drug pricing, review the relationship between pricing and manufacturer patient programs, reduce the costs of drugs under Medicare and reform government program reimbursement methodologies for drug products. For example, there have been several recent U.S. congressional inquiries and proposed federal and proposed and enacted state legislation designed to, among other things, bring more transparency to drug pricing, review the relationship between pricing and manufacturer patient programs, reduce the costs of drugs under Medicare and reform government program reimbursement methodologies for drug products. At the federal level, Congress and the Trump administration have each indicated that it will continue to seek new legislative and/or administrative measures to control drug costs.

For example, on May 11, 2018, the Administration issued a plan to lower drug prices. Under this blueprint for action, the Administration indicated that the Department of Health and Human Services, or HHS, will: take steps to end the gaming of regulatory and patent processes by drug makers to unfairly protect monopolies; advance biosimilars and generics to boost price competition; evaluate the inclusion of prices in drug makers' advertisements to enhance price competition; speed access to and lower the cost of new drugs by clarifying policies for sharing information between insurers and drug makers; avoid excessive pricing by relying more on value-based pricing by expanding outcome-based payments in Medicare and Medicaid; work to give Part D plan sponsors more negotiation power with drug makers; examine which Medicare Part B drugs could be negotiated for a lower price by Part D plans, and improving the design of the Part B Competitive Acquisition Program; update Medicare's drug-pricing dashboard to increase transparency; prohibit Part D contracts that include "gag rules" that prevent pharmacists from informing patients when they could pay less out-of-pocket by not using insurance; and require that Part D plan

members be provided with an annual statement of plan payments, out-of-pocket spending, and drug price increases. More recently, on January 31, 2019, the HHS Office of Inspector General proposed modifications to the federal Anti-Kickback Statute discount safe harbor for the purpose of reducing the cost of drug products to consumers which, among other things, if finalized, will affect discounts paid by manufacturers to Medicare Part D plans, Medicaid managed care organizations and pharmacy benefit managers working with these organizations.

At the state level, individual states are increasingly aggressive in passing legislation and implementing regulations designed to control pharmaceutical and biological product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing. In addition, regional health care authorities and individual hospitals are increasingly using bidding procedures to determine what pharmaceutical products and which suppliers will be included in their prescription drug and other health care programs. These measures could reduce the ultimate demand for our products, once approved, or put pressure on our product pricing. 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.

Review and Approval of Medicinal Products in the European Union

In order to market any product outside of the United States, a company must also comply with numerous and varying regulatory requirements of other countries and jurisdictions regarding quality, safety and efficacy and governing, among other things, clinical trials, marketing authorization, commercial sales and distribution of products. Whether or not it obtains FDA approval for a product, an applicant will need to obtain the necessary approvals by the comparable non-U.S. regulatory authorities before it can commence clinical trials or marketing of the product in those countries or jurisdictions. The approval process ultimately varies between countries and jurisdictions and can involve additional product testing and additional administrative review periods. The time required to obtain approval in other countries and jurisdictions might differ from and be longer than that required to obtain FDA approval. Regulatory approval in one country or jurisdiction does not ensure regulatory approval in another, but a failure or delay in obtaining regulatory approval in one country or jurisdiction may negatively impact the regulatory process in others. Specifically, however, the process governing approval of medicinal products in the European Union, or EU, generally follows the same lines as in the United States. It entails satisfactory completion of preclinical studies and adequate and well-controlled clinical trials to establish the safety and efficacy of the product for each proposed indication. It also requires the submission to the relevant competent authorities of an MAA and granting of a marketing authorization by these authorities before the product can be marketed and sold in the EU.

Clinical Trial Approval

The Clinical Trials Directive 2001/20/EC, the Directive 2005/28/EC on GCP and the related national implementing provisions of the individual member states of the European Union, or EU Member States, govern the system for the approval of clinical trials in the EU. Under this system, an applicant must obtain prior approval from the competent national authority of the EU Member States in which the clinical trial is to be conducted. Furthermore, the applicant may only start a clinical trial at a specific study site after the competent ethics committee has issued a favorable opinion. The clinical trial application must be accompanied by, among other documents, an investigational medicinal product dossier (the Common Technical Document) with supporting information prescribed by Directive 2001/20/EC, Directive 2005/28/EC, where relevant the implementing national provisions of the individual EU Member States and further detailed in applicable guidance documents.

In April 2014, the new Clinical Trials Regulation, (EU) No 536/2014, was adopted. The Clinical Trials Regulation was published on June 16, 2014 but is not expected to apply until later in 2019. The Clinical Trials Regulation will be directly applicable in all the EU Member States, repealing the current Clinical Trials Directive 2001/20/EC and replacing any national legislation that was put in place to implement the Directive. Conduct of all clinical trials performed in the EU will continue to be bound by currently applicable provisions until the new Clinical Trials Regulation becomes applicable. The extent to which on-going clinical trials will be governed by the Clinical Trials Regulation will depend on when the Clinical Trials Regulation becomes applicable and on the duration of the individual clinical trial. If a clinical trial continues for more than three years from the day on which the Clinical Trials Regulation becomes applicable the Clinical Trials Regulation will at that time begin to apply to the clinical trial.

The new Clinical Trials Regulation aims to simplify and streamline the approval of clinical trials in the EU. The main characteristics of the regulation include: a streamlined application procedure via a single entry point, the "EU Portal and Database"; a single set of documents to be prepared and submitted for the application as well as simplified reporting procedures for clinical trial sponsors; and a harmonized procedure for the assessment of applications for clinical trials, which is divided in two parts. Part I is assessed by the appointed reporting Member State, whose assessment report is submitted for review by the sponsor and all other competent authorities of all EU Member States in which an application for authorization of a clinical trial has been submitted (Concerned Member States). Part II is assessed separately by each Concerned Member State. Strict deadlines have been established for the assessment of clinical trial applications. The role of the relevant ethics committees in the assessment procedure will continue to be governed by the national law of the Concerned Member State. However, overall related timelines will be defined by the Clinical Trials Regulation.

PRIME Designation in the EU

In March 2016, the EMA launched an initiative to facilitate development of product candidates in indications, often rare, for which few or no therapies currently exist. The PRiority Medicines, or PRIME, scheme is intended to encourage drug development in areas of unmet medical need and provides accelerated assessment of products representing substantial innovation reviewed under the centralized procedure. Products from small- and medium-sized enterprises, or SMEs, may qualify for earlier entry into the PRIME scheme than larger companies. Many benefits accrue to sponsors of product candidates with PRIME designation, including but not limited to, early and proactive regulatory dialogue with the EMA, frequent discussions on clinical trial designs and other development program elements, and accelerated MAA assessment once a dossier has been submitted. Importantly, a dedicated Agency contact and rapporteur from the Committee for Human Medicinal Products, or CHMP, or Committee for Advanced Therapies, are appointed early in PRIME scheme facilitating increased understanding of the product at EMA's Committee level. A kick-off meeting initiates these relationships and includes a team of multidisciplinary experts at the EMA to provide guidance on the overall development and regulatory strategies.

Marketing Authorization

To obtain a marketing authorization for a product under EU regulatory systems, an applicant must submit an MAA either under a centralized procedure administered by the EMA, or one of the procedures administered by competent authorities in the EU Member States (decentralized procedure, national procedure or mutual recognition procedure). A marketing authorization may be granted only to an applicant established in the EU. Regulation (EC) No 1901/2006 provides that prior to obtaining a marketing authorization in the EU, applicants have to demonstrate compliance with all measures included in an EMA-approved Paediatric Investigation Plan, or PIP, covering all subsets of the pediatric population, unless the EMA has granted (1) a product-specific waiver, (2) a class waiver or (3) a deferral for one or more of the measures included in the PIP.

The centralized procedure provides for the grant of a single marketing authorization by the European Commission that is valid across the European Economic Area (i.e. the EU as well as Iceland, Liechtenstein and Norway). Pursuant to Regulation (EC) No 726/2004, the centralized procedure is compulsory for specific products, including for medicines produced by certain biotechnological processes, products designated as orphan medicinal products, advanced therapy medicinal products and products with a new active substance indicated for the treatment of certain diseases. For products with a new active substance indicated for the treatment of other diseases and products that are highly innovative or for which a centralized process is in the interest of patients, the centralized procedure may be optional. The centralized procedure may at the request of the applicant also be used in certain other cases. We anticipate that the centralized procedure will be mandatory for the product candidates we are developing.

Under the centralized procedure, the CHMP is responsible for conducting the initial assessment of a product and for several post-authorization and maintenance activities, such as the assessment of modifications or extensions to an existing marketing authorization. Under the centralized procedure in the EU, the maximum timeframe for the evaluation of an MAA is 210 days, excluding clock stops, when additional information or written or oral explanation is to be provided by the applicant in response to questions of the CHMP. Accelerated evaluation might be granted by the CHMP in exceptional cases, when a medicinal product is of major interest from the point of view of public health and in particular from the viewpoint of therapeutic innovation. If the CHMP accepts such request, the time limit of 210 days will be reduced to 150 days but it is possible that the CHMP can revert to the standard time limit for the centralized procedure if it considers that it is no longer appropriate to conduct an accelerated assessment. At the end of this period, the CHMP provides a scientific opinion on whether or not a marketing authorization should be granted in relation to a medicinal product. Within 15 calendar days of receipt of a final opinion from the CHMP, the European Commission must prepare a draft decision concerning an application for marketing authorization. This draft decision must take the opinion and any relevant provisions of EU law into account. Before arriving at a final decision on an application for centralized authorization of a medicinal product the European Commission must consult the Standing Committee on Medicinal Products for Human Use. The Standing Committee is composed of representatives of the EU Member States and chaired by a non-voting European Commission representative. The European Parliament also has a related "droit de regard". The European Parliament's role is to ensure that the European Commission has not exceeded its powers in deciding to grant or refuse to grant a marketing authorization.

The European Commission may grant a so-called "marketing authorization under exceptional circumstances". Such authorization is intended for products for which the applicant can demonstrate that it is unable to provide comprehensive data on the efficacy and safety under normal conditions of use, because the indications for which the product in question is intended are encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence, or in the present state of scientific knowledge, comprehensive information cannot be provided, or it would be contrary to generally accepted principles of medical ethics to collect such information. Consequently, marketing authorization under exceptional circumstances may be granted subject to certain specific obligations, which may include the following:

- the applicant must complete an identified program of studies within a time period specified by the competent authority, the results of which form the basis of a reassessment of the benefit/risk profile;
- the medicinal product in question may be supplied on medical prescription only and may in certain cases be administered only under strict medical supervision, possibly in a hospital and in the case of a radiopharmaceutical, by an authorized person; and
- the package leaflet and any medical information must draw the attention of the medical practitioner to the fact that the particulars available concerning the medicinal product in question are as yet inadequate in certain specified respects.

A marketing authorization under exceptional circumstances is subject to annual review to reassess the risk-benefit balance in an annual reassessment procedure. Continuation of the authorization is linked to the annual reassessment and a negative assessment could potentially result in the marketing authorization being suspended or revoked. The renewal of a marketing authorization of a medicinal product under exceptional circumstances, however, follows the same rules as a "normal" marketing authorization. Thus, a marketing authorization under exceptional circumstances is granted for an initial five years, after which the authorization will become valid indefinitely, unless the EMA decides that safety grounds merit one additional five-year renewal.

The European Commission may also grant a so-called "conditional marketing authorization" prior to obtaining the comprehensive clinical data required for an application for a full marketing authorization. Such conditional marketing authorizations may be granted for product candidates (including medicines designated as orphan medicinal products), if (i) the risk-benefit balance of the product candidate is positive, (ii) it is likely that the applicant will be in a position to provide the required comprehensive clinical trial data, (iii) the product fulfills an unmet medical need and (iv) the benefit to public health of the immediate availability on the market of the medicinal product concerned outweighs the risk inherent in the fact that additional data are still required. A conditional marketing authorization may contain specific obligations to be fulfilled by the marketing authorization holder, including obligations with respect to the completion of ongoing or new studies, and with respect to the collection of pharmacovigilance data. Conditional marketing authorizations are valid for one year, and may be renewed annually, if the risk-benefit balance remains positive, and after an assessment of the need for additional or modified conditions and/or specific obligations. The timelines for the centralized procedure described above also apply with respect to the review by the CHMP of applications for a conditional marketing authorization.

The EU medicines rules expressly permit the EU Member States to adopt national legislation prohibiting or restricting the sale, supply or use of any medicinal product containing, consisting of or derived from a specific type of human or animal cell, such as embryonic stem cells. While the products we have in development do not make use of embryonic stem cells, it is possible that the national laws in certain EU Member States may prohibit or restrict us from commercializing our products, even if they have been granted an EU marketing authorization.

Unlike the centralized authorization procedure, the decentralized marketing authorization procedure requires a separate application to, and leads to separate approval by, the competent authorities of each EU Member State in which the product is to be marketed. This application is identical to the application that would be submitted to the EMA for authorization through the centralized procedure. The reference EU Member State prepares a draft assessment and drafts of the related materials within 120 days after receipt of a valid application. The resulting assessment report is submitted to the concerned EU Member States who, within 90 days of receipt, must decide whether to approve the assessment report and related materials. If a concerned EU Member State cannot approve the assessment report and related materials due to concerns relating to a potential serious risk to public health, disputed elements may be referred to the European Commission, whose decision is binding on all EU Member States.

The mutual recognition procedure similarly is based on the acceptance by the competent authorities of the EU Member States of the marketing authorization of a medicinal product by the competent authorities of other EU Member States. The holder of a national marketing authorization may submit an application to the competent authority of an EU Member State requesting that this authority recognize the marketing authorization delivered by the competent authority of another EU Member State.

Regulatory Data Protection in the EU

In the EU, innovative medicinal products approved on the basis of a complete independent data package qualify for eight years of data exclusivity upon marketing authorization and an additional two years of market exclusivity pursuant to Directive 2001/83/EC. Regulation (EC) No 726/2004 repeats

this entitlement for medicinal products authorized in accordance the centralized authorization procedure. Data exclusivity prevents applicants for authorization of generics of these innovative products from referencing the innovator's data to assess a generic (abridged) application for a period of eight years. During an additional two-year period of market exclusivity, a generic MAA can be submitted and authorized, and the innovator's data may be referenced, but no generic medicinal product can be placed on the EU market until the expiration of the market exclusivity. The overall ten-year period will be extended to a maximum of 11 years if, during the first eight years of those ten years, the marketing authorization holder obtains an authorization for one or more new therapeutic indications which, during the scientific evaluation prior to their authorization, are held to bring a significant clinical benefit in comparison with existing therapies. Even if a compound is considered to be an NCE so that the innovator gains the prescribed period of data exclusivity, another company nevertheless could also market another version of the product if such company obtained marketing authorization based on an MAA with a complete independent data package of pharmaceutical tests, preclinical tests and clinical trials.

Periods of Authorization and Renewals

A marketing authorization has an initial validity for five years in principle. The marketing authorization may be renewed after five years on the basis of a re-evaluation of the risk-benefit balance by the EMA or by the competent authority of the EU Member State. To this end, the marketing authorization holder must provide the EMA or the competent authority with a consolidated version of the file in respect of quality, safety and efficacy, including all variations introduced since the marketing authorization was granted, at least six months before the marketing authorization ceases to be valid. The European Commission or the competent authorities of the EU Member States may decide, on justified grounds relating to pharmacovigilance, to proceed with one further five-year period of marketing authorization. Once subsequently definitively renewed, the marketing authorization shall be valid for an unlimited period. Any authorization which is not followed by the actual placing of the medicinal product on the EU market (in case of centralized procedure) or on the market of the authorizing EU Member State within three years after authorization ceases to be valid (the so-called sunset clause).

Paediatric Studies and Exclusivity

Prior to obtaining a marketing authorization in the European Union, applicants must demonstrate compliance with all measures included in an EMA-approved PIP covering all subsets of the paediatric population, unless the EMA has granted a product-specific waiver, a class waiver, or a deferral for one or more of the measures included in the PIP. The respective requirements for all marketing authorization procedures are laid down in Regulation (EC) No 1901/2006, the so-called Paediatric Regulation. This requirement also applies when a company wants to add a new indication, pharmaceutical form or route of administration for a medicine that is already authorized. The Paediatric Committee of the EMA, or PDCO, may grant deferrals for some medicines, allowing a company to delay development of the medicine for children until there is enough information to demonstrate its effectiveness and safety in adults. The PDCO may also grant waivers when development of a medicine for children is not needed or is not appropriate, such as for diseases that only affect the elderly population. Before an MAA can be filed, or an existing marketing authorization can be amended, the EMA determines that companies actually comply with the agreed studies and measures listed in each relevant PIP. If an applicant obtains a marketing authorization in all EU Member States, or a marketing authorization granted in the centralized procedure by the European Commission, and the study results for the paediatric population are included in the product information, even when negative, the medicine is then eligible for an additional six-month period of qualifying patent protection through extension of the term of the Supplementary Protection Certificate.

Orphan Drug Designation and Exclusivity

Regulation (EC) No. 141/2000, as implemented by Regulation (EC) No. 847/2000 provides that a drug can be designated as an orphan drug by the European Commission if its sponsor can establish: that the product is intended for the diagnosis, prevention or treatment of (1) a life-threatening or chronically debilitating condition affecting not more than five in ten thousand persons in the EU when the application is made, or (2) a life-threatening, seriously debilitating or serious and chronic condition in the EU and that without incentives it is unlikely that the marketing of the drug in the EU would generate sufficient return to justify the necessary investment. For either of these conditions, the applicant must demonstrate that there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorized in the EU or, if such method exists, the drug will be of significant benefit to those affected by that condition.

Once authorized, orphan medicinal products are entitled to ten years of market exclusivity in all EU Member States and in addition a range of other benefits during the development and regulatory review process including scientific assistance for study protocols, authorization through the centralized marketing authorization procedure covering all member countries and a reduction or elimination of registration and marketing authorization fees. However, marketing authorization may be granted to a similar medicinal product with the same orphan indication during the ten-year period with the consent of the marketing authorization holder for the original orphan medicinal product or if the manufacturer of the original orphan medicinal product is unable to supply sufficient quantities. Marketing authorization may also be granted to a similar medicinal product with the same orphan indication if this product is safer, more effective or otherwise clinically superior to the original orphan medicinal product. The period of market exclusivity may, in addition, be reduced to six years if it can be demonstrated on the basis of available evidence that the original orphan medicinal product is sufficiently profitable not to justify maintenance of market exclusivity.

Regulatory Requirements After a Marketing Authorization has been Obtained

In case an authorization for a medicinal product in the EU is obtained, the holder of the marketing authorization is required to comply with a range of requirements applicable to the manufacturing, marketing, promotion and sale of medicinal products. These include:

- Compliance with the EU's stringent pharmacovigilance or safety reporting rules must be ensured. These rules can impose post-authorization studies and additional monitoring obligations.
- The manufacturing of authorized medicinal products, for which a separate manufacturer's license is mandatory, must also be conducted in strict compliance with the applicable EU laws, regulations and guidance, including Directive 2001/83/EC, Directive 2003/94/EC, Regulation (EC) No 726/2004 and the European Commission Guidelines for Good Manufacturing Practice. These requirements include compliance with EU cGMP standards when manufacturing medicinal products and active pharmaceutical ingredients, including the manufacture of active pharmaceutical ingredients outside of the EU with the intention to import the active pharmaceutical ingredients into the EU.
- The marketing and promotion of authorized drugs, including industry-sponsored continuing medical education and advertising directed toward the prescribers of drugs and/or the general public, are strictly regulated in the EU notably under Directive 2001/83EC, as amended, and are also subject to EU Member State laws. Direct-to-consumer advertising of prescription medicines is prohibited across the EU.

Brexit and the Regulatory Framework in the United Kingdom

On June 23, 2016, the electorate in the United Kingdom voted in favor of leaving the EU, commonly referred to as Brexit. Thereafter, on March 29, 2017, the country formally notified the EU of its intention

to withdraw pursuant to Article 50 of the Lisbon Treaty. The withdrawal of the United Kingdom from the EU was meant to take effect either on the effective date of the withdrawal agreement or, in the absence of agreement, two years after the United Kingdom provides a notice of withdrawal pursuant to the EU Treaty, which was March 29, 2019. That date has now been extended to October 31, 2019. Discussions between the United Kingdom and the European Union have focused on finalizing withdrawal issues and transition agreements, but have been extremely difficult to date. Limited progress to date in these negotiations and ongoing uncertainty within the UK Government and Parliament sustains the possibility of the United Kingdom leaving the European Union on the given deadline without a withdrawal agreement and associated transition period in place, which is likely to cause significant market and economic disruption.

Since the regulatory framework for pharmaceutical products in the United Kingdom covering quality, safety and efficacy of pharmaceutical products, clinical trials, marketing authorization, commercial sales and distribution of pharmaceutical products is derived from EU directives and regulations, Brexit could materially impact the future regulatory regime that applies to products and the approval of product candidates in the United Kingdom. It remains to be seen how, if at all, Brexit will impact regulatory requirements for product candidates and products in the United Kingdom.

General Data Protection Regulation

The collection, use, disclosure, transfer, or other processing of personal data regarding individuals in the EU, including personal health data, is subject to the EU General Data Protection Regulation, or GDPR, which became effective on May 25, 2018. The GDPR is wide-ranging in scope and imposes numerous requirements on companies that process personal data, including requirements relating to processing health and other sensitive data, obtaining consent of the individuals to whom the personal data relates, providing information to individuals regarding data processing activities, implementing safeguards to protect the security and confidentiality of personal data, providing notification of data breaches, and taking certain measures when engaging third-party processors. The GDPR also imposes strict rules on the transfer of personal data to countries outside the EU, including the U.S., and permits data protection authorities to impose large penalties for violations of the GDPR, including potential fines of up to €20 million or 4% of annual global revenues, whichever is greater. The GDPR also confers a private right of action on data subjects and consumer associations to lodge complaints with supervisory authorities, seek judicial remedies, and obtain compensation for damages resulting from violations of the GDPR. Compliance with the GDPR will be a rigorous and time-intensive process that may increase the cost of doing business or require companies to change their business practices to ensure full compliance.

Pricing Decisions for Approved Products

In the EU, pricing and reimbursement schemes vary widely from country to country. Some countries provide that products may be marketed only after a reimbursement price has been agreed. Some countries may require the completion of additional studies that compare the cost-effectiveness of a particular product candidate to currently available therapies or so-called health technology assessments, in order to obtain reimbursement or pricing approval. For example, EU Member States have the option to restrict the range of products for which their national health insurance systems provide reimbursement and to control the prices of medicinal products for human use. EU Member States may approve a specific price for a product or it may instead adopt a system of direct or indirect controls on the profitability of the company placing the product on the market. Other EU Member States allow companies to fix their own prices for products, but monitor and control prescription volumes and issue guidance to physicians to limit prescriptions. Recently, many countries in the EU have increased the amount of discounts required on pharmaceuticals and these efforts could continue as countries attempt to manage health care expenditures, especially in light of the severe fiscal and debt crises experienced by many countries in the EU. The downward pressure on health care costs in general, particularly prescription products, has become intense.

As a result, increasingly high barriers are being erected to the entry of new products. Political, economic and regulatory developments may further complicate pricing negotiations, and pricing negotiations may continue after reimbursement has been obtained. Reference pricing used by various EU Member States, and parallel trade, i.e., arbitrage between low-priced and high-priced EU Member States, can further reduce prices. There can be no assurance that any country that has price controls or reimbursement limitations for pharmaceutical products will allow favorable reimbursement and pricing arrangements for any products, if approved in those countries.

Employees

As of June 30, 2019, we had 62 full-time employees, including a total of 28 employees with M.D. or Ph.D. degrees. Of these full-time employees, 47 employees are engaged in research and development. None of our employees are represented by labor unions or covered by collective bargaining agreements. We consider our relationship with our employees to be good.

Facilities

Our principal facilities consist of office and laboratory space. We occupy approximately 28,731 square feet of office space in Cambridge, Massachusetts under a lease that currently expires in June 2028.

Legal Proceedings

We are not currently subject to any material legal proceedings.

MANAGEMENT

Executive Officers and Directors

The following table sets forth the name, age as of June 30, 2019 and position of each of our executive officers and directors.

Name	Age	Position
Robert J. Gould, Ph.D.	64	Chief Executive Officer and President, Director
Bryan Stuart	42	Chief Operating Officer
Owen Wallace, Ph.D.	50	Chief Scientific Officer
Diego Cadavid, M.D.	53	Senior Vice President, Clinical Development
Mark Levin ⁽²⁾⁽³⁾	68	Chairman of the Board of Directors
James J. Collins, Ph.D. ⁽³⁾	54	Director
Alan Ezekowitz, MBChB, D.Phil ⁽¹⁾⁽²⁾	65	Director
James Geraghty ⁽¹⁾⁽²⁾⁽³⁾	64	Director
Kate Haviland ⁽¹⁾	43	Director

- (1) Member of the Audit Committee.
- (2) Member of the Compensation Committee.
- (3) Member of the Nominating and Corporate Governance Committee.

Executive Officers

Robert J. Gould, Ph.D. has served as our president and chief executive officer and as a member of our board of directors since June 2016. Dr. Gould previously served as president and chief executive officer of Epizyme, Inc., or Epizyme, a biopharmaceutical company, from March 2010 to September 2015. Prior to joining Epizyme, he served as director of novel therapeutics at the Broad Institute of Massachusetts Institute of Technology, or MIT, and Harvard, a research institute, from December 2006 to March 2010. Dr. Gould spent 23 years at Merck Research Laboratories, or Merck, a healthcare company, where he held a variety of leadership positions, culminating in the role of vice president, licensing and external research. Dr. Gould received a B.A. from Spring Arbor University and a Ph.D. from the University of Iowa and completed postdoctoral studies at the Johns Hopkins University. We believe that Dr. Gould's extensive leadership experience in the life sciences industry and his extensive knowledge of our company based on his current role as our chief executive officer qualify him to serve on our board of directors.

Bryan Stuart has served as our chief operating officer since December 2018. Mr. Stuart previously served as president and chief executive officer of Yarra Therapeutics, LLC, or Yarra, a subsidiary of Array Biopharma, Inc., a biopharmaceutical company focused on genetically defined rare diseases, from December 2017 to August 2018. Prior to joining Yarra, Mr. Stuart served as president of Kastle Therapeutics, LLC, or Kastle, a biopharmaceutical company focused on developing and commercializing treatments for rare diseases, from July 2015 to March 2017 and as president and chief executive officer from March 2017 to November 2017. Prior to joining Kastle, Mr. Stuart was the chief business officer of Civitas Therapeutics, Inc., a biopharmaceutical company, from August 2012 to October 2014, where he led the business development, capital raising, commercial and portfolio management functions, including the sale of Civitas to Acorda Therapeutics, Inc. He previously led business development, corporate development and strategy at both EKR Therapeutics Inc. (acquired by Chiesi Farmaceutici S.p.A.) and Ovation Pharmaceuticals Inc. (acquired by Lundbeck A/S), where he played key roles in each company's growth and ultimate sale. Mr. Stuart began his career as a healthcare investment banker at William Blair & Company. Mr. Stuart received an MBA from the Kellogg School of Management at Northwestern University and a B.S. from the University of Illinois.

Owen Wallace, Ph.D. has served as our chief scientific officer since April 2017. Dr. Wallace previously served as head, global discovery chemistry at Novartis Institutes for BioMedical Research, or Novartis Institutes, a pharmaceutical company, from May 2013 to April 2017. Prior to joining Novartis Institutes, he

held various positions at Eli Lilly & Company, a pharmaceutical company, including site scientific leader and group senior director from July 2010 to June 2013, senior director, discovery chemistry from August 2009 to July 2010, director, discovery chemistry from December 2005 to August 2009 and head, discovery chemistry research from February 2002 to December 2005. Prior to that, Dr. Wallace was a senior research investigator at Bristol-Myers Squibb, a biopharmaceutical company, from March 1995 to May 2000. Dr. Wallace received his Ph.D. in Organic Chemistry from Yale University and his B.Sc. (Hons) in Chemistry from University College Cork in Ireland.

Diego Cadavid, M.D. has served as our senior vice president, clinical development since July 2018 and served as our vice president, clinical development from September 2016 to July 2018. Dr. Cadavid currently serves as an adjunct professor at the University of Massachusetts Medical School. Dr. Cadavid previously served as senior medical director in the MS Clinical Development Group at Biogen Inc., or Biogen, a biotechnology company, from January 2014 to September 2016 and as a director of the Neurology Clinical Group at Biogen from April 2008 to December 2013. Before joining Biogen, Dr. Cadavid spent nine years at Rutgers-New Jersey Medical School where he was Associate Professor of Neurology and Neuroscience. While working at Biogen, Dr. Cadavid served as a consultant at the Center for Immunology and Inflammatory Diseases at the Massachusetts General Hospital in Boston. Dr. Cadavid received an M.D. from Pontificia Universidad Javeriana in Bogota, Colombia.

Non-Employee Directors

Mark Levin has served as a member of our board of directors since August 2015 and chairman of our board of directors since August 2016. Mr. Levin currently serves as a partner at Third Rock Ventures, LLC, which he co-founded in 2007. Mr. Levin served as our interim president and chief executive officer from August 2015 to July 2016 and as interim president and chief executive officer of Voyager Therapeutics, Inc., or Voyager, a biotechnology company, from June 2013 to September 2014. He has served as the chairman of the board of directors of Voyager since June 2013. Mr. Levin was formerly on the boards of publicly traded life sciences companies Eleven Biotherapeutics, Inc. from September 2008 to November 2014 and Foundation Medicine, Inc. from 2010 to June 2014. Mr. Levin served as founding chief executive officer of Millennium Pharmaceuticals, Inc., a biopharmaceutical company since acquired by Takeda Pharmaceutical Company Limited, from 1993 to 2005. Mr. Levin received both a B.S. and an M.S. in Chemical and Biochemical Engineering from Washington University in St. Louis. We believe Mr. Levin's experience working with and serving on the boards of directors of life sciences companies and his experience working in the venture capital industry qualifies him to serve on our board of directors.

James J. Collins, Ph.D. has served on our board of directors since January 2017. Dr. Collins has served as the Termeer Professor of Medical Engineering and Science in the Institute for Medical Engineering and Science and the Department of Biological Engineering at MIT since December 2014. Prior to his joining MIT, from October 1990 to November 2014, Dr. Collins served as a professor in biomedical engineering at Boston University. Dr. Collins received a B.S. in Physics from the College of the Holy Cross and a doctorate in Medical Engineering from the University of Oxford. From 1987 to 1990, he was a Rhodes Scholar. We believe Dr. Collins' extensive industry expertise qualifies him to serve on our board of directors.

Alan Ezekowitz, MBChB, D.Phil has served on our board of directors since December 2016. Dr. Ezekowitz served as the president and chief executive officer of Abide Therapeutics, Inc., or Abide, a biopharmaceutical company that he co-founded, from 2011 to May 2019, when Abide was acquired by H. Lundbeck A/S. Prior to founding Abide, Dr. Ezekowitz was the senior vice president and franchise head for disease areas including bone, respiratory, immunology, muscle, dermatology and urology at Merck from March 2006 to March 2011. Prior to joining Merck, Dr. Ezekowitz was the Charles Wilder Professor of Pediatrics at the Harvard Medical School from June 1995 to March 2005 and served as the chief of pediatric services at the Massachusetts General Hospital for Children and the Partners Healthcare System. Additionally, he directed the Laboratory of Developmental Immunology at Massachusetts General Hospital. Dr. Ezekowitz received his medical training at the University of Cape Town in South Africa and

received a Doctor of Philosophy degree from Oxford University. We believe Dr. Ezekowitz's leadership experience in the life sciences industry qualifies him to serve on our board of directors.

James Geraghty has served on our board of directors since July 2016. Mr. Geraghty is an industry leader with over 30 years of strategic and leadership experience, including more than 20 years as a senior member of executive teams at biotechnology companies developing and commercializing innovative therapies. From May 2013 to December 2016, Mr. Geraghty was an Entrepreneur in Residence at Third Rock Ventures, a leading biotech venture and company-formation fund. From April 2011 to December 2012, Mr. Geraghty served as a senior vice president of Sanofi, a global healthcare company. Prior to that, he served in various senior management roles at Genzyme Corporation, or Genzyme, a biotechnology company, from 1992 to April 2011, including as senior vice president, international development from January 2007 to April 2011. Mr. Geraghty currently serves as chairman of the board of directors of Orchard Therapeutics plc, Idera Pharmaceuticals, Inc., or Idera, and Pieris Pharmaceuticals, Inc., each publicly traded companies, and as a member of the board of directors of Voyager, a publicly traded company. He previously served as chairman of the board of Juniper Pharmaceuticals, Inc. and as a director of bluebird bio Inc. and GTC Biotherapeutics, Inc. Mr. Geraghty received a B.A. in English from Georgetown University, an M.S. in Psychology from the University of Pennsylvania and a J.D. From Yale Law School. We believe Mr. Geraghty's public company board and management experience and his broad and deep knowledge of the industry in which we operate qualifies him to serve on our board of directors.

Kate Haviland has served on our board of directors since June 2018. Ms. Haviland has served as chief operating officer of Blueprint Medicines Corporation, or Blueprint, a precision therapy company, since February 2019. Prior to her serving as chief operating officer, Ms. Haviland served as chief business officer of Blueprint from January 2016 to January 2019. Prior to that, from April 2014 to December 2015, Ms. Haviland served as vice president, rare diseases and oncology program leadership at Idera, a clinical-stage biopharmaceutical company, where she oversaw all aspects of the product development strategy for Idera's rare disease and oncology pipeline programs, including preclinical research, manufacturing and drug supply, regulatory affairs, clinical development and execution and commercial planning. Prior to joining Idera, from June 2012 to April 2014, Ms. Haviland served as head of commercial development at Sarepta Therapeutics, Inc., a commercial-stage biopharmaceutical company, where she was responsible for product development and commercial planning and for cultivating relationships with key opinion leaders and patient advocacy groups. In addition, Ms. Haviland previously served as executive director of commercial development at PTC Therapeutics, Inc., a biopharmaceutical company, from March 2007 to June 2012 and held corporate development and project management roles at Genzyme, a biotechnology company, from July 2005 to April 2007. Ms. Haviland received a B.A. from Wesleyan University with a double major in biochemistry/molecular biology and economics and an M.B.A. from Harvard Business School. We believe Ms. Haviland's extensive experience working with life sciences companies qualifies her to serve on our board of directors.

Board Composition and Election of Directors

Board Composition

Our board of directors is currently authorized to have eight members and currently consists of six members. Upon the closing of this offering, we will reduce the authorized number of members of our board of directors to six. Our directors hold office until their successors have been elected and qualified or until the earlier of their death, resignation or removal.

Our certificate of incorporation and bylaws that will become effective upon the closing of this offering provide that the authorized number of directors may be changed only by resolution of our board of directors. Our certificate of incorporation and bylaws will also provide that our directors may be removed only for cause by the affirmative vote of the holders of 75% of our shares of capital stock present in person or by proxy and entitled to vote, and that any vacancy on our board of directors, including a vacancy resulting from an enlargement of our board of directors, may be filled only by vote of a majority of our directors then in office.

In accordance with the terms of our certificate of incorporation and bylaws that will become effective upon the closing of this offering, our board of directors will be divided into three classes, class I, class II and class III, with members of each class serving staggered three-year terms. Upon the closing of this offering, the members of the classes will be divided as follows:

- the class I directors will be Alan Ezekowitz and Mark Levin, and their term will expire at the annual meeting of stockholders to be held in 2020;
- the class II directors will be James Collins and James Geraghty, and their term will expire at the annual meeting of stockholders to be held in 2021; and
- the class III directors will be Robert Gould and Kate Haviland, and their term will expire at the annual meeting of stockholders to be held in 2022.

Upon the expiration of the term of a class of directors, directors in that class will be eligible to be elected for a new three-year term at the annual meeting of stockholders in the year in which their term expires.

The classification of our board of directors may have the effect of delaying or preventing changes in our control or management. See "Description of Capital Stock—Delaware Anti-Takeover Law and Certain Charter and Bylaw Provisions."

Director Independence

Applicable Nasdaq rules require a majority of a listed company's board of directors to be comprised of independent directors within one year of listing. In addition, Nasdaq rules require that, subject to specified exceptions, each member of a listed company's audit, compensation and nominating and corporate governance committees be independent under the Securities Exchange Act of 1934, as amended, or the Exchange Act. Audit committee members must also satisfy the independence criteria set forth in Rule 10A-3 under the Exchange Act and compensation committee members must also satisfy the independence criteria set forth in Rule 10C-1 under the Exchange Act. Under applicable Nasdaq rules, a director will only qualify as an "independent director" if, in the opinion of the listed company's board of directors, that person does not have a relationship that would interfere with the exercise of independent judgment in carrying out the responsibilities of a director. In order to be considered independent for purposes of Rule 10A-3, a member of an audit committee of a listed company may not, other than in his or her capacity as a member of the audit committee, the board of directors, or any other board committee, accept, directly or indirectly, any consulting, advisory, or other compensatory fee from the listed company or any of its subsidiaries or otherwise be an affiliated person of the listed company or any of its subsidiaries. In order to be considered independent for purposes of Rule 10C-1, the board must consider, for each member of a compensation committee of a listed company, all factors specifically relevant to determining whether a director has a relationship to such company which is material to that director's ability to be independent from management in connection with the duties of a compensation committee member, including, but not limited to: (1) the source of compensation of the director, including any consulting advisory or other compensatory fee paid by such company to the director; and (2) whether the director is affiliated with the company or any of its subsidiaries or affiliates.

In June 2019, our board of directors undertook a review of the composition of our board of directors and its committees and the independence of each director. Based upon information requested from and provided by each director concerning his or her background, employment and affiliations, including family relationships, our board of directors has determined that each of our directors, with the exception of Dr. Gould, is an "independent director" as defined under applicable Nasdaq rules, including, in the case of all the members of our audit committee, the independence criteria set forth in Rule 10A-3 under the Exchange Act, and in the case of all the members of our compensation committee, the independence criteria set forth in Rule 10C-1 under the Exchange Act. In making such determination, our board of directors considered the relationships that each such non-employee director has with our company and all other facts and circumstances that our board of directors deemed relevant in determining his or her

independence, including the beneficial ownership of our capital stock by each non-employee director. Dr. Gould is not an independent director under these rules because he is our president and chief executive officer.

There are no family relationships among any of our directors or executive officers.

Board Committees

Our board of directors has established an audit committee, a compensation committee and a nominating and corporate governance committee, each of which operates under a charter that has been approved by our board. The composition of each committee became effective as of the date of this prospectus.

Audit Committee

The members of our audit committee are Alan Ezekowitz, James Geraghty and Kate Haviland. Alan Ezekowitz is the chair of the audit committee. Our audit committee's responsibilities include:

- appointing, approving the compensation of, and assessing the independence of our registered public accounting firm;
- overseeing the work of our independent registered public accounting firm, including through the receipt and consideration of reports from that firm;
- reviewing and discussing with management and our independent registered public accounting firm our annual and quarterly financial statements and related disclosures;
- monitoring our internal control over financial reporting, disclosure controls and procedures and code of business conduct and ethics;
- overseeing our risk assessment and risk management policies;
- establishing procedures for the receipt and retention of accounting related complaints and concerns;
- meeting independently with our internal auditing staff, if any, our independent registered public accounting firm and management;
- reviewing and approving or ratifying any related person transactions; and
- preparing the audit committee report required by SEC rules.

All audit and non-audit services, other than *de minimis* non-audit services, to be provided to us by our independent registered public accounting firm must be approved in advance by our audit committee.

Our board of directors has determined that we do not have an "audit committee financial expert" as defined by applicable SEC rules serving on our audit committee. Our board of directors believes that, given the size and stage of development of our company, an audit committee financial expert is not necessary at this time because the collective financial and business expertise of the members of the audit committee is sufficient to satisfy the functions of the audit committee under the terms of the audit committee charter. In making this determination, our board of directors considered the formal education and nature and scope of our audit committee members' previous experience. We believe that the composition of our audit committee meets the requirements for independence under current Nasdaq and SEC rules and regulations.

Compensation Committee

The members of our compensation committee are Mark Levin, Alan Ezekowitz and James Geraghty. Mark Levin is the chair of the compensation committee. Our compensation committee's responsibilities include:

- reviewing and approving, or making recommendations to our board of directors with respect to, the compensation of our chief executive officer and our other executive officers;
- overseeing an evaluation of our senior executives;
- overseeing and administering our cash and equity incentive plans;
- reviewing and making recommendations to our board of directors with respect to director compensation;
- reviewing and discussing annually with management our "Compensation Discussion and Analysis" disclosure if and to the extent then required by SEC rules; and
- preparing the compensation committee report if and to the extent then required by SEC rules.

We believe that the composition of our compensation committee meets the requirements for independence under current Nasdaq and SEC rules and regulations.

Nominating and Corporate Governance Committee

The members of our nominating and corporate governance committee are James Geraghty, James Collins and Mark Levin. James Geraghty is the chair of the nominating and corporate governance committee. Our nominating and corporate governance committee's responsibilities include:

- recommending to our board of directors the persons to be nominated for election as directors and to each of our board's committees;
- reviewing and making recommendations to our board with respect to our board leadership structure;
- reviewing and making recommendations to our board with respect to management succession planning;
- developing and recommending to our board of directors corporate governance principles; and
- overseeing an annual evaluation of our board of directors.

We believe that the composition of our nominating and corporate governance committee meets the requirements for independence under current Nasdaq and SEC rules and regulations.

Compensation Committee Interlocks and Insider Participation

None of our executive officers serves, or in the past year has served, as a member of the board of directors or compensation committee, or other committee serving an equivalent function, of any other entity that has one or more of its executive officers serving as a member of our board of directors or our compensation committee. None of the members of our compensation committee is, or has ever been, an officer or employee of our company.

Code of Ethics and Code of Conduct

We have adopted a written code of business conduct and ethics, which became effective at the time of this offering, that applies to our directors, officers and employees, including our principal executive officer, principal financial officer, principal accounting officer or controller, or persons performing similar functions. We have posted a current copy of the code on our website, www.fulcrumtx.com. In addition, we intend to post on our website all disclosures that are required by law or Nasdaq listing standards concerning any amendments to, or waivers from, any provision of the code.

EXECUTIVE COMPENSATION

The following discussion relates to the compensation of our president and chief executive officer, Robert J. Gould, our chief operating officer, Bryan Stuart, and our senior vice president, clinical development, Diego Cadavid, for fiscal year 2018. Dr. Gould, Mr. Stuart and Dr. Cadavid are collectively referred to in this prospectus as our named executive officers.

In preparing to become a public company, we have begun a thorough review of all elements of our executive compensation program, including the function and design of our equity incentive programs. We have begun, and expect to continue in the coming months, to evaluate the need for revisions to our executive compensation program to ensure that our program is competitive with the companies with which we compete for executive talent and is appropriate for a public company.

Summary Compensation Table

The following table sets forth information regarding compensation awarded to, earned by or paid to each of our named executive officers for the year ended December 31, 2018.

<u>Name and Principal Position</u>	<u>Year</u>	<u>Salary (\$)</u>	<u>Bonus \$(¹)</u>	<u>Stock awards \$(²)</u>	<u>Option awards \$(³)</u>	<u>Total (\$)</u>
Robert J. Gould <i>President and Chief Executive Officer</i>	2018	442,900	203,734	207,000	—	853,634
Bryan Stuart ⁽⁴⁾ <i>Chief Operating Officer</i>	2018	16,667	—	—	1,685,290	1,701,957
Diego Cadavid <i>Senior Vice President, Clinical Development</i>	2018	348,383	111,825	27,600	62,556	550,364

- (1) Except where noted otherwise, the amounts reported in the "Bonus" column reflect discretionary annual cash bonuses paid to our named executive officers for their performance.
- (2) The amounts reported in the "Stock awards" column reflect the aggregate fair value of stock-based compensation awarded during the year computed in accordance with the provisions of Financial Accounting Standards Board, or FASB, Accounting Standards Codification, or ASC, Topic 718. See Note 8 to our consolidated financial statements appearing at the end of this prospectus regarding assumptions underlying the valuation of equity awards.
- (3) The amounts reported in the "Option awards" column reflect the aggregate fair value of stock-based compensation awarded during the year computed in accordance with the provisions of FASB ASC Topic 718. See Note 8 to our consolidated financial statements appearing at the end of this prospectus regarding assumptions underlying the valuation of equity awards. These amounts reflect the accounting cost for these stock options and do not reflect the actual economic value that may be realized by the named executive officer upon the vesting of the stock options, the exercise of the stock options or the sale of the common stock underlying such stock options.
- (4) Mr. Stuart commenced employment with us on December 17, 2018.

Narrative to Summary Compensation Table

Base Salary. In 2018, we paid Dr. Gould an annualized base salary of \$442,900. In January 2019, our board of directors set Dr. Gould's 2019 annual base salary at \$460,000. In 2018, we paid Mr. Stuart an annualized base salary of \$400,000. In January 2019, our board of directors set Mr. Stuart's 2019 annual base salary at \$400,000. In 2018, we paid Dr. Cadavid an annualized base salary of \$342,784 until July 16, 2018, after which Dr. Cadavid was promoted to the position of senior vice president, clinical development, and we paid Dr. Cadavid an annualized base salary of \$355,000. In January 2019, our board of directors set

Dr. Cadavid's 2019 annual base salary at \$366,000. Effective upon the effectiveness of the registration statement of which this prospectus forms a part, Dr. Gould, Mr. Stuart and Dr. Cadavid will receive annual base salaries of \$500,000, \$415,000 and \$375,000, respectively.

We use base salaries to recognize the experience, skills, knowledge and responsibilities required of all our employees, including our named executive officers. None of our named executive officers is currently party to an employment agreement or other agreement or arrangement that provides for automatic or scheduled increases in base salary.

Annual Bonus. Our board of directors may, in its discretion, award bonuses to our named executive officers from time to time. Our employment agreements with our named executive officers provide that they will be eligible for annual performance-based bonuses up to a specified percentage of their salary, subject to approval by our board of directors. Performance-based bonuses, which are calculated as a percentage of base salary, are designed to motivate our employees to achieve annual goals based on our strategic, financial and operating performance objectives. From time to time, our board of directors has approved discretionary annual cash bonuses to our named executive officers with respect to their prior year performance. The 2018 target bonus amounts, expressed as a percentage of annual base salary, for our named executive officers were 40% for Dr. Gould, 35% for Mr. Stuart and 30% for Dr. Cadavid.

With respect to 2018 performance, our board of directors awarded bonuses of \$203,734 and \$111,825 to Dr. Gould and Dr. Cadavid, respectively. Because he joined us in December 2018, Mr. Stuart did not receive an annual bonus for 2018.

Equity Incentives. Although we do not have a formal policy with respect to the grant of equity incentive awards to our executive officers, or any formal equity ownership guidelines applicable to them, we believe that equity grants provide our executives with a strong link to our long-term performance, create an ownership culture and help to align the interests of our executives and our stockholders. In addition, we believe that equity grants with a time-based vesting feature promote executive retention because this feature incents our executive officers to remain in our employment during the vesting period. Accordingly, our board of directors periodically reviews the equity incentive compensation of our named executive officers and from time to time may grant equity incentive awards to them in the form of stock options.

In connection with the commencement of employment with us, we granted a restricted stock award for 428,571 shares of our common stock to Dr. Gould in July 2016, an option to purchase 303,571 shares of our common stock to Mr. Stuart in December 2018, and a restricted stock award for 57,142 shares of our common stock to Dr. Cadavid in October 2016. In addition, we granted a restricted stock award for 64,287 shares of our common stock to Dr. Gould in January 2018, a restricted stock award for 8,572 shares of our common stock to Dr. Cadavid in January 2018 and an option to purchase 17,857 shares of our common stock to Dr. Cadavid in July 2018. The equity awards granted in 2018 to Dr. Gould and Dr. Cadavid vest in equal quarterly installments over a term of four years from the applicable vesting commencement date. The options granted in 2018 to Mr. Stuart vest as to 25% of the shares underlying the option on the first anniversary of the vesting commencement date and as to an additional 6.25% of the original number of shares underlying the option quarterly thereafter.

In January 2019, we granted options to purchase 346,092, 58,928 and 80,928 shares of our common stock to Dr. Gould, Mr. Stuart and Dr. Cadavid, respectively. The options granted in January 2019 to Dr. Gould and to Dr. Cadavid vest in equal quarterly installments over a term of four years from the vesting commencement date. The options granted in January 2019 to Mr. Stuart vest as to 25% of the shares underlying the option on the first anniversary of the vesting commencement date and as to an additional 6.25% of the original number of shares underlying the option quarterly thereafter. Our board of directors has also granted options to purchase 107,142, 28,571 and 12,784 shares of our common stock to Dr. Gould, Mr. Stuart and Dr. Cadavid, respectively, effective upon the commencement of trading of our

common stock on the Nasdaq Global Market, which we refer to as the IPO grants. The IPO grants vest in equal quarterly installments over a term of four years from July 1, 2019.

Prior to this offering, our executives were eligible to receive equity awards under our 2016 Stock Incentive Plan, as amended to date, or the 2016 Plan. During 2018 and 2019, all restricted stock awards and stock options (other than the IPO grants) were granted pursuant to the 2016 Plan. Following the closing of this offering, our employees and executives will be eligible to receive stock options and other stock-based awards pursuant to our 2019 Stock Incentive Plan, or the 2019 Plan.

Prior to June 2018, we used restricted stock awards to compensate our executive officers in the form of initial grants in connection with the commencement of employment and also at various times, often but not necessarily annually, if we had performed as expected or better than expected. Since June 2018, we typically use stock options to compensate our executive officers in connection with the commencement of employment and also at various times.

Prior to this offering, awards of restricted stock and stock options to our executive officers have been made by our board of directors. None of our executive officers is currently party to an employment agreement that provides for the automatic award of restricted stock or stock options. We have granted restricted stock and option awards to our executive officers with time-based vesting. The restricted stock and option awards that we have granted to our executive officers in connection with commencement of employment typically become exercisable as to 25% of the shares underlying the award on the first anniversary of the grant date and as to an additional 6.25% of the original number of shares underlying the award quarterly thereafter. The restricted stock and option awards that we have granted to our executive officers at times other than in connection with employment typically become exercisable in equal quarterly installments over a term of four years from the applicable vesting commencement date. Vesting rights cease upon termination of employment and exercise rights for options cease shortly after termination. Prior to the exercise of an option, the holder has no rights as a stockholder with respect to the shares subject to such option, including no voting rights and no right to receive dividends or dividend equivalents.

We have historically granted stock options with exercise prices that are equal to the fair market value of our common stock on the date of grant as determined by our board of directors, based on a number of objective and subjective factors. The exercise price of all stock options granted after the closing of this offering will be equal to the fair market value of shares of our common stock on the date of grant, which will be determined by reference to the closing market price of our common stock on the date of grant.

Outstanding Equity Awards at December 31, 2018

The following table sets forth information regarding all outstanding stock options and restricted stock held by each of our named executive officers as of December 31, 2018.

Name	Option Awards				Stock Awards	
	Number of securities underlying unexercised options (#) exercisable	Number of securities underlying unexercised options (#) unexercisable	Option exercise price (\$)	Option expiration date	Number of shares or units of stock that have not vested (#)	Market value of shares or units of stock that have not vested (\$) ⁽¹⁾
Robert J. Gould	—	—	—	—	160,715(2)	2,571,440
	—	—	—	—	21,429(3)	342,864
	—	—	—	—	48,216(4)	771,456
Bryan Stuart	—	303,571(5)	\$ 7.84	12/17/2028	—	—
Diego Cadavid	1,116	16,741(6)	\$ 4.83	7/10/2028	25,000(7)	400,000
					2,679(8)	42,864
					6,429(9)	102,864

- (1) The market price of our common stock is based on the initial public offering price of \$16.00 per share.
- (2) Dr. Gould's restricted stock award for 428,571 shares vests over four years, with 25% of the shares vested on June 20, 2017, and 6.25% of the original number of shares vesting thereafter in equal quarterly installments through June 20, 2020, subject to continued service.
- (3) Dr. Gould's restricted stock award for 42,857 shares vests over four years, in equal quarterly installments through January 1, 2021, subject to continued service.
- (4) Dr. Gould's restricted stock award for 64,287 shares vests over four years, in equal quarterly installments through January 1, 2022, subject to continued service.
- (5) Mr. Stuart's option award for 303,571 shares vests over four years, with 25% of the shares vesting on December 17, 2019, and 6.25% of the original number of shares vesting thereafter in equal quarterly installments through December 17, 2022, subject to continued service.
- (6) Dr. Cadavid's option award for 17,857 shares vests over four years, in equal quarterly installments through July 16, 2022, subject to continued service.
- (7) Dr. Cadavid's restricted stock award for 57,142 shares vests over four years, with 25% of the shares vested on September 19, 2017, and 6.25% of the original number of shares vesting thereafter in equal quarterly installments through September 19, 2020, subject to continued service.
- (8) Dr. Cadavid's restricted stock award for 5,357 shares vests over four years, in equal quarterly installments through January 1, 2021, subject to continued service.
- (9) Dr. Cadavid's restricted stock award for 8,572 shares vests over four years, in equal quarterly installments through January 1, 2022, subject to continued service.

Employment Agreements

We have entered into written employment agreements with each of our named executive officers, which became effective as of effectiveness of the registration statement of which this prospectus forms a part, and we intend to enter into employment agreements on the same form with our other executive officers. These agreements set forth the terms of the executive officer's compensation, including his base salary, and annual performance bonus opportunity. In addition, the agreements provide that, subject to eligibility requirements under the plan documents governing such programs and our policies, the executive

officers are eligible to participate in company-sponsored benefit programs that are generally available to all of our similarly-situated employees. Each executive officer will also be eligible to receive equity awards at such times and on such terms and conditions as the board of directors may determine.

Pursuant to their respective employment agreements, each of our named executive officers is entitled to an annual base salary as follows: Robert J. Gould is entitled to receive an annual base salary of \$500,000; Bryan Stuart is entitled to receive an annual base salary of \$415,000; and Diego Cadavid is entitled to receive an annual base salary of \$375,000. Each named executive officer's base salary is reviewed by our compensation committee and the board of directors on an annual or more frequent basis and is subject to change in the discretion of our board of directors or compensation committee.

Under their respective employment agreements, each of our named executive officers is also eligible to earn an annual performance bonus, with a target bonus amount equal to a specified percentage of such officer's annual base salary, based upon the board's assessment of the executive's performance and our attainment of targeted goals as set by the board of directors in its sole discretion. The bonus may be in the form of cash, equity award, or a combination of cash and equity. Dr. Gould will be eligible for an annual discretionary bonus of up to 45% of his base salary. Mr. Stuart will be eligible for an annual discretionary bonus of up to 35% of his base salary. Dr. Cadavid will be eligible for an annual discretionary bonus of up to 30% of his base salary.

Potential Payments upon Termination or Change in Control

The employment agreements and the employment of each of Dr. Gould, Mr. Stuart and Dr. Cadavid may be terminated as follows: (1) upon the death or "disability" (as disability is defined in the applicable employment agreement) of such executive officer; (2) at our election, with or without "cause" (as cause is defined in the applicable employment agreement); and (3) at such executive officer's election, with or without "good reason" (as good reason is defined in the applicable employment agreement).

In the event of the termination of Dr. Gould's employment by us without cause, or by him for good reason, prior to or more than 12 months following a "change in control" (as change in control is defined in his employment agreement), Dr. Gould is entitled to his base salary that has accrued and to which he is entitled as of the termination date and other accrued benefits, collectively, the accrued obligations. In addition, subject to his execution and nonrevocation of a release of claims in our favor and his continued compliance with his non-solicitation, confidential information and assignment of inventions agreement and any similar agreement with us, he is entitled to (1) continued payment of his base salary, in accordance with our regular payroll procedures, for a period of 12 months and (2) provided he is eligible for and timely elects to continue receiving group medical insurance under COBRA and the payments would not result in the violation of nondiscrimination requirements of applicable law, payment by us of the portion of health coverage premiums we pay for similarly-situated, active employees who receive the same type of coverage, for a period of up to 12 months following his date of termination.

In the event of the termination of Dr. Gould's employment by us without cause, or by him for good reason, within 12 months following a change in control, Dr. Gould is entitled to the accrued obligations. In addition, subject to his execution and nonrevocation of a release of claims in our favor and his continued compliance with his non-solicitation, confidential information and assignment of inventions agreement and any similar agreement with us, Dr. Gould is entitled to (1) continued payment of his then-current base salary (or, if higher, his base salary in effect immediately prior to the change in control), in accordance with our regular payroll procedures, for a period of 18 months, (2) provided he is eligible for and timely elects to continue receiving group medical insurance under COBRA and the payments would not result in the violation of nondiscrimination requirements of applicable law, payment by us of the portion of health coverage premiums we pay for similarly-situated, active employees who receive the same type of coverage, for a period of up to 18 months following his date of termination, (3) a lump sum payment equal to 100% of his target bonus for the year in which his employment is terminated or, if higher, his target bonus

immediately prior to the change in control and (4) full vesting acceleration of his then-unvested equity awards that vest solely based on the passage of time, such that his time-based equity awards become fully exercisable and non-forfeitable as of the termination date.

If Dr. Gould's employment is terminated for any other reason, including as a result of his death or disability, for cause, or voluntarily by Dr. Gould without good reason, our obligations under the employment agreement cease immediately, and Dr. Gould is only entitled to the accrued obligations.

In the event of the termination of Mr. Stuart's or Dr. Cadavid's employment by us without cause, or by such executive officer for good reason, prior to or more than 12 months following a "change in control" (as change in control is defined in his employment agreement), such executive officer is entitled to the accrued obligations. In addition, subject to his execution and nonrevocation of a release of claims in our favor and his continued compliance with his non-solicitation, confidential information and assignment of inventions agreement and any similar agreement with us, such executive officer is entitled to (1) continued payment of his base salary, in accordance with our regular payroll procedures, for a period of 12 months and (2) provided he is eligible for and timely elects to continue receiving group medical insurance under COBRA and the payments would not result in the violation of nondiscrimination requirements of applicable law, payment by us of the portion of health coverage premiums we pay for similarly-situated, active employees who receive the same type of coverage, for a period of up to 12 months following his date of termination.

In the event of the termination of Mr. Stuart's or Dr. Cadavid's employment by us without cause, or by such executive officer for good reason, within 12 months following a change in control, such executive officer is entitled to the accrued obligations. In addition, subject to his execution and nonrevocation of a release of claims in our favor and his continued compliance with his non-solicitation, confidential information and assignment of inventions agreement and any similar agreement with us, such executive officer is entitled to (1) continued payment of his then-current base salary (or, if higher, his base salary in effect immediately prior to the change in control), in accordance with our regular payroll procedures, for a period of 12 months, (2) provided he is eligible for and timely elects to continue receiving group medical insurance under COBRA and the payments would not result in the violation of nondiscrimination requirements of applicable law, payment by us of the portion of health coverage premiums we pay for similarly-situated, active employees who receive the same type of coverage, for a period of up to 12 months following his date of termination, (3) a lump sum payment equal to 100% of his target bonus for the year in which his employment is terminated or, if higher, his target bonus immediately prior to the change in control and (4) full vesting acceleration of his then-unvested equity awards that vest solely based on the passage of time, such that his time-based equity awards become fully exercisable and non-forfeitable as of the termination date.

If Mr. Stuart's or Dr. Cadavid's employment is terminated for any other reason, including as a result of such executive officer's death or disability, for cause, or voluntarily by such executive officer without good reason, our obligations under the employment agreement cease immediately, and such executive officer is only entitled to the accrued obligations.

Employee Non-Solicitation, Confidentiality and Assignment of Inventions Agreements

In connection with the employment agreements, each of our named executive officers has entered into a standard form agreement with respect to non-solicitation, confidential information and assignment of inventions.

Under their respective agreements, each named executive officer has agreed that we own all inventions that are developed by such executive officer during his employment with us that (i) are related to our business or our customers or suppliers or any of our products or services being researched, developed, manufactured or sold by us or which may be used with such products or services, (ii) result from tasks assigned to the executive officer by us or (iii) result from the use of our premises or personal property

(whether tangible or intangible) owned, leased or contracted for by us. Each named executive officer also agreed to provide us with a non-exclusive, royalty-free, paid-up, irrevocable, worldwide license for any prior inventions that such executive officer incorporates into any of our products, processes, machines or other works, in the course of such executive officer's employment with us. Under their respective agreements, each named executive officer has further agreed not to solicit our employees, consultants, customers, business or prospective customers during his employment and for a period of one year after the termination of his employment, and to protect our confidential and proprietary information indefinitely.

Stock Option and Other Compensation Plans

In this section we describe our 2016 Plan, our 2019 Plan and our 2019 Employee Stock Purchase Plan, or the 2019 ESPP. Prior to this offering, we granted awards to eligible participants under the 2016 Plan. We expect to grant future awards to eligible participants from time to time only under the 2019 Plan.

2016 Stock Incentive Plan

The 2016 Plan was initially approved by our board of directors and stockholders in July 2016 and was subsequently amended in 2017, 2018 and 2019, in each case to increase the total number of shares reserved for issuance under the plan. The 2016 Plan provides for the grant of incentive stock options, nonstatutory options, stock appreciation rights, awards of restricted stock, restricted stock units and other stock-based awards. Our employees, officers, directors, consultants and advisors are eligible to receive awards under the 2016 Plan; however, incentive stock options may only be granted to our employees. The type of award granted under the 2016 Plan and the terms of such award are set forth in the applicable award agreement. Pursuant to the terms of the 2016 Plan, our board of directors (or a committee delegated by our board of directors) administers the plan and, subject to any limitations in the plan, selects the recipients of awards and determines:

- the number of shares of our common stock covered by options and the dates upon which the options become exercisable;
- the type of options to be granted;
- the duration of options, which may not be in excess of ten years;
- the exercise price of options, which must be at least equal to the fair market value of our common stock on the date of grant; and
- the number of shares of our common stock subject to and the terms of any stock appreciation rights, restricted stock awards, restricted stock units or other stock-based awards and the terms and conditions of such awards, including conditions for repurchase, issue price and repurchase price (though the measurement price of stock appreciation rights must be at least equal to the fair market value of our common stock on the date of grant and the duration of such awards may not be in excess of ten years).

The maximum number of shares of common stock authorized for issuance under the 2016 Plan is 3,566,428 shares. Our board of directors may amend, suspend or terminate the 2016 Plan (or any portion of the 2016 Plan) at any time, except that stockholder approval may be required to comply with applicable law.

Effect of Certain Changes in Capitalization

Upon the occurrence of any stock split, reverse stock split, stock dividend, recapitalization, combination of shares, reclassification of shares, spin-off or other similar change in capitalization or event, or any dividend or distribution to holders of our common stock other than an ordinary cash dividend,

under the terms of the 2016 Plan, we are required to equitably adjust (or make substitute awards, if applicable), in the manner determined by our board of directors:

- the number and class of securities available under the 2016 Plan;
- the number and class of securities and exercise price per share of each outstanding option;
- the share and per-share provisions and the measurement price of each outstanding stock appreciation right;
- the number of shares subject to and the repurchase price per share subject to each outstanding restricted stock award or restricted stock unit award; and
- the share and per-share-related provisions and the purchase price, if any, of each outstanding other stock-based award.

Effect of Certain Corporate Transactions

Upon the occurrence of a merger or other reorganization event (as defined in the 2016 Plan), our board of directors may, on such terms as our board determines (except to the extent specifically provided otherwise in an applicable award agreement or other agreement between the participant and us), take any one or more of the following actions pursuant to the 2016 Plan as to all or any (or any portion of) outstanding awards, other than awards of restricted stock:

- provide that outstanding awards will be assumed, or substantially equivalent awards will be substituted, by the acquiring or succeeding corporation (or an affiliate of the acquiring or succeeding corporation);
- upon written notice to a participant, provide that all of the participant's unexercised awards will terminate immediately prior to the consummation of the reorganization event unless exercised by the participant (to the extent then exercisable) within a specified period following the date of the notice;
- provide that outstanding awards will become exercisable, realizable or deliverable, or restrictions applicable to an award will lapse, in whole or in part, prior to or upon such reorganization event;
- in the event of a reorganization event pursuant to which holders of shares of our common stock will receive a cash payment for each share surrendered in the reorganization event, make or provide for a cash payment to participants with respect to each award held by a participant equal to (1) the number of shares of our common stock subject to the vested portion of the award (after giving effect to any acceleration of vesting that occurs upon or immediately prior to the reorganization event) multiplied by (2) the excess, if any, of the cash payment for each share surrendered in the reorganization event over the exercise, measurement or purchase price of such award and any applicable tax withholdings, in exchange for the termination of the award;
- provide that, in connection with our liquidation or dissolution, awards will convert into the right to receive liquidation proceeds (if applicable, net of the exercise measurement or purchase price thereof and any applicable tax withholdings); or
- any combination of the foregoing.

Our board of directors is not obligated under the 2016 Plan to treat all awards, all awards held by a participant, or all awards of the same type, identically.

In the case of certain restricted stock units, no assumption or substitution is permitted, and the restricted stock units will instead be settled in accordance with the terms of the applicable restricted stock unit agreement.

Upon the occurrence of a reorganization event other than our liquidation or dissolution, our repurchase and other rights with respect to outstanding restricted stock awards will continue for the benefit of the succeeding company and will, unless our board of directors determines otherwise, apply to the cash, securities, or other property which our common stock was converted into or exchanged for in the reorganization event in the same manner and to the same extent as they applied to the common stock subject to the restricted stock award. However, the board may provide for the termination or deemed satisfaction of such repurchase or other rights under the restricted stock award agreement or any other agreement between a participant and us, either initially or by amendment. Upon our liquidation or dissolution, except to the extent specifically provided to the contrary in the restricted stock award agreement or any other agreement between the plan participant and us, all restrictions and conditions on all restricted stock awards then outstanding will automatically be deemed terminated or satisfied.

Our board of directors may at any time provide that any award under the 2016 Plan will become immediately exercisable in whole or in part, free of some or all restrictions or conditions, or otherwise realizable in whole or in part, as the case may be.

As of June 30, 2019, there were 1,663,967 shares of restricted common stock outstanding under the 2016 Plan, including 507,593 shares of unvested restricted common stock subject to repurchase by us. In addition, as of June 30, 2019, there were options to purchase 1,592,753 shares of common stock outstanding under the 2016 Plan at a weighted average exercise price of \$7.81 per share, options to purchase 28,205 shares of our common stock had been exercised under the 2016 Plan and 281,503 shares of common stock were available for future issuance under the 2016 Plan. No further awards will be made under the 2016 Plan on or after the effectiveness of the registration statement for this offering; however, awards outstanding under the 2016 Plan will continue to be governed by their existing terms.

2019 Stock Incentive Plan

In June 2019, our board of directors adopted and, in July 2019, our stockholders approved, the 2019 Plan, which became effective immediately prior to the effectiveness of the registration statement of which this prospectus forms a part. The 2019 Plan provides for the grant of incentive stock options, nonstatutory stock options, stock appreciation rights, restricted stock awards, restricted stock units and other stock-based awards. The number of shares of our common stock reserved for issuance under the 2019 Plan is the sum of: (1) 2,017,142; plus (2) the number of shares (up to 2,367,035 shares) as is equal to the sum of (x) the number of shares of our common stock reserved for issuance under the 2016 Plan that remained available for grant under the 2016 Plan immediately prior to the effectiveness of the registration statement of which this prospectus forms a part and (y) the number of shares of our common stock subject to outstanding awards under the 2016 Plan that expire, terminate or are otherwise surrendered, cancelled, forfeited or repurchased by us at their original issuance price pursuant to a contractual repurchase right; plus (3) an annual increase, to be added on the first day of each fiscal year, beginning with the fiscal year ending December 31, 2020 and continuing until, and including, the fiscal year ending December 31, 2029, equal to the lowest of (i) 2,000,000 shares of our common stock, (ii) 4% of the number of shares of our common stock outstanding on the first day of such fiscal year and (iii) an amount determined by our board of directors.

Our employees, officers, directors, consultants and advisors are eligible to receive awards under the 2019 Plan. Incentive stock options, however, may only be granted to our employees. Our board of directors has granted under the 2019 Plan options to purchase 308,486 shares of our common stock to certain of our employees and non-employee directors effective upon the commencement of trading of our common stock on the Nasdaq Global Market.

Pursuant to the terms of the 2019 Plan, our board of directors (or a committee delegated by our board of directors) administers the plan and, subject to any limitations in the plan, selects the recipients of awards and determines:

- the number of shares of our common stock covered by options and the dates upon which the options become exercisable;
- the type of options to be granted;
- the duration of options, which may not be in excess of ten years;
- the exercise price of options, which must be at least equal to the fair market value of our common stock on the date of grant; and
- the number of shares of our common stock subject to and the terms of any stock appreciation rights, restricted stock awards, restricted stock units or other stock-based awards and the terms and conditions of such awards, including conditions for repurchase, issue price and repurchase price (though the measurement price of stock appreciation rights must be at least equal to the fair market value of our common stock on the date of grant and the duration of such awards may not be in excess of ten years).

If our board of directors delegates authority to one or more of our officers to grant awards under the 2019 Plan, the officers will have the power to make awards to all of our employees, except officers and executive officers (as such terms are defined in the 2019 plan). Our board of directors will fix the terms of the awards to be granted by any such officer, the maximum number of shares subject to awards that such officer may make, and the time period in which such awards may be granted.

The 2019 Plan contains limits on awards that may be made under the 2019 Plan to our non-employee directors. In any calendar year, the value (calculated based on grant date fair value for financial reporting purposes) of shares of our common stock subject to awards granted under the 2019 Plan to an individual non-employee director, plus the amount of cash compensation paid to such individual non-employee director may not exceed \$750,000 in the case of an incumbent director, \$1,000,000 in the case of the chairman of our board of directors, or \$1,000,000 in the case of a new director during his or her first year of service. However, our board of directors may make exceptions to this limit for individual non-employee directors in extraordinary circumstances, provided that the non-employee director receiving such additional compensation may not participate in the decision to award such compensation.

Effect of Certain Changes in Capitalization

Upon the occurrence of any stock split, reverse stock split, stock dividend, recapitalization, combination of shares, reclassification of shares, spin-off or other similar change in capitalization or event, or any dividend or distribution to holders of our common stock other than an ordinary cash dividend, under the terms of the 2019 Plan, we are required to equitably adjust (or make substitute awards, if applicable), in the manner determined by our board of directors:

- the number and class of securities available under the 2019 Plan;
- the share counting rules and sublimits of the 2019 Plan;
- the number and class of securities and exercise price per share of each outstanding option;
- the share and per-share provisions and the measurement price of each outstanding stock appreciation right;
- the number of shares subject to, and the repurchase price per share subject to, each outstanding award of restricted stock; and

- the share and per-share related provisions and the purchase price, if any, of each outstanding award of restricted stock units and each other stock-based award.

Effect of Certain Corporate Transactions

Upon the occurrence of a merger or other reorganization event (as defined in the 2019 Plan), our board of directors may, on such terms as our board determines (except to the extent specifically provided otherwise in an applicable award agreement or other agreement between the participant and us), take any one or more of the following actions pursuant to the 2019 Plan as to all or any (or any portion of) outstanding awards, other than awards of restricted stock:

- provide that outstanding awards will be assumed, or substantially equivalent awards will be substituted, by the acquiring or succeeding corporation (or an affiliate of the acquiring or succeeding corporation);
- upon written notice to a participant, provide that all of the participant's unvested awards will be forfeited immediately prior to the consummation of the reorganization event, and/or vested but unexercised awards will terminate immediately prior to the consummation of the reorganization event unless exercised by the participant (to the extent then exercisable) within a specified period following the date of the notice;
- provide that outstanding awards will become exercisable, realizable or deliverable, or restrictions applicable to an award will lapse, in whole or in part, prior to or upon such reorganization event;
- in the event of a reorganization event pursuant to which holders of shares of our common stock will receive a cash payment for each share surrendered in the reorganization event, make or provide for a cash payment to participants with respect to each award held by a participant equal to (1) the number of shares of our common stock subject to the vested portion of the award (after giving effect to any acceleration of vesting that occurs upon or immediately prior to such reorganization event) multiplied by (2) the excess, if any, of the cash payment for each share surrendered in the reorganization event over the exercise, measurement or purchase price of such award and any applicable tax withholdings, in exchange for the termination of such award;
- provide that, in connection with our liquidation or dissolution, awards will convert into the right to receive liquidation proceeds (if applicable, net of the exercise, measurement or purchase price thereof and any applicable tax withholdings); or
- any combination of the foregoing.

Our board of directors is not obligated under the 2019 Plan to treat all awards, all awards held by a participant, or all awards of the same type, identically.

In the case of certain restricted stock units, no assumption or substitution is permitted, and the restricted stock units will instead be settled in accordance with the terms of the applicable restricted stock unit agreement.

Upon the occurrence of a reorganization event other than our liquidation or dissolution, our repurchase and other rights with respect to outstanding awards of restricted stock will continue for the benefit of the succeeding company and will, unless our board of directors determines otherwise, apply to the cash, securities, or other property which our common stock was converted into or exchanged for pursuant to the reorganization event in the same manner and to the same extent as they applied to the common stock subject to the restricted stock award. However, the board may provide for the termination or deemed satisfaction of such repurchase or other rights under the restricted stock award agreement or in any other agreement between a participant and us, either initially or by amendment. Upon our liquidation or dissolution, except to the extent specifically provided to the contrary in the restricted stock award

agreement or any other agreement between the participant and us, all restrictions and conditions on all restricted stock awards then outstanding will automatically be deemed terminated or satisfied.

At any time, our board of directors may provide that any award under the 2019 Plan will become immediately exercisable in whole or in part, free of some or all restrictions or conditions, or otherwise realizable in whole or in part as the case may be.

Except with respect to certain actions requiring stockholder approval under the Code or Nasdaq rules, our board of directors may amend, modify or terminate any outstanding award under the 2019 Plan, including but not limited to, substituting for the award another award of the same or a different type, changing the date of exercise or realization, and converting an incentive stock option to a nonstatutory stock option, subject to certain participant consent requirements. However, unless our stockholders approve such action, the 2019 Plan provides that we may not (except as otherwise permitted in connection with a change in capitalization or reorganization event):

- amend any outstanding stock option or stock appreciation right granted under the 2019 Plan to provide an exercise or measurement price per share that is lower than the then-current exercise or measurement price per share of such outstanding award;
- cancel any outstanding stock option or stock appreciation right (whether or not granted under the 2019 Plan) and grant a new award under the 2019 Plan in substitution for the cancelled award (other than substitute awards permitted in connection with a merger or consolidation of an entity with us or our acquisition of property or stock of another entity) covering the same or a different number of shares of our common stock and having an exercise or measurement price per share lower than the then-current exercise or measurement price per share of the cancelled award;
- cancel in exchange for a cash payment any outstanding option or stock appreciation right with an exercise or measurement price per share above the then-current fair market value of our common stock (valued in the manner determined by (or in the manner approved by) our board of directors); or
- take any other action that constitutes a "repricing" within the meaning of Nasdaq rules or rules of any other exchange or marketplace on which our common stock is listed or traded.

No award may be granted under the 2019 Plan on or after the date that is ten years following the effectiveness of the registration statement related to this offering. Our board of directors may amend, suspend or terminate the 2019 Plan at any time, except that stockholder approval may be required to comply with applicable law or stock market requirements.

2019 Employee Stock Purchase Plan

In June 2019, our board of directors adopted and, in July 2019, our stockholders approved, the 2019 ESPP, which became effective immediately prior to the effectiveness of the registration statement of which this prospectus forms a part. The 2019 ESPP is administered by our board of directors or by a committee appointed by our board of directors. The 2019 ESPP initially provides participating employees with the opportunity to purchase up to an aggregate of 252,142 shares of our common stock. The number of shares of our common stock reserved for issuance under the 2019 ESPP will automatically increase on the first day of each fiscal year, beginning with the fiscal year ending on December 31, 2020 and continuing until, and including, the fiscal year ending on December 31, 2029, in an amount equal to the lowest of (i) 428,571 shares of our common stock, (ii) 1% of the number of shares of our common stock outstanding on such date and (iii) an amount determined by our board of directors.

All of our employees and employees of any designated subsidiary, as defined in the 2019 ESPP, are eligible to participate in the 2019 ESPP, provided that:

- such person is customarily employed by us or a designated subsidiary for more than 20 hours a week and for more than five months in a calendar year;
- such person has been employed by us or by a designated subsidiary for at least three months prior to enrolling in the 2019 ESPP; and
- such person was our employee or an employee of a designated subsidiary on the first day of the applicable offering period under the 2019 ESPP.

We retain the discretion to determine which eligible employees may participate in an offering under applicable regulations.

We expect to make one or more offerings to our eligible employees to purchase stock under the 2019 ESPP beginning at such time and on such dates as our board of directors may determine, or on the first business day thereafter. Each offering will consist of a six-month offering period during which payroll deductions will be made and held for the purchase of our common stock at the end of the offering period. Our board of directors or a committee designated by the board of directors may, at its discretion, choose a different period of not more than 12 months for offerings.

On each offering commencement date, each participant will be granted an option to purchase, on the last business day of the offering period, up to a number of shares of our common stock determined by multiplying \$2,083 by the number of full months in the offering period and dividing that product by the closing price of our common stock on the first day of the offering period. No employee may be granted an option under the 2019 ESPP that permits the employee's rights to purchase shares under the 2019 ESPP and any other employee stock purchase plan of ours or of any of our subsidiaries to accrue at a rate that exceeds \$25,000 of the fair market value of our common stock (determined as of the first day of each offering period) for each calendar year in which the option is outstanding. In addition, no employee may purchase shares of our common stock under the 2019 ESPP that would result in the employee owning 5% or more of the total combined voting power or value of our stock or the stock of any of our subsidiaries.

On the commencement date of each offering period, each eligible employee may authorize up to a maximum of 15% of his or her compensation to be deducted by us during the offering period. Each employee who continues to be a participant in the 2019 ESPP on the last business day of the offering period will be deemed to have exercised an option to purchase from us the number of whole shares of our common stock that his or her accumulated payroll deductions on such date will pay for, not in excess of the maximum numbers set forth above. Under the terms of the 2019 ESPP, the purchase price will be determined by our board of directors or the committee for each offering period and will be at least 85% of the applicable closing price of our common stock. If our board of directors or the committee does not make a determination of the purchase price, the purchase price will be 85% of the lesser of the closing price of our common stock on the first business day of the offering period or on the last business day of the offering period.

An employee may at any time prior to the close of business on the fifteenth business day (or such other number of days as is determined by us) prior to the end of the offering period, and for any reason, permanently withdraw from participating in the offering and permanently withdraw the balance accumulated in the employee's account. If an employee elects to discontinue his or her payroll deductions during an offering period but does not elect to withdraw his or her funds, funds previously deducted will be applied to the purchase of common stock at the end of the offering period. If a participating employee's employment ends before the last business day of an offering period, no additional payroll deductions will be taken and the balance in the employee's account will be paid to the employee.

We will be required to make equitable adjustments to the extent determined by our board of directors or a committee thereof to the number and class of securities available under the 2019 ESPP, the share limitations under the 2019 ESPP, and the purchase price for an offering period under the 2019 ESPP to reflect stock splits, reverse stock splits, stock dividends, recapitalizations, combinations of shares, reclassifications of shares, spin-offs and other similar changes in capitalization or events or any dividends or distributions to holders of our common stock other than ordinary cash dividends.

In connection with a merger or other reorganization event, as defined in the 2019 ESPP, our board of directors or a committee of our board of directors may take any one or more of the following actions as to outstanding options to purchase shares of our common stock under the 2019 ESPP on such terms as our board of directors or committee thereof determines:

- provide that options will be assumed, or substantially equivalent options will be substituted, by the acquiring or succeeding corporation (or an affiliate of the acquiring or succeeding corporation);
- upon written notice to employees, provide that all outstanding options will be terminated immediately prior to the consummation of such reorganization event and that all such outstanding options will become exercisable to the extent of accumulated payroll deductions as of a date specified by board of directors or committee thereof in such notice, which date will not be less than ten days preceding the effective date of the reorganization event;
- upon written notice to employees, provide that all outstanding options will be cancelled as of a date prior to the effective date of the reorganization event and that all accumulated payroll deductions will be returned to participating employees on such date;
- in the event of a reorganization event under the terms of which holders of our common stock will receive upon consummation thereof a cash payment for each share surrendered in the reorganization event, change the last day of the offering period to be the date of the consummation of the reorganization event and make or provide for a cash payment to each employee equal to (1) the cash payment for each share surrendered in the reorganization event times the number of shares of our common stock that the employee's accumulated payroll deductions as of immediately prior to the reorganization event could purchase at the applicable purchase price, where the cash payment for each share surrendered in the reorganization event is treated as the fair market value of our common stock on the last day of the applicable offering period for purposes of determining the purchase price and where the number of shares that could be purchased is subject to the applicable limitations under the 2019 ESPP minus (2) the result of multiplying such number of shares by the purchase price; and/or
- provide that, in connection with our liquidation or dissolution, options will convert into the right to receive liquidation proceeds (net of the purchase price thereof).

Our board of directors may at any time, and from time to time, amend or suspend the 2019 ESPP or any portion of the 2019 ESPP. We will obtain stockholder approval for any amendment if such approval is required by Section 423 of the Code. Further, our board of directors may not make any amendment that would cause the 2019 ESPP to fail to comply with Section 423 of the Internal Revenue Code. The 2019 ESPP may be terminated at any time by our board of directors. Upon termination, we will refund all amounts in the accounts of participating employees.

401(k) Plan

We maintain a defined contribution employee retirement plan for our employees, including our named executive officers. The plan is intended to qualify as a tax-qualified 401(k) plan so that contributions to the 401(k) plan, and income earned on such contributions, are not taxable to participants until withdrawn or distributed from the 401(k) plan (except in the case of contributions under the 401(k) plan designated as Roth contributions). Under the 401(k) plan, each employee is fully vested in his or her

deferred salary contributions and our discretionary match. Employee contributions are held and invested by the plan's trustee as directed by participants. The 401(k) plan provides us with the discretion to match employee contributions, but to date we have not provided any employer matching contributions.

Limitation of Liability and Indemnification

Our certificate of incorporation, which will become effective upon the closing of this offering, limits the personal liability of directors for breach of fiduciary duty to the maximum extent permitted by the Delaware General Corporation Law, or the DGCL, and provides that no director will have personal liability to us or to our stockholders for monetary damages for breach of fiduciary duty as a director. However, these provisions do not eliminate or limit the liability of any of our directors:

- for any breach of the director's duty of loyalty to us or our stockholders;
- for acts or omissions not in good faith or that involve intentional misconduct or a knowing violation of law;
- for voting for or assenting to unlawful payments of dividends, stock repurchases or other distributions; or
- for any transaction from which the director derived an improper personal benefit.

Any amendment to or repeal of these provisions will not eliminate or reduce the effect of these provisions in respect of any act, omission or claim that occurred or arose prior to such amendment or repeal. If the DGCL is amended to provide for further limitations on the personal liability of directors of corporations, then the personal liability of our directors will be further limited to the greatest extent permitted by the DGCL.

In addition, our certificate of incorporation, which will become effective upon the closing of this offering, provides that we must indemnify our directors and officers and we must advance expenses, including attorneys' fees, to our directors and officers in connection with legal proceedings, subject to very limited exceptions.

We maintain a general liability insurance policy that covers specified liabilities of our directors and officers arising out of claims based on acts or omissions in their capacities as directors or officers. In addition, we intend to enter into indemnification agreements with all of our executive officers and directors prior to the completion of this offering. These indemnification agreements may require us, among other things, to indemnify each such executive officer or director for some expenses, including attorneys' fees, judgments, fines and settlement amounts incurred by him or her in any action or proceeding arising out of his or her service as one of our executive officers or directors.

Some of our non-employee directors may, through their relationships with their employers, be insured or indemnified against specified liabilities incurred in their capacities as members of our board of directors.

Insofar as indemnification for liabilities arising under the Securities Act of 1933, or the Securities Act, may be permitted to directors, executive officers or persons controlling us, in the opinion of the SEC, such indemnification is against public policy as expressed in the Securities Act and is therefore unenforceable.

Rule 10b5-1 Sales Plans

Our directors and executive officers may adopt written plans, known as Rule 10b5-1 plans, in which they will contract with a broker to buy or sell shares of our common stock on a periodic basis. Under a Rule 10b5-1 plan, a broker executes trades pursuant to parameters established by the director or officer when entering into the plan, without further direction from the director or officer. It also is possible that the director or officer could amend or terminate the plan when not in possession of material, nonpublic

information. In addition, our directors and executive officers may buy or sell additional shares outside of a Rule 10b5-1 plan when they are not in possession of material, nonpublic information.

Director Compensation

The table below shows all compensation to our non-employee directors during the year ended December 31, 2018.

Name	Fees earned or paid in cash (\$)	Stock awards (\$) ⁽¹⁾	Option awards (\$) ⁽²⁾⁽³⁾	Total (\$)
James J. Collins	35,000	—	11,576	46,576
Alan Ezekowitz	35,000	—	11,549	46,549
James Geraghty	35,000	—	11,480	46,480
Kate Haviland ⁽⁴⁾	17,500	—	82,459	99,959
Mark Levin	—	—	—	—
James Tananbaum ⁽⁵⁾	—	—	—	—

- (1) As of December 31, 2018, the aggregate number of shares of our common stock held pursuant to restricted stock awards by each non-employee director was as follows: Dr. Collins, 23,571 shares; Mr. Ezekowitz, 23,571 shares; Mr. Geraghty, 80,714 shares; Ms. Haviland, 0 shares; Mr. Levin, 0 shares and Mr. Tananbaum, 0 shares.
- (2) The amounts reported in the "Option awards" column reflect the aggregate fair value of stock-based compensation awarded during the year computed in accordance with the provisions of ASC 718. See Note 8 to our consolidated financial statements appearing at the end of this prospectus regarding assumptions underlying the valuation of equity awards. These amounts reflect the accounting cost for these stock options and do not reflect the actual economic value that may be realized by the directors upon the vesting of the stock options, the exercise of the stock options or the sale of the common underlying such stock options.
- (3) As of December 31, 2018, the aggregate number of shares of our common stock subject to outstanding option awards for each non-employee director was as follows: Dr. Collins, 3,571 shares; Mr. Ezekowitz, 3,571 shares; Mr. Geraghty, 3,571 shares; Ms. Haviland, 23,571 shares; Mr. Levin, 0 shares and Mr. Tananbaum, 0 shares.
- (4) Kate Haviland joined our board of directors in June 2018.
- (5) James Tananbaum resigned from our board of directors effective as of April 3, 2019.

In January 2019, Mr. Collins and Mr. Ezekowitz were each granted options to purchase 3,571 shares of our common stock. In May 2019, Mr. Geraghty was granted an option to purchase 3,571 shares of our common stock. Our board of directors has also granted an option to purchase 9,285 shares of our common stock to each of Mr. Geraghty and Ms. Haviland and an option to purchase 5,714 shares of our common stock to each of Dr. Collins and Mr. Ezekowitz, in each case effective upon the commencement of trading of our common stock on the Nasdaq Global Market.

Prior to this offering, we paid cash fees and granted restricted stock awards and options to purchase shares of our common stock to certain of our non-employee directors for their service on our board of directors pursuant to a non-employee and non-affiliate director compensation policy. We have historically reimbursed our non-employee directors for reasonable travel and out-of-pocket expenses incurred in connection with attending board of director and committee meetings.

Dr. Gould, one of our directors who also serves as our president and chief executive officer, does not receive any additional compensation for his service as a director. Dr. Gould is one of our named executive

officers and, accordingly, the compensation that we pay to Dr. Gould is discussed above under "—Summary Compensation Table" and "—Narrative to Summary Compensation Table."

In June 2019, our board of directors approved a director compensation program that became effective on the effective date of the registration statement of which this prospectus is a part. Under this director compensation program, we will pay our non-employee directors a cash retainer for service on the board of directors and for service on each committee on which the director is a member. The chairman of the board and of each committee will receive additional retainers for such service. These fees are payable in arrears in four equal quarterly installments on the last day of each quarter, provided that the amount of such payment will be prorated for any portion of such quarter that the director is not serving on our board of directors and no fee will be payable in respect of any period prior to the completion of this offering. The fees paid to non-employee directors for service on the board of directors and for service on each committee of the board of directors on which the director is a member are as follows:

	Member Annual Fee	Chairman Supplemental Annual Fee
Board of Directors	\$ 35,000	\$ 30,000
Audit Committee	\$ 7,500	\$ 7,500
Compensation Committee	\$ 5,000	\$ 5,000
Nominating and Corporate Governance Committee	\$ 4,000	\$ 4,000

We also will continue to reimburse our non-employee directors for reasonable travel and other expenses incurred in connection with attending meetings of our board of directors and any committee of our board of directors on which he or she serves.

In addition, under our director compensation program, each non-employee director will receive, upon his or her initial election or appointment to our board of directors, an option to purchase 18,571 shares of our common stock under the 2019 Plan. Each of these options will vest as to 2.7778% of the shares of our common stock underlying such option at the end of each successive one month period following the grant date until the third anniversary of the grant date, subject to the non-employee director's continued service as a director. Further, on the date of the first board meeting held after each annual meeting of stockholders, each non-employee director that has served on our board of directors for at least six months will receive, under the 2019 Plan, an option to purchase 9,285 shares of our common stock under the 2019 Plan. Each of these options will vest with respect to all of the shares underlying such option on the first anniversary of the grant date or, if earlier, immediately prior to the first annual meeting of stockholders occurring after the grant date, subject to the non-employee director's continued service as a director. All options issued to our non-employee directors under our director compensation program will be issued at exercise prices equal to the fair market value of our common stock on the date of grant and will become exercisable in full upon specified change in control events.

TRANSACTIONS WITH RELATED PERSONS

Since January 1, 2016, we have engaged in the following transactions in which the amounts involved exceeded \$120,000 and any of our directors, executive officers or holders of more than 5% of our voting securities, or any member of the immediate family of, or person sharing the household with, the foregoing persons, had or will have a direct or indirect material interest. We believe that all of these transactions were on terms as favorable as could have been obtained from unrelated third parties.

Convertible Promissory Note

On April 14, 2016, we issued and sold a convertible promissory note to Third Rock Ventures III, L.P. in the aggregate principal amount of \$3,500,000. The note accrued interest at a rate of 6% per annum. All principal and interest under the note was converted into shares of Series A preferred stock in connection with our initial closing of our Series A preferred stock financing in July 2016.

Series A Preferred Stock Financing

From July 18, 2016 to June 6, 2018, we issued and sold an aggregate of 60,000,000 shares of our Series A preferred stock, consisting of (i) 53,313,014 shares sold at a price per share of \$1.00 in cash, for an aggregate purchase price of \$53,313,014 and (ii) 6,686,986 shares issued upon conversion of \$6,868,986 in outstanding principal and accrued and unpaid interest under the notes issued on October 15, 2015 and April 14, 2016, at a price per share of \$1.00 in cash. The following table sets forth the aggregate numbers of shares of our Series A preferred stock that we issued and sold to our 5% stockholders and their affiliates in this transaction and the aggregate amount of consideration for such shares:

<u>Purchaser⁽¹⁾⁽²⁾</u>	<u>Date</u>	<u>Shares of Series A Preferred Stock Sold for Cash</u>	<u>Cash Purchase Price</u>	<u>Shares of Series A Preferred Stock Received upon Conversion of Promissory Note</u>	<u>Purchase Price Funded by Conversion of Promissory Note</u>
Third Rock Ventures III, L.P.	7/18/2016	5,156,507	\$ 5,156,507	6,686,986	\$ 6,686,986
Third Rock Ventures III, L.P.	11/15/2016	5,156,507	\$ 5,156,507	—	—
Third Rock Ventures III, L.P.	2/17/2017	6,333,333	\$ 6,333,333	—	—
Third Rock Ventures III, L.P.	5/3/2017	3,166,667	\$ 3,166,667	—	—
Third Rock Ventures IV, L.P.	5/3/2017	3,166,666	\$ 3,166,666	—	—
Third Rock Ventures III, L.P.	1/4/2018	3,166,667	\$ 3,166,667	—	—
Third Rock Ventures IV, L.P.	1/4/2018	3,166,667	\$ 3,166,667	—	—
Third Rock Ventures III, L.P.	3/13/2018	3,166,667	\$ 3,166,667	—	—
Third Rock Ventures IV, L.P.	3/13/2018	3,166,666	\$ 3,166,666	—	—
Third Rock Ventures III, L.P.	5/9/2018	3,166,666	\$ 3,166,666	—	—
Third Rock Ventures IV, L.P.	5/9/2018	3,166,667	\$ 3,166,667	—	—
Third Rock Ventures III, L.P.	6/6/2018	3,166,667	\$ 3,166,667	—	—
Third Rock Ventures IV, L.P.	6/6/2018	3,166,667	\$ 3,166,667	—	—

(1) See "Principal Stockholders" for additional information about shares held by these entities.

(2) Mr. Levin, a member of our board of directors, is a partner of Third Rock Ventures.

Series B Preferred Stock Financing

In August 2018, we issued and sold an aggregate of 40,000,000 shares of our Series B preferred stock at a price per share of \$2.00 in cash, for an aggregate purchase price of \$80,000,000. The following table sets forth the aggregate numbers of shares of our Series B preferred stock that we sold to our 5%

stockholders and their affiliates in this transaction and the aggregate amount of consideration for such shares:

<u>Purchaser⁽¹⁾</u>	<u>Shares of Series B Preferred Stock</u>	<u>Cash Purchase Price</u>
Foresite Capital Fund IV, L.P. ⁽²⁾	10,500,000	\$ 21,000,000

- (1) See "Principal Stockholders" for additional information about shares held by these entities.
- (2) Mr. Tananbaum, a former member of our board of directors who served during this transaction, is founder and chief executive officer of Foresite Capital Management.

Agreement with GSK

On February 8, 2019, we entered into a right of reference and license agreement with affiliates of GlaxoSmithKline plc, or GSK, pursuant to which GSK granted us a right of reference to certain INDs filed with the FDA and controlled by GSK or its affiliates relating to losmapimod and an exclusive worldwide license under certain patent rights related to losmapimod. The agreement also provides us with an exclusive worldwide license to certain of GSK's preclinical and clinical data with respect to losmapimod. As partial consideration for the right of reference and licenses granted under the agreement, we issued 12,500,000 shares of our Series B preferred stock to GSK at the time we entered into the right of reference and license agreement.

We also agreed to provide GSK the opportunity to purchase shares of common stock in this offering or in a concurrent private placement equal to the proportion that the shares of common stock held by GSK (assuming conversion of all preferred stock into common stock upon consummation of this offering) bear to the total number of shares of common stock immediately prior to the closing of this offering (assuming conversion of all preferred stock into common stock upon consummation of this offering and all outstanding options).

See "Business—Right of Reference and License Agreement with GlaxoSmithKline" for additional information regarding this agreement.

Consulting Services Provided by Third Rock Ventures, LLC

Since inception, we have received consulting and management services from Third Rock Ventures LLC, or Third Rock Ventures, which through its affiliates, has a significant interest in us. We have paid Third Rock Ventures \$1.9 million for these services since January 1, 2016, including the reimbursement of expenses. We do not have a written agreement in place with Third Rock Ventures with respect to the provision of consulting and management services. The consulting and management services fees are payable to Third Rock Ventures pursuant to invoices submitted to us by Third Rock Ventures quarterly. The consulting and management services fees paid to Third Rock Ventures did not exceed 5% of the consolidated gross revenue of Third Rock Ventures during any of the past three fiscal years. From time to time and at our request, partners and associates of Third Rock Ventures provide us with certain strategic and ordinary course business operations consulting services. We have issued an aggregate of 142,284 shares of our common stock to these consultants in exchange for their continuing consulting services. We may continue to occasionally engage Third Rock Ventures or their partners or associates for consulting services following this offering.

Registration Rights

We are a party to an investor rights agreement with the holders of our preferred stock, including our 5% stockholders and their affiliates and entities affiliated with some of our directors. This investor rights

agreement provides these holders the right, subject to certain conditions, beginning six months following the completion of this offering, to demand that we file a registration statement or to request that their shares be covered by a registration statement that we are otherwise filing.

See "Description of Capital Stock—Registration Rights" for additional information regarding these registration rights.

Indemnification Agreements

Our certificate of incorporation, which will become effective upon the closing of this offering, provides that we will indemnify our directors and officers to the fullest extent permitted by Delaware law. In addition, we intend to enter into indemnification agreements with all of our directors and executive officers prior to the completion of this offering. These indemnification agreements may require us, among other things, to indemnify each such director or executive officer for some expenses, including attorneys' fees, judgments, fines and settlement amounts incurred by him or her in any action or proceeding arising out of his or her service as one of our directors or executive officers.

Policies and Procedures for Related Person Transactions

Our board of directors has adopted written policies and procedures, which became effective at the time of this offering, for the review of any transaction, arrangement or relationship in which our company is a participant, the amount involved exceeds \$120,000 and one of our executive officers, directors, director nominees or 5% stockholders, or their immediate family members, each of whom we refer to as a "related person," has a direct or indirect material interest.

If a related person proposes to enter into such a transaction, arrangement or relationship, which we refer to as a "related person transaction," the related person must report the proposed related person transaction to our general counsel, and if none, our chief operating officer or chief financial officer. The policy calls for the proposed related person transaction to be reviewed and, if deemed appropriate, approved by our audit committee. Whenever practicable, the reporting, review and approval will occur prior to entry into the transaction. If advance review and approval is not practicable, the audit committee will review, and, in its discretion, may ratify the related person transaction. The policy also permits the chairman of the audit committee to review and, if deemed appropriate, approve proposed related person transactions that arise between committee meetings, subject to ratification by the committee at its next meeting. Any related person transactions that are ongoing in nature will be reviewed annually.

A related person transaction reviewed under the policy will be considered approved or ratified if it is authorized by the audit committee after full disclosure of the related person's interest in the transaction. As appropriate for the circumstances, the audit committee will review and consider:

- the related person's interest in the related person transaction;
- the approximate dollar value of the amount involved in the related person transaction;
- the approximate dollar value of the amount of the related person's interest in the transaction without regard to the amount of any profit or loss;
- whether the transaction was undertaken in the ordinary course of our business;
- whether the terms of the transaction are no less favorable to us than terms that could have been reached with an unrelated third party;
- the purpose of, and the potential benefits to us of, the transaction; and
- any other information regarding the related person transaction or the related person in the context of the proposed transaction that would be material to investors in light of the circumstances of the particular transaction.

Our audit committee may approve or ratify the transaction only if it determines that, under all of the circumstances, the transaction is in, or is not inconsistent with, our best interests. Our audit committee may impose any conditions on the related person transaction that it deems appropriate.

In addition to the transactions that are excluded by the instructions to the SEC's related person transaction disclosure rule, our board of directors has determined that the following transactions do not create a material direct or indirect interest on behalf of related persons and, therefore, are not related person transactions for purposes of this policy:

- interests arising solely from the related person's position as an executive officer of another entity, whether or not the person is also a director of the entity, that is a participant in the transaction where the related person and all other related persons own in the aggregate less than a 10% equity interest in such entity, the related person and his or her immediate family members are not involved in the negotiation of the terms of the transaction and do not receive any special benefits as a result of the transaction and the amount involved in the transaction is less than the greater of \$200,000 or 5% of the annual gross revenues of the company receiving payment under the transaction; and
- a transaction that is specifically contemplated by provisions of our certificate of incorporation or bylaws.

The policy provides that transactions involving compensation of executive officers shall be reviewed and approved by our compensation committee in the manner specified in the compensation committee's charter.

We did not have a written policy regarding the review and approval of related person transactions prior to this offering. Nevertheless, with respect to such transactions, it has been the practice of our board of directors to consider the nature of and business reasons for such transactions, how the terms of such transactions compared to those which might be obtained from unaffiliated third parties and whether such transactions were otherwise fair to and in the best interests of, or not contrary to, our best interests.

PRINCIPAL STOCKHOLDERS

The following table sets forth information with respect to the beneficial ownership of our common stock as of June 30, 2019 by:

- each of our directors;
- each of our named executive officers;
- all of our directors and executive officers as a group; and
- each person, or group of affiliated persons, who is known by us to beneficially own more than 5% of our common stock.

The column entitled "Percentage of Shares Beneficially Owned—Before Offering" is based on a total of 18,840,014 shares of our common stock outstanding as of June 30, 2019, assuming the automatic conversion of all outstanding shares of our preferred stock into an aggregate of 16,071,418 shares of our common stock upon the closing of this offering. The column entitled "Percentage of Shares Beneficially Owned—After Offering" is based on 23,340,014 shares of our common stock to be outstanding after this offering, including the 4,500,000 shares of our common stock that we are selling in this offering, but not including any additional shares issuable upon exercise of outstanding options.

Beneficial ownership is determined in accordance with the rules and regulations of the SEC and includes voting or investment power with respect to our common stock. Shares of our common stock subject to options that are currently exercisable or exercisable within 60 days after June 30, 2019 are considered outstanding and beneficially owned by the person holding the options for the purpose of calculating the percentage ownership of that person but not for the purpose of calculating the percentage ownership of any other person. Except as otherwise noted, the persons and entities in this table have sole voting and investing power with respect to all of the shares of our common stock beneficially owned by them, subject to community property laws, where applicable. Except as otherwise set forth below, the address of each beneficial owner is c/o Fulcrum Therapeutics, Inc., 26 Landsdowne Street, Cambridge, MA 02139.

Name and Address of Beneficial Owner	Number of Shares Beneficially Owned	Percentage of Shares Beneficially Owned	
		Before Offering (%)	After Offering (%)
5% Stockholders			
Entities affiliated with Third Rock Ventures ⁽¹⁾	8,142,856	43.2	34.9
Glaxo Group Limited ⁽²⁾	1,785,714	9.5	7.7
Foresite Capital Fund IV, L.P. ⁽³⁾	1,500,000	8.0	6.4
Directors and Named Executive Officers			
Robert J. Gould ⁽⁴⁾	600,607	3.2	2.6
Bryan Stuart	—	*	*
Diego Cadavid ⁽⁵⁾	90,709	*	*
Mark Levin ⁽⁶⁾	5,880,952	31.2	25.2
James J. Collins ⁽⁷⁾	28,927	*	*
Alan Ezekowitz ⁽⁸⁾	29,820	*	*
James Geraghty ⁽⁹⁾	87,856	*	*
Kate Haviland ⁽¹⁰⁾	7,365	*	*
All current executive officers and directors as a group (9 persons) ⁽¹¹⁾	6,865,886	36.4	29.4

* Less than one percent

- (1) Consists of (i) (a) 285,714 shares of common stock and (b) 5,595,238 shares of common stock issuable upon the conversion of preferred stock held by Third Rock Ventures III, L.P., or TRV III LP, and (ii) 2,261,904 shares of common stock issuable upon the conversion of preferred stock held by Third Rock Ventures IV, L.P., or TRV IV LP. Third Rock Ventures GP III, L.P., or TRV GP III, is the sole general partner of TRV III LP. TRV GP III, LLC, or TRV III LLC, is the sole general partner of TRV GP III. Each of TRV GP III, TRV III LLC, and Mark Levin, Kevin Starr and Robert Tepper, the managers of TRV III LLC, may be deemed to share voting and dispositive power over the shares of record held by TRV III LP. Each of TRV GP III, TRV III LLC, and Mark Levin, Kevin Starr and Robert Tepper disclaims beneficial ownership of all shares held by TRV III LP except to the extent of their pecuniary interest therein. Third Rock Ventures GP IV, L.P., or TRV GP IV, is the sole general partner of TRV IV LP. TRV GP IV, LLC, or TRV IV LLC, is the sole general partner of TRV GP IV. Abbie Celniker, Ph.D., Robert Tepper, M.D., Craig Muir and Cary Pfeffer, M.D. are the managing members of TRV IV LLC who collectively make voting and investment decisions with respect to shares held by TRV IV LP. The address of TRV III LP and TRV IV LP is 29 Newbury Street, Boston, MA 02116.
- (2) Consists of 1,785,714 shares of common stock issuable upon the conversion of preferred stock held by Glaxo Group Limited, an indirect wholly-owned subsidiary of GlaxoSmithKline plc, which beneficially owns the shares held by Glaxo Group Limited. The address of Glaxo Group Limited is 980 Great West Road, Brentford, Middlesex TW8 9GS England.
- (3) Consists of 1,500,000 shares of common stock issuable upon the conversion of preferred stock held by Foresite Capital Fund, IV, L.P., or FCF IV. Foresite Capital Management IV, LLC, or FCM IV, the general partner of FCF IV, may be deemed to have sole voting and dispositive power over these shares. James B. Tananbaum, in his capacity as managing member of FCM IV, may be deemed to have sole voting and dispositive power over these shares. Each of FCM IV and its members and Mr. Tananbaum disclaims beneficial ownership of any of these shares except to the extent of any pecuniary interest therein. The address of FCF IV is 600 Montgomery Street, Suite 4500, San Francisco, CA 94111.
- (4) Consists of 557,345 shares of common stock held by Dr. Gould and 43,262 shares of common stock underlying options held by Dr. Gould that are exercisable as of June 30, 2019 or will become exercisable within 60 days after such date.
- (5) Consists of 71,071 shares of common stock held by Dr. Cadavid and 19,638 shares of common stock underlying options held by Dr. Cadavid that are exercisable as of June 30, 2019 or will become exercisable within 60 days after such date.
- (6) Consists of the shares described in Note 1 above held by TRV III LP. Mr. Levin, a member of our board of directors, is a manager of TRV III LLC, which is the sole general partner of TRV GP III, which is the sole general partner of TRV III LP and may be deemed to be the indirect beneficial owner of such shares. Mr. Levin disclaims beneficial ownership over such shares, except to the extent of his proportionate pecuniary interest therein.
- (7) Consists of 23,571 shares of common stock held by Dr. Collins and 5,356 shares of common stock underlying options held by Dr. Collins that are exercisable as of June 30, 2019 or will become exercisable within 60 days after such date.
- (8) Consists of 23,571 shares of common stock held by Dr. Ezekowitz and 6,249 shares of common stock underlying options held by Dr. Ezekowitz that are exercisable as of June 30, 2019 or will become exercisable within 60 days after such date.
- (9) Consists of 80,714 shares of common stock held by Mr. Geraghty and 7,142 shares of common stock underlying options held by Mr. Geraghty that are exercisable as of June 30, 2019 or will become exercisable within 60 days after such date.
- (10) Consists of 7,365 shares of common stock underlying options held by Ms. Haviland that are exercisable as of June 30, 2019 or will become exercisable within 60 days after such date.
- (11) Includes 101,574 shares of common stock underlying options that are exercisable as of June 30, 2019 or will become exercisable within 60 days after such date.

DESCRIPTION OF CAPITAL STOCK

The following description of our capital stock and provisions of our certificate of incorporation and bylaws are summaries and are qualified by reference to the certificate of incorporation and the bylaws that will be in effect upon the closing of this offering. We will file copies of these documents with the SEC as exhibits to our registration statement of which this prospectus is a part. The description of the capital stock reflects changes to our capital structure that will occur upon the closing of this offering.

Upon the closing of this offering, our authorized capital stock will consist of 200,000,000 shares of our common stock, par value \$0.001 per share, and 5,000,000 shares of our preferred stock, par value \$0.001 per share, all of which preferred stock will be undesignated.

As of June 30, 2019, we had issued and outstanding:

- 2,768,596 shares of our common stock held by 78 stockholders of record;
- 60,000,000 shares of our Series A preferred stock held by 3 stockholders of record, convertible into 8,571,427 shares of our common stock; and
- 52,500,000 shares of our Series B preferred stock held by 21 stockholders of record, convertible into 7,499,991 shares of our common stock.

Upon the closing of this offering, all of the outstanding shares of our preferred stock will automatically convert into an aggregate of 16,071,418 shares of our common stock.

Common Stock

Holders of our common stock are entitled to one vote for each share held on all matters submitted to a vote of stockholders and do not have cumulative voting rights. Each election of directors by our stockholders will be determined by a plurality of the votes cast by the stockholders entitled to vote on the election. Holders of common stock are entitled to receive proportionately any dividends as may be declared by our board of directors, subject to any preferential dividend rights of outstanding preferred stock.

In the event of our liquidation or dissolution, the holders of our common stock are entitled to receive proportionately all assets available for distribution to stockholders after the payment of all debts and other liabilities and subject to the prior rights of any of our outstanding preferred stock. Holders of our common stock have no preemptive, subscription, redemption or conversion rights. The rights, preferences and privileges of holders of our common stock are subject to and may be adversely affected by the rights of the holders of shares of any series of our preferred stock that we may designate and issue in the future.

Preferred Stock

Under the terms of our certificate of incorporation that will become effective upon the closing of this offering, our board of directors is authorized to issue shares of preferred stock in one or more series without stockholder approval. Our board of directors has the discretion to determine the rights, preferences, privileges and restrictions, including voting rights, dividend rights, conversion rights, redemption privileges and liquidation preferences, of each series of preferred stock.

The purpose of authorizing our board of directors to issue preferred stock and determine its rights and preferences is to eliminate delays associated with a stockholder vote on specific issuances. The issuance of preferred stock, while providing flexibility in connection with possible acquisitions, future financings and other corporate purposes, could have the effect of making it more difficult for a third party to acquire, or could discourage a third party from seeking to acquire, a majority of our outstanding voting stock. Upon the closing of this offering, there will be no shares of preferred stock outstanding, and we have no present plans to issue any shares of preferred stock.

Options and Unvested Restricted Stock

As of June 30, 2019, options to purchase an aggregate of 1,592,753 shares of our common stock, at a weighted average exercise price of \$7.81 per share, were outstanding, and 898,310 shares of unvested restricted common stock were outstanding.

Delaware Anti-Takeover Law and Certain Charter and Bylaw Provisions

Delaware Law

We are subject to Section 203 of the DGCL. Subject to certain exceptions, Section 203 prevents a publicly held Delaware corporation from engaging in a "business combination" with any "interested stockholder" for three years following the date that the person became an interested stockholder, unless either the interested stockholder attained such status with the approval of our board of directors, the business combination is approved by our board of directors and stockholders in a prescribed manner or the interested stockholder acquired at least 85% of our outstanding voting stock in the transaction in which it became an interested stockholder. A "business combination" includes, among other things, a merger or consolidation involving us and the "interested stockholder" and the sale of more than 10% of our assets. In general, an "interested stockholder" is any entity or person beneficially owning 15% or more of our outstanding voting stock and any entity or person affiliated with or controlling or controlled by such entity or person. The restrictions contained in Section 203 are not applicable to any of our existing stockholders that will own 15% or more of our outstanding voting stock upon the closing of this offering.

Staggered Board; Removal of Directors

Our certificate of incorporation and our bylaws to be effective upon the closing of this offering divide our board of directors into three classes with staggered three-year terms. In addition, our certificate of incorporation and our bylaws to be effective upon the closing of this offering provide that directors may be removed only for cause and only by the affirmative vote of the holders of 75% of our shares of capital stock present in person or by proxy and entitled to vote. Under our certificate of incorporation and our bylaws to be effective upon the closing of this offering, any vacancy on our board of directors, including a vacancy resulting from an enlargement of our board of directors, may be filled only by vote of a majority of our directors then in office. Furthermore, our certificate of incorporation to be effective upon the closing of this offering provides that the authorized number of directors may be changed only by the resolution of our board of directors. The classification of our board of directors and the limitations on the ability of our stockholders to remove directors, change the authorized number of directors and fill vacancies could make it more difficult for a third party to acquire, or discourage a third party from seeking to acquire, control of our company.

Stockholder Action; Special Meeting of Stockholders; Advance Notice Requirements for Stockholder Proposals and Director Nominations

Our certificate of incorporation and our bylaws to be effective upon the closing of this offering provide that any action required or permitted to be taken by our stockholders at an annual meeting or special meeting of stockholders may only be taken if it is properly brought before such meeting and may not be taken by written action in lieu of a meeting. Our certificate of incorporation and our bylaws to be effective upon the closing of this offering also provide that, except as otherwise required by law, special meetings of the stockholders can only be called by our board of directors. In addition, our bylaws to be effective upon the closing of this offering establish an advance notice procedure for stockholder proposals to be brought before an annual meeting of stockholders, including proposed nominations of candidates for election to our board of directors. Stockholders at an annual meeting may only consider proposals or nominations specified in the notice of meeting or brought before the meeting by or at the direction of our board of directors, or by a stockholder of record on the record date for the meeting who is entitled to vote

at the meeting and who has delivered timely written notice in proper form to our secretary of the stockholder's intention to bring such business before the meeting. These provisions could have the effect of delaying until the next stockholder meeting stockholder actions that are favored by the holders of a majority of our outstanding voting securities. These provisions also could discourage a third party from making a tender offer for our common stock because even if the third party acquired a majority of our outstanding voting stock, it would be able to take action as a stockholder, such as electing new directors or approving a merger, only at a duly called stockholders meeting and not by written consent.

Super-Majority Voting

The DGCL provides generally that the affirmative vote of a majority of the shares entitled to vote on any matter is required to amend a corporation's certificate of incorporation or bylaws unless a corporation's certificate of incorporation or bylaws, as the case may be, requires a greater percentage. Our bylaws to be effective upon the closing of this offering may be amended or repealed by a majority vote of our board of directors or the affirmative vote of the holders of at least 75% of the votes that all our stockholders would be entitled to cast in any annual election of directors. In addition, the affirmative vote of the holders of at least 75% of the votes that all our stockholders would be entitled to cast in any election of directors is required to amend or repeal or to adopt any provisions inconsistent with any of the provisions of our certificate of incorporation described above.

Exclusive Forum Selection

Our certificate of incorporation to be effective upon the closing of this offering provides that, unless we consent in writing to the selection of an alternative forum, the Court of Chancery of the State of Delaware (or, if the Court of Chancery of the State of Delaware does not have jurisdiction, the federal district court for the District of Delaware) shall be the sole and exclusive forum for (1) any derivative action or proceeding brought on our behalf, (2) any action asserting a claim of breach of a fiduciary duty owed by any of our directors, officers, other employees or stockholders to our company or our stockholders, (3) any action asserting a claim arising pursuant to any provision of the DGCL or as to which the DGCL confers jurisdiction on the Court of Chancery of the State of Delaware or (4) any action asserting a claim arising pursuant to any provision of our certificate of incorporation or bylaws (in each case, as they may be amended from time to time) or governed by the internal affairs doctrine. This exclusive forum provision will not apply to actions arising under the Securities Act or the Exchange Act. Although our certificate of incorporation contains the choice of forum provision described above, it is possible that a court could rule that such a provision is inapplicable for a particular claim or action or that such provision is unenforceable.

Registration Rights

We have entered into an amended and restated investor rights agreement dated as of August 24, 2018, or the investor rights agreement, with holders of our preferred stock. Beginning six months following the closing of this offering, holders of a total of 16,357,132 shares of our common stock will have the right to require us to register these shares under the Securities Act under specified circumstances. We refer to the shares with these registration rights as registrable securities. After registration pursuant to these rights, the registrable securities will become freely tradable without restriction under the Securities Act.

Demand and Form S-3 Registration Rights

Beginning 180 days after this offering, subject to specified limitations set forth in the investor rights agreement, at any time, the holders of at least 40% of the then outstanding registrable securities may demand that we register at least 40% of the registrable securities then outstanding under the Securities Act for purposes of a public offering having an aggregate offering price to the public of not less than

\$5.0 million. We are not obligated to file a registration statement pursuant to this provision on more than two occasions.

In addition, subject to specified limitations set forth in the investor rights agreement, at any time after we become eligible to file a registration statement on Form S-3, the holders of at least 25% of the then outstanding registrable securities may request that we register their registrable securities on Form S-3 for purposes of a public offering for which the reasonably anticipated aggregate offering price to the public would be at least \$3.0 million. We are not obligated to file a registration statement pursuant to this provision on more than two occasions in any 12-month period.

Incidental Registration Rights

If, at any time after the closing of this offering, we propose to register for our own account any of our securities under the Securities Act, the holders of registrable securities will be entitled to notice of the registration and, subject to specified exceptions, have the right to require us to use our commercially reasonable efforts to register all or a portion of the registrable securities then held by them in that registration.

In the event that any registration in which the holders of registrable securities participate pursuant to our investor rights agreement is an underwritten public offering, we have agreed to enter into an underwriting agreement in usual and customary form and use our reasonable best efforts to facilitate such offering.

Expenses

Pursuant to the investor rights agreement, we are required to pay all registration expenses, including all registration and filing fees, exchange listing fees, printing expenses, fees and expenses of one counsel selected by the selling stockholders to represent the selling stockholders, state Blue Sky fees and expenses, and the expense of any special audits incident to or required by any such registration, but excluding underwriting discounts, selling commissions, stock transfer taxes applicable to the sale any registrable securities and the fees and expenses of the selling stockholders' own counsel (other than the counsel selected to represent all selling stockholders). If a registration is withdrawn at the request of the stockholders initiating the registration, then the stockholders will bear the expenses of the registration.

The investor rights agreement contains customary cross-indemnification provisions, pursuant to which we are obligated to indemnify the selling stockholders in the event of material misstatements or omissions in the registration statement attributable to us or any violation or alleged violation whether by action or inaction by us under the Securities Act, the Exchange Act, any state securities or Blue Sky law or any rule or regulation promulgated under the Securities Act, the Exchange Act or any state securities or Blue Sky law in connection with such registration statement or the qualification or compliance of the offering, and they are obligated to indemnify us for material misstatements or omissions in the registration statement attributable to them.

Transfer Agent and Registrar

The transfer agent and registrar for our common stock is Computershare Trust Company N.A.

Nasdaq Global Market

Our common stock has been approved for listing on the Nasdaq Global Market under the symbol "FULC."

SHARES ELIGIBLE FOR FUTURE SALE

Prior to this offering, there has been no public market for our common stock, and a liquid trading market for our common stock may not develop or be sustained after this offering. Future sales of substantial amounts of our common stock in the public market, including shares issued upon exercise of outstanding options, or the anticipation of these sales, could adversely affect market prices prevailing from time to time and could impair our ability to raise capital through sales of equity securities.

Upon the closing of this offering, we will have outstanding 23,340,014 shares of our common stock, based on the 2,768,596 shares of our common stock that were outstanding on June 30, 2019, after giving effect to the issuance of 4,500,000 shares of our common stock in this offering, assuming no exercise by the underwriters of their option to purchase additional shares of our common stock, and the conversion of all outstanding shares of our preferred stock into an aggregate of 16,071,418 shares of our common stock upon the closing of this offering. Of these shares, all shares sold in this offering will be freely tradable without restriction under the Securities Act of 1933, as amended, or the Securities Act, unless purchased by our "affiliates," as that term is defined in Rule 144 under the Securities Act. The remaining 18,840,014 shares of our common stock will be "restricted securities" under Rule 144, and substantially all of these restricted securities will be subject to the 180-day lock-up period under the lock-up agreements as described below. These restricted securities may be sold in the public market upon release or waiver of any applicable lock-up agreements and only if registered or pursuant to an exemption from registration, such as Rule 144 or Rule 701 under the Securities Act.

Rule 144

In general, under Rule 144, beginning 90 days after the date of this prospectus, any person who is not our affiliate and has held their shares for at least six months, including the holding period of any prior owner other than one of our affiliates, may sell those shares without restriction, subject to the availability of current public information about us. In addition, under Rule 144, any person who is not our affiliate and has not been our affiliate at any time during the preceding three months and has held their shares for at least one year, including the holding period of any prior owner other than one of our affiliates, would be entitled to sell an unlimited number of shares immediately upon the closing of this offering without regard to whether current public information about us is available.

Beginning 90 days after the date of this prospectus, a person who is our affiliate or who was our affiliate at any time during the preceding three months and who has beneficially owned restricted securities for at least six months, including the holding period of any prior owner other than one of our affiliates, is entitled to sell a number of shares within any three-month period that does not exceed the greater of:

- 1% of the number of shares of our common stock then outstanding, which will equal approximately 233,400 shares immediately after this offering; and
- the average weekly trading volume in our common stock on the Nasdaq Global Market during the four calendar weeks preceding the date of filing of a Notice of Proposed Sale of Securities Pursuant to Rule 144 with respect to the sale.

Sales under Rule 144 by our affiliates are also subject to manner of sale provisions and notice requirements and to the availability of current public information about us.

Upon waiver or expiration of the 180-day lock-up period described below, approximately 18,840,014 shares of our common stock will be eligible for sale under Rule 144. We cannot estimate the number of shares of our common stock that our existing stockholders will elect to sell under Rule 144.

Rule 701

In general, under Rule 701 of the Securities Act, any of our employees, consultants or advisors, other than our affiliates, who purchased shares from us in connection with a qualified compensatory stock plan or other written agreement is eligible to resell these shares 90 days after the date of this prospectus in reliance on Rule 144, but without compliance with the various restrictions, including the availability of public information about us, holding period and volume limitations, contained in Rule 144. Substantially all Rule 701 shares are subject to the 180-day lock-up period described below and will be eligible for sale in accordance with Rule 701 upon expiration of the restrictions set forth in those agreements.

Lock-up Agreements

We, each of our executive officers and directors and the other holders of substantially all of our outstanding securities have agreed that, without the prior written consent of Morgan Stanley & Co. LLC, BofA Securities, Inc. and SVB Leerink LLC, on behalf of the underwriters, we and they will not, subject to limited exceptions, during the period ending 180 days after the date of this prospectus:

- offer, pledge, sell, contract to sell, sell any option or contract to purchase, purchase any option or contract to sell, grant any option, right or warrant to purchase, lend or otherwise transfer or dispose of, directly or indirectly, any shares of common stock or any securities convertible into or exercisable or exchangeable for shares of common stock, or make any public announcement of an intention to do any of the foregoing;
- file, or demand filing of, any registration statement with the SEC relating to the offering of any shares of common stock or any securities convertible into or exercisable or exchangeable for common stock; or
- enter into any swap or other arrangement that transfers to another, in whole or in part, any of the economic consequences of ownership of the common stock, whether any such transaction is to be settled by delivery of common stock or such other securities, in cash or otherwise.

These agreements are subject to certain exceptions, as described in the section of this prospectus entitled "Underwriters."

Registration Rights

Beginning six months after the closing of this offering, the holders of an aggregate of 16,357,132 shares of our common stock will have rights, subject to certain conditions, to require us to file registration statements covering their shares or to include their shares in registration statements that we may file for ourselves or other stockholders. After registration pursuant to these rights, these shares will become freely tradable without restriction under the Securities Act. See "Description of Capital Stock—Registration Rights" for additional information regarding these registration rights.

Stock Options and Form S-8 Registration Statement

As of June 30, 2019, we had outstanding options to purchase an aggregate of 1,592,753 shares of our common stock under the 2016 Plan, of which options to purchase 109,951 shares were vested. Following this offering, we intend to file a registration statement on Form S-8 under the Securities Act to register all of the shares of our common stock subject to outstanding options and reserved for future options and other awards under the 2016 Plan, the 2019 Plan and the 2019 ESPP. See "Executive Compensation—Stock Option and Other Compensation Plans" for additional information regarding these plans. Accordingly, shares of our common stock registered under the registration statements will be available for sale in the open market, subject to Rule 144 volume limitations applicable to affiliates, and subject to any vesting restrictions and lock-up agreements applicable to these shares.

**MATERIAL U.S. FEDERAL INCOME AND ESTATE TAX CONSIDERATIONS
FOR NON-U.S. HOLDERS OF COMMON STOCK**

The following is a discussion of material U.S. federal income and estate tax considerations relating to the ownership and disposition of shares of our common stock acquired in this offering by a non-U.S. holder. For purposes of this discussion, the term "non-U.S. holder" means a beneficial owner (other than a partnership or other pass-through entity) of our common stock that is not, for U.S. federal income tax purposes:

- an individual who is a citizen or resident of the United States;
- a corporation, or other entity treated as a corporation, created or organized in or under the laws of the United States, any state thereof or the District of Columbia;
- an estate the income of which is subject to U.S. federal income taxation regardless of its source; or
- a trust if (1) a U.S. court is able to exercise primary supervision over the administration of the trust and one or more U.S. persons have authority to control all substantial decisions of the trust or (2) the trust has a valid election in effect under applicable U.S. Treasury Regulations to be treated as a U.S. person.

This discussion does not address the tax treatment of partnerships or other entities that are pass-through entities for U.S. federal income tax purposes or persons who hold shares of our common stock through partnerships or such other pass-through entities. The tax treatment of a partner in a partnership or other entity that is treated as a pass-through entity for U.S. federal income tax purposes generally will depend upon the status of the partner and the activities of the partnership. A partner in a partnership or other pass-through entity that will hold our common stock should consult his, her or its own tax advisor regarding the tax consequences of the ownership and disposition of our common stock through a partnership or other pass-through entity, as applicable.

This discussion is based on current provisions of the U.S. Internal Revenue Code of 1986, as amended, which we refer to as the Code, existing and proposed U.S. Treasury Regulations promulgated thereunder, current administrative rulings and judicial decisions, all as in effect as of the date of this prospectus and all of which are subject to change or to differing interpretation, possibly with retroactive effect. Any change or differing interpretation could alter the tax consequences to non-U.S. holders described in this prospectus. There can be no assurance that the Internal Revenue Service, or the IRS, will not challenge one or more of the tax consequences described in this prospectus.

This discussion addresses only non-U.S. holders that hold shares of our common stock as a capital asset (generally, property held for investment) for U.S. federal income tax purposes. This discussion does not address all aspects of U.S. federal income and estate taxation that may be relevant to a particular non-U.S. holder in light of that non-U.S. holder's individual circumstances nor does it address any aspects of U.S. state, local or non-U.S. taxes, the alternative minimum tax, or the Medicare tax on net investment income. This discussion also does not consider any specific facts or circumstances that may apply to a non-U.S. holder and does not address the special tax rules applicable to particular non-U.S. holders, such as:

- financial institutions;
- brokers or dealers in securities;
- tax-exempt or governmental organizations;
- pension plans;
- owners that hold our common stock as part of a straddle, hedge, conversion transaction, synthetic security or other integrated investment or who have elected to mark securities to market;

- insurance companies;
- controlled foreign corporations;
- passive foreign investment companies;
- non-U.S. governments; and
- certain U.S. expatriates.

THIS DISCUSSION IS FOR INFORMATION ONLY AND IS NOT, AND IS NOT INTENDED TO BE, LEGAL OR TAX ADVICE. PROSPECTIVE INVESTORS SHOULD CONSULT THEIR OWN TAX ADVISORS REGARDING THE U.S. FEDERAL, STATE, LOCAL, ESTATE AND NON-U.S. INCOME AND OTHER TAX CONSIDERATIONS OF ACQUIRING, HOLDING AND DISPOSING OF OUR COMMON STOCK, INCLUDING THE CONSEQUENCES OF ANY PROPOSED CHANGES IN APPLICABLE LAWS.

Distributions

As discussed under the heading "Dividend Policy" above, we do not expect to pay cash dividends to holders of our common stock in the foreseeable future. If we make distributions in respect of our common stock, those distributions generally will constitute dividends for U.S. federal income tax purposes to the extent paid from our current or accumulated earnings and profits, as determined under U.S. federal income tax principles. If a distribution exceeds our current and accumulated earnings and profits, the excess will be treated as a tax-free return of the non-U.S. holder's investment, up to the non-U.S. holder's tax basis in the common stock. Any remaining excess will be treated as capital gain, subject to the tax treatment described below under the heading "Gain on Sale, Exchange or Other Taxable Disposition of Our Common Stock."

Subject to the discussions below under the headings "Information Reporting and Backup Withholding" and "FATCA", dividends paid to a non-U.S. holder generally will be subject to withholding of U.S. federal income tax at a 30% rate or such lower rate as may be specified by an applicable income tax treaty between the United States and such holder's country of residence. A non-U.S. holder of our common stock who claims the benefit of an applicable income tax treaty between the United States and such holder's country of residence generally will be required to provide a properly executed IRS Form W-8BEN or W-8BEN-E (or successor form) and satisfy applicable certification and other requirements. A non-U.S. holder that is eligible for a reduced rate of U.S. withholding tax under an income tax treaty may obtain a refund or credit of any excess amounts withheld by timely filing an appropriate claim with the IRS. Non-U.S. holders are urged to consult their own tax advisors regarding their entitlement to benefits under a relevant income tax treaty and the specific methods available to them to satisfy these requirements.

Dividends that are treated as effectively connected with a trade or business conducted by a non-U.S. holder within the United States, and, if an applicable income tax treaty so provides, that are attributable to a permanent establishment or a fixed base maintained by the non-U.S. holder within the United States, are generally exempt from the 30% withholding tax if the non-U.S. holder satisfies applicable certification and disclosure requirements (generally including provision of a properly executed IRS Form W-8ECI (or applicable successor form) certifying that the dividends are effectively connected with the non-U.S. holder's conduct of a trade or business within the United States). However, such U.S. effectively connected income is taxed on a net income basis at the same U.S. federal income tax rates applicable to U.S. persons (as defined in the Code). Any U.S. effectively connected income received by a non-U.S. holder that is classified as a corporation for U.S. federal income tax purposes may also, under certain circumstances, be subject to an additional "branch profits tax" at a 30% rate or such lower rate as may be specified by an applicable income tax treaty between the United States and such holder's country of residence.

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

A non-U.S. holder generally will not be subject to U.S. federal income tax on gain recognized on the non-U.S. holder's sale, exchange or other disposition of our common stock unless:

- the gain is effectively connected with the non-U.S. holder's conduct of a trade or business in the United States, and, if an applicable income tax treaty so provides, the gain is attributable to a permanent establishment or fixed base maintained by the non-U.S. holder in the United States, in which case, the non-U.S. holder generally will be taxed on a net income basis at the U.S. federal income tax rates applicable to U.S. persons (as defined in the Code) and, if the non-U.S. holder is a foreign corporation, an additional branch profits tax at a rate of 30% (or a lower rate as may be specified by an applicable income tax treaty between the United States and such holder's country of residence) may also apply;
- the non-U.S. holder is a non-resident alien present in the United States for 183 days or more in the taxable year of the disposition and certain other requirements are met, in which case the non-U.S. holder will be subject to a 30% tax (or such lower rate as may be specified by an applicable income tax treaty between the United States and such holder's country of residence) on the net gain derived from the disposition, which may be offset by certain U.S.-source capital losses of the non-U.S. holder, if any; or
- we are, or have been, at any time during the five-year period preceding such disposition (or the non-U.S. holder's holding period, if shorter) a "U.S. real property holding corporation," unless our common stock is regularly traded on an established securities market and the non-U.S. holder held no more than 5% of our outstanding common stock, directly or indirectly, during the shorter of the five-year period ending on the date of the disposition or the period that the non-U.S. holder held our common stock. If we are determined to be a "U.S. real property holding corporation" and the foregoing exception does not apply, then the non-U.S. holder generally will be taxed on its net gain derived from the disposition at the U.S. federal income tax rates applicable to U.S. persons (as defined in the Code). Generally, a corporation is a "U.S. real property holding corporation" only if the fair market value of its "U.S. real property interests" (as defined in the Code and applicable regulations) equals or exceeds 50% of the sum of the fair market value of its worldwide real property interests plus its other assets used or held for use in a trade or business. Although there can be no assurance, we do not believe that we are, or have been, a "U.S. real property holding corporation" for U.S. federal income tax purposes, or that we are likely to become one in the future. No assurance can be provided that our common stock will be regularly traded on an established securities market for purposes of the rule described above.

U.S. Federal Estate Tax

Shares of our common stock that are owned or treated as owned by an individual who is not a citizen or resident of the United States (as specially defined for U.S. federal estate tax purposes) at the time of such individual's death are considered U.S.-situs assets and will be included in the individual's gross estate for U.S. federal estate tax purposes. Such shares, therefore, may be subject to U.S. federal estate tax, unless an applicable estate tax or other treaty provides otherwise.

Information Reporting and Backup Withholding

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

Form W-8), or otherwise meets documentary evidence requirements for establishing that it is a non-U.S. holder, or otherwise establishes an exemption. Dividends paid to non-U.S. holders subject to withholding of U.S. federal income tax, as described above under the heading "—Distributions," will generally be exempt from U.S. backup withholding.

Information reporting and backup withholding generally will apply to the proceeds of a disposition of our common stock by a non-U.S. holder effected by or through the U.S. office of any broker, U.S. or non-U.S., unless the holder certifies its status as a non-U.S. holder and satisfies certain other requirements, or otherwise establishes an exemption. Generally, information reporting and backup withholding will not apply to a payment of disposition proceeds to a non-U.S. holder where the transaction is effected outside the United States through a non-U.S. office of a broker. However, for information reporting purposes, dispositions effected through a non-U.S. office of a broker with substantial U.S. ownership or operations generally will be treated in a manner similar to dispositions effected through a U.S. office of a broker. Non-U.S. holders should consult their own tax advisors regarding the application of the information reporting and backup withholding rules to them.

Copies of information returns may be made available to the tax authorities of the country in which the non-U.S. holder resides or is incorporated under the provisions of a specific treaty or agreement.

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

FATCA

Provisions of the Code commonly referred to as the Foreign Account Tax Compliance Act, or FATCA, generally impose a 30% withholding tax on dividends on, and, subject to the discussion below with respect to proposed U.S. Treasury Regulations excluding gross proceeds from such required withholding, gross proceeds from the sale or other disposition of, our common stock if paid to a foreign entity unless (i) if the foreign entity is a "foreign financial institution," the foreign entity undertakes certain due diligence, reporting, withholding and certification obligations, (ii) if the foreign entity is not a "foreign financial institution," the foreign entity identifies certain of its U.S. investors, if any, or (iii) the foreign entity is otherwise excepted under FATCA.

Withholding under FATCA generally applies to payments of dividends on our common stock. While withholding under FATCA may apply to payments of gross proceeds from a sale or other disposition of our common stock, under recently proposed U.S. Treasury Regulations withholding on payments of gross proceeds is not required. Although such regulations are not final, applicable withholding agents may rely on the proposed regulations until final regulations are issued.

If withholding under FATCA is required on any payment related to our common stock, investors not otherwise subject to withholding (or that otherwise would be entitled to a reduced rate of withholding) on such payment may be required to seek a refund or credit from the IRS. An intergovernmental agreement between the United States and an applicable foreign country may modify the requirements described in this section. Non-U.S. holders should consult their own tax advisors regarding the possible implications of FATCA on their investment in our common stock and the entities through which they hold our common stock, including, without limitation, the process and deadlines for meeting the applicable requirements to prevent the imposition of the 30% withholding tax under FATCA.

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

UNDERWRITERS

Under the terms and subject to the conditions in an underwriting agreement dated the date of this prospectus, the underwriters named below severally agreed to purchase, and we agreed to sell to them, severally, the number of shares indicated below:

<u>Name</u>	<u>Number of Shares</u>
Morgan Stanley & Co. LLC	1,800,000
BofA Securities, Inc.	1,530,000
SVB Leerink LLC	1,170,000
Total:	<u>4,500,000</u>

The underwriters are collectively referred to as the "underwriters". The underwriters are offering the shares of common stock subject to their acceptance of the shares from us and subject to prior sale. The underwriting agreement provides that the obligations of the several underwriters to pay for and accept delivery of the shares of common stock offered by this prospectus are subject to the approval of certain legal matters by their counsel and to certain other conditions. The underwriters are obligated to take and pay for all of the shares of common stock offered by this prospectus if any such shares are taken. However, the underwriters are not be required to take or pay for the shares covered by the underwriters' over-allotment option described below.

The underwriters initially propose to offer part of the shares of common stock directly to the public at the offering price listed on the cover page of this prospectus and part to certain dealers at a price that represents a concession not in excess of \$0.672 per share under the public offering price. After the initial offering of the shares of common stock, the offering price and other selling terms may from time to time be varied by the underwriters.

We have granted to the underwriters an option, exercisable for 30 days from the date of this prospectus, to purchase up to 675,000 additional shares of common stock at the public offering price listed on the cover page of this prospectus, less underwriting discounts and commissions. The underwriters may exercise this option solely for the purpose of covering over-allotments, if any, made in connection with the offering of the shares of common stock offered by this prospectus. To the extent the option is exercised, each underwriter will become obligated, subject to certain conditions, to purchase about the same percentage of the additional shares of common stock as the number listed next to the underwriter's name in the preceding table bears to the total number of shares of common stock listed next to the names of all underwriters in the preceding table.

The following table shows the per share and total public offering price, underwriting discounts and commissions, and proceeds before expenses to us. These amounts are shown assuming both no exercise and full exercise of the underwriters' option to purchase up to an additional 675,000 shares of common stock.

	<u>Per Share</u>	<u>Total</u>	
		<u>No Exercise</u>	<u>Full Exercise</u>
Public offering price	\$ 16.00	\$ 72,000,000	\$ 82,800,000
Underwriting discounts and commissions to be paid by us ⁽¹⁾	1.12	5,040,000	5,796,000
Proceeds, before expenses, to us	<u>\$ 14.88</u>	<u>\$ 66,960,000</u>	<u>\$ 77,004,000</u>

(1) Does not include an advisory fee of \$200,000 payable by us upon consummation of the offering.

The estimated offering expenses payable by us, exclusive of the underwriting discounts and commissions, are approximately \$2.9 million. We have agreed to reimburse the underwriters for expenses relating to clearance of this offering with the Financial Industry Regulatory Authority up to \$30,000.

The underwriters have informed us that they do not intend sales to discretionary accounts to exceed 5% of the total number of shares of common stock offered by them.

Our common stock has been approved for listing on the Nasdaq Global Market under the symbol "FULC".

We and all of our directors and officers and the other holders of substantially all of our outstanding securities have agreed that, without the prior written consent of the underwriters, we and they will not, subject to limited exceptions, during the period ending 180 days after the date of this prospectus (the "restricted period"):

- offer, pledge, sell, contract to sell, sell any option or contract to purchase, purchase any option or contract to sell, grant any option, right or warrant to purchase, lend or otherwise transfer or dispose of, directly or indirectly, any shares of common stock or any securities convertible into or exercisable or exchangeable for shares of common stock, or make any public announcement of an intention to do any of the foregoing;
- file, or demand filing of, any registration statement with the SEC relating to the offering of any shares of common stock or any securities convertible into or exercisable or exchangeable for common stock; or
- enter into any swap or other arrangement that transfers to another, in whole or in part, any of the economic consequences of ownership of the common stock,

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

The restrictions on transfers or other dispositions by holders of our outstanding securities described in the immediately preceding paragraph do not apply to:

- transactions relating to shares of common stock or other securities acquired in this offering or in open market transactions after the completion of this offering, provided that no filing under Section 16(a) of the Exchange Act shall be required or shall be voluntarily made in connection with subsequent sales of common stock or other securities acquired in such open market transactions;
- transfers of shares of common stock or any security convertible into or exercisable or exchangeable for common stock as a bona fide gift or gifts, or to a charitable organization or educational institution in a transaction not involving a disposition for value;
- transfers of shares of common stock or any security convertible into or exercisable or exchangeable for common stock to any member of the immediate family of the signatory or any trust for the direct or indirect benefit of the signatory or the immediate family of the signatory in a transaction not involving a disposition for value;
- transfers of shares of common stock or any security convertible into or exercisable or exchangeable for common stock (i) by will, other testamentary document or intestate succession to the legal representative, heir, beneficiary or a member of the immediate family of the signatory upon the death of the signatory or (ii) solely by operation of law pursuant to a qualified domestic order or in connection with a divorce settlement;

- if the signatory is an entity, transfers or distributions of shares of common stock or any security convertible into common stock to general or limited partners, members or stockholders of the signatory, the signatory's direct and indirect affiliates, or to an investment fund or other entity that controls or manages, or is under common control with, the signatory;
- transfers or dispositions of shares of common stock or any security convertible into or exercisable or exchangeable for common stock to us pursuant to any contractual arrangement in effect on the date of the lock-up agreement and disclosed to the underwriters that provides for the repurchase of the signatory's common stock or other securities by us or in connection with the termination of the signatory's employment with or service to us; provided that, subject to certain limited exceptions, no filing under Section 16(a) of the Exchange Act reporting a reduction in beneficial ownership of shares of common stock shall be required or shall be voluntarily made during the restricted period in connection with any such transfers or dispositions;
- the conversion of outstanding shares of preferred stock described in this prospectus and outstanding as of the date of this prospectus into shares of common stock as described in this prospectus, provided that the shares of common stock received upon conversion shall be subject to the restrictions set forth in the lock-up agreement;
- the exercise of stock options to purchase shares of common stock granted under plans described in this prospectus and any related transfer to us of shares of common stock, subject to certain limitations, including that any shares of common stock received upon exercise shall be subject to the restrictions on transfer set forth in the lock-up agreement; provided that, subject to certain limited exceptions, no filing under Section 16(a) of the Exchange Act reporting a reduction in beneficial ownership of shares of common stock shall be required or shall be voluntarily made during the restricted period;
- the establishment of a trading plan pursuant to Rule 10b5-1 under the Exchange Act for the transfer of shares of common stock, provided that (i) such plan does not provide for the transfer of common stock during the restricted period and (ii) to the extent a public announcement or filing under the Exchange Act, if any, is required or voluntarily made regarding the establishment of such plan, such announcement or filing shall include a statement to the effect that no transfer of common stock may be made under such plan during the restricted period; or
- (i) transfers of shares of common stock (or any securities convertible into or exercisable or exchangeable for common stock) pursuant to a bona fide third-party tender offer for shares of our capital stock made to all holders of securities, merger, consolidation or other similar transaction approved by our board of directors the result of which is a change of control or (ii) entry into any lock-up, voting or similar agreement pursuant to which the signatory may agree to transfer, sell, tender or otherwise dispose of shares of common stock or such other securities in connection with such a change of control;

provided that in the case of any transfer, disposition or distribution pursuant to the second, third, fourth or fifth bullet (i) each transferee, donee or distributee shall agree to be subject to the restrictions described in the immediately preceding paragraph and (ii) no filing under Section 16(a) of the Exchange Act, reporting a reduction in beneficial ownership of shares of common stock, shall be required or shall be voluntarily made during the restricted period (other than, in the case of a transfer or other disposition pursuant to the third bullet above, any Form 4 or Form 5 required to be filed under the Exchange Act if the signatory is subject to Section 16 reporting with respect to us under the Exchange Act and indicating by footnote disclosure or otherwise the nature of the transfer or disposition).

The restrictions on transfers or other dispositions by us described in the paragraph above do not apply to:

- the shares to be sold in this offering;
- the issuance by us of shares of common stock upon the exercise of an option or a warrant or the conversion of a security outstanding on the date of this prospectus pursuant to stock plans disclosed in this prospectus;
- the grant by us of any options to purchase shares of common stock or other awards granted under a stock incentive plan or stock purchase plan described in this prospectus, and the issuance by us of shares of common stock upon the exercise thereof, provided that we will cause each recipient of such grant to execute and deliver to the underwriters a lock-up agreement if such recipient has not already delivered one;
- the filing by the us of any registration statement on Form S-8 or a successor form thereto relating to the shares of common stock granted pursuant to or reserved for issuance under a stock incentive plan or stock purchase plan described in this prospectus; or
- shares of common stock or other securities issued in connection with a joint venture, equipment leasing arrangement, licensing or collaboration transaction or other strategic transaction with an unaffiliated third party, provided that (x) the aggregate number of shares issued pursuant to this exception will not exceed 5% of the total number of outstanding shares of common stock immediately following the issuance and sale of the shares to be sold in this offering and (y) the recipient of any such shares of common stock and securities issued pursuant to this exception during the restricted period will enter into a lock-up agreement.

The underwriters, in their sole discretion, may release the common stock and other securities subject to the lock-up agreements described above in whole or in part at any time.

In order to facilitate the offering of the common stock, the underwriters may engage in transactions that stabilize, maintain or otherwise affect the price of the common stock. Specifically, the underwriters may sell more shares than they are obligated to purchase under the underwriting agreement, creating a short position. A short sale is covered if the short position is no greater than the number of shares available for purchase by the underwriters under the over-allotment option. The underwriters can close out a covered short sale by exercising the over-allotment option or purchasing shares in the open market. In determining the source of shares to close out a covered short sale, the underwriters will consider, among other things, the open market price of shares compared to the price available under the over-allotment option. The underwriters may also sell shares in excess of the over-allotment option, creating a naked short position. The underwriters must close out any naked short position by purchasing shares in the open market. A naked short position is more likely to be created if the underwriters are concerned that there may be downward pressure on the price of the common stock in the open market after pricing that could adversely affect investors who purchase in this offering. As an additional means of facilitating this offering, the underwriters may bid for, and purchase, shares of common stock in the open market to stabilize the price of the common stock. These activities may raise or maintain the market price of the common stock above independent market levels or prevent or retard a decline in the market price of the common stock. The underwriters are not required to engage in these activities and may end any of these activities at any time.

We and the underwriters have agreed to indemnify each other against certain liabilities, including liabilities under the Securities Act.

A prospectus in electronic format may be made available on websites maintained by one or more underwriters, or selling group members, if any, participating in this offering. The underwriters may agree to allocate a number of shares of common stock for sale to their online brokerage account holders.

Internet distributions will be allocated to underwriters that may make Internet distributions on the same basis as other allocations.

The underwriters and their respective affiliates are full service financial institutions engaged in various activities, which may include securities trading, commercial and investment banking, financial advisory, investment management, investment research, principal investment, hedging, financing and brokerage activities. Certain of the underwriters and their respective affiliates have, from time to time, performed, and may in the future perform, various financial advisory and investment banking services for us, for which they received or will receive customary fees and expenses.

In addition, in the ordinary course of their various business activities, the underwriters and their respective affiliates may make or hold a broad array of investments and actively trade debt and equity securities (or related derivative securities) and financial instruments (including bank loans) for their own account and for the accounts of their customers and may at any time hold long and short positions in such securities and instruments. Such investment and securities activities may involve our securities and instruments. The underwriters and their respective affiliates may also make investment recommendations or publish or express independent research views in respect of such securities or instruments and may at any time hold, or recommend to clients that they acquire, long or short positions in such securities and instruments.

Pricing of the Offering

Prior to this offering, there has been no public market for our common stock. The initial public offering price has been determined by negotiations between us and the underwriters. Among the factors considered in determining the initial public offering price are our future prospects and those of our industry in general, our sales, earnings and certain other financial and operating information in recent periods, and the price-earnings ratios, price-sales ratios, market prices of securities, and certain financial and operating information of companies engaged in activities similar to ours.

Selling Restrictions

European Economic Area

In relation to each Member State of the European Economic Area which has implemented the Prospectus Directive (each, a "Relevant Member State") an offer to the public of any shares of our common stock may not be made in that Relevant Member State, except that an offer to the public in that Relevant Member State of any shares of our common stock may be made at any time under the following exemptions under the Prospectus Directive, if they have been implemented in that Relevant Member State:

- (a) to any legal entity which is a qualified investor as defined in the Prospectus Directive;
- (b) to fewer than 100 or, if the Relevant Member State has implemented the relevant provision of the 2010 PD Amending Directive, 150, natural or legal persons (other than qualified investors as defined in the Prospectus Directive), as permitted under the Prospectus Directive, subject to obtaining the prior consent of the underwriters for any such offer; or
- (c) in any other circumstances falling within Article 3(2) of the Prospectus Directive, provided that no such offer of shares of our common stock shall result in a requirement for the publication by us or any underwriter of a prospectus pursuant to Article 3 of the Prospectus Directive.

For the purposes of this provision, the expression an "offer to the public" in relation to any shares of our common stock in any Relevant Member State means the communication in any form and by any means of sufficient information on the terms of the offer and any shares of our common stock to be offered so as to enable an investor to decide to purchase any shares of our common stock, as the same may be varied in that Member State by any measure implementing the Prospectus Directive in that Member State, the expression "Prospectus Directive" means Directive 2003/71/EC (and amendments thereto, including the 2010 PD Amending Directive, to the extent implemented in the Relevant Member State), and includes any relevant implementing measure in the Relevant Member State, and the expression "2010 PD Amending Directive" means Directive 2010/73/EU.

United Kingdom

Each underwriter has represented and agreed that:

- (a) it has only communicated or caused to be communicated and will only communicate or cause to be communicated an invitation or inducement to engage in investment activity (within the meaning of Section 21 of the Financial Services and Markets Act 2000 ("FSMA") received by it in connection with the issue or sale of the shares of our common stock in circumstances in which Section 21(1) of the FSMA does not apply to us; and
- (b) it has complied and will comply with all applicable provisions of the FSMA with respect to anything done by it in relation to the shares of our common stock in, from or otherwise involving the United Kingdom.

Japan

No registration pursuant to Article 4, paragraph 1 of the Financial Instruments and Exchange Law of Japan (Law No. 25 of 1948, as amended) (the "FIEL") has been made or will be made with respect to the solicitation of the application for the acquisition of the shares of common stock.

Accordingly, the shares of common stock have not been, directly or indirectly, offered or sold and will not be, directly or indirectly, offered or sold in Japan or to, or for the benefit of, any resident of Japan (which term as used herein means any person resident in Japan, including any corporation or other entity organized under the laws of Japan) or to others for re-offering or re-sale, directly or indirectly, in Japan or to, or for the benefit of, any resident of Japan except pursuant to an exemption from the registration requirements, and otherwise in compliance with, the FIEL and the other applicable laws and regulations of Japan.

For Qualified Institutional Investors ("QII")

Please note that the solicitation for newly-issued or secondary securities (each as described in Paragraph 2, Article 4 of the FIEL) in relation to the shares of common stock constitutes either a "QII only private placement" or a "QII only secondary distribution" (each as described in Paragraph 1, Article 23-13 of the FIEL). Disclosure regarding any such solicitation, as is otherwise prescribed in Paragraph 1, Article 4 of the FIEL, has not been made in relation to the shares of common stock. The shares of common stock may only be transferred to QIIs.

For Non-QII Investors

Please note that the solicitation for newly-issued or secondary securities (each as described in Paragraph 2, Article 4 of the FIEL) in relation to the shares of common stock constitutes either a "small number private placement" or a "small number private secondary distribution" (each as is described in Paragraph 4, Article 23-13 of the FIEL). Disclosure regarding any such solicitation, as is otherwise prescribed in Paragraph 1, Article 4 of the FIEL, has not been made in relation to the shares of common stock. The shares of common stock may only be transferred en bloc without subdivision to a single investor.

Canada

Shares of our common stock may be sold only to purchasers purchasing, or deemed to be purchasing, as principal that are accredited investors, as defined in National Instrument 45-106 *Prospectus Exemptions* or subsection 73.3(1) of the *Securities Act* (Ontario), and are permitted clients, as defined in National Instrument 31-103 *Registration Requirements, Exemptions and Ongoing Registrant Obligations*. Any resale of shares of our common stock must be made in accordance with an exemption from, or in a transaction not subject to, the prospectus requirements of applicable securities laws.

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

Pursuant to section 3A.3 (or, in the case of securities issued or guaranteed by the government of a non-Canadian jurisdiction, section 3A.4) of National Instrument 33-105 Underwriting Conflicts (NI 33-105), the underwriters are not required to comply with the disclosure requirements of NI 33-105 regarding underwriter conflicts of interest in connection with this offering.

Israel

This prospectus does not constitute a prospectus under the Israeli Securities Law, 5728-1968, and has not been filed with or approved by the Israel Securities Authority. In Israel, this prospectus is being distributed only to, and is directed only at, investors listed in the first addendum, or the Addendum, to the Israeli Securities Law, consisting primarily of joint investment in trust funds, provident funds, insurance companies, banks, portfolio managers, investment advisors, members of the Tel Aviv Stock Exchange, underwriters purchasing for their own account, venture capital funds, and entities with shareholders' equity in excess of NIS 50 million, each as defined in the Addendum (as it may be amended from time to time, collectively referred to as institutional investors). Institutional investors may be required to submit written confirmation that they fall within the scope of the Addendum. In addition, we may distribute and direct this prospectus in Israel, at our sole discretion, to certain other exempt investors or to investors who do not qualify as institutional or exempt investors, provided that the number of such non-qualified investors in Israel shall be no greater than 35 in any 12-month period.

Switzerland

The shares may not be publicly offered in Switzerland and will not be listed on the SIX Swiss Exchange, or SIX, or on any other stock exchange or regulated trading facility in Switzerland. This prospectus has been prepared without regard to the disclosure standards for issuance prospectuses under art. 652a or art. 1156 of the Swiss Code of Obligations or the disclosure standards for listing prospectuses under art. 27 ff. of the SIX Listing Rules or the listing rules of any other stock exchange or regulated trading facility in Switzerland. Neither this prospectus nor any other offering or marketing material relating to the shares or this offering may be publicly distributed or otherwise made publicly available in Switzerland. Neither this prospectus nor any other offering or marketing material relating to this offering, us, or the shares have been or will be filed with or approved by any Swiss regulatory authority. In particular, this prospectus will not be filed with, and the offer of shares will not be supervised by, the Swiss Financial Market Supervisory Authority FINMA, or FINMA, and the offer of shares has not been and will not be authorized under the Swiss Federal Act on Collective Investment Schemes, or CISA. The investor protection afforded to acquirers of interests in collective investment schemes under the CISA does not extend to acquirers of shares.

Dubai International Financial Centre

This prospectus relates to an Exempt Offer in accordance with the Offered Securities Rules of the Dubai Financial Services Authority, or DFSA. This prospectus is intended for distribution only to persons of a type specified in the Offered Securities Rules of the DFSA. It must not be delivered to, or relied on by, any other person. The DFSA has no responsibility for reviewing or verifying any documents in connection with Exempt Offers. The DFSA has not approved this prospectus nor taken steps to verify the information set forth herein and has no responsibility for the prospectus. The shares to which this prospectus relates may be illiquid and/or subject to restrictions on their resale. Prospective purchasers of the shares offered

should conduct their own due diligence on the shares. If you do not understand the contents of this prospectus you should consult an authorized financial advisor.

United Arab Emirates

The shares have not been, and are not being, publicly offered, sold, promoted or advertised in the United Arab Emirates (including the Dubai International Financial Centre) other than in compliance with the laws of the United Arab Emirates (and the Dubai International Financial Centre) governing the issue, offering and sale of securities. Further, this prospectus does not constitute a public offer of securities in the United Arab Emirates (including the Dubai International Financial Centre) and is not intended to be a public offer. This prospectus has not been approved by or filed with the Central Bank of the United Arab Emirates, the Securities and Commodities Authority or the Dubai Financial Services Authority.

Australia

No placement document, prospectus, product disclosure statement or other disclosure document has been lodged with the Australian Securities and Investments Commission, or ASIC, in relation to this offering. This prospectus does not constitute a prospectus, product disclosure statement or other disclosure document under the Corporations Act 2001, or the Corporations Act, and does not purport to include the information required for a prospectus, product disclosure statement or other disclosure document under the Corporations Act.

Any offer in Australia of the shares may only be made to persons, or the Exempt Investors, who are "sophisticated investors" (within the meaning of section 708(8) of the Corporations Act), "professional investors" (within the meaning of section 708(11) of the Corporations Act) or otherwise pursuant to one or more exemptions contained in section 708 of the Corporations Act so that it is lawful to offer the shares without disclosure to investors under Chapter 6D of the Corporations Act.

The shares applied for by Exempt Investors in Australia must not be offered for sale in Australia in the period of 12 months after the date of allotment under this offering, except in circumstances where disclosure to investors under Chapter 6D of the Corporations Act would not be required pursuant to an exemption under section 708 of the Corporations Act or otherwise or where the offer is pursuant to a disclosure document which complies with Chapter 6D of the Corporations Act. Any person acquiring shares must observe such Australian on-sale restrictions.

This prospectus contains general information only and does not take into account the investment objectives, financial situation or particular needs of any particular person. It does not contain any securities recommendations or financial product advice. Before making an investment decision, investors need to consider whether the information in this prospectus is appropriate for their needs, objectives and circumstances, and, if necessary, seek expert advice on those matters.

Hong Kong

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

"professional investors" as defined in the Securities and Futures Ordinance and any rules made under that Ordinance.

Singapore

This prospectus has not been registered as a prospectus with the Monetary Authority of Singapore. Accordingly, this prospectus and any other document or material in connection with the offer or sale, or invitation for subscription or purchase, of our shares may not be circulated or distributed, nor may our shares be offered or sold, or be made the subject of an invitation for subscription or purchase, whether directly or indirectly, to persons in Singapore other than (1) to an institutional investor under Section 274 of the Securities and Futures Act, Chapter 289 of Singapore, or the SFA, (2) to a relevant person or any person pursuant to Section 275(1A), and in accordance with the conditions specified in Section 275 of the SFA, or (3) otherwise pursuant to, and in accordance with the conditions of, any other applicable provision of the SFA, in each case subject to compliance with conditions set forth in the SFA.

Where our shares are subscribed or purchased under Section 275 by a relevant person which is: (a) a corporation (which is not an accredited investor as defined in Section 4A of the SFA) the sole business of which is to hold investments and the entire share capital of which is owned by one or more individuals, each of whom is an accredited investor; or (b) a trust (where the trustee is not an accredited investor) whose sole purpose is to hold investments and each beneficiary of the trust is an individual who is an accredited investor; shares, debentures and units of shares and debentures of that corporation or the beneficiaries' rights and interest (howsoever described) in that trust shall not be transferred within six months after that corporation or that trust has acquired the shares under Section 275 of the SFA, except: (1) to an institutional investor (for corporations under Section 274 of the SFA) or to a relevant person defined in Section 275(2) of the SFA, or to any person pursuant to an offer that is made on terms that such shares, debentures and units of shares and debentures of that corporation or such rights and interest in that trust are acquired at a consideration of not less than \$200,000 (or its equivalent in a foreign currency) for each transaction, whether such amount is to be paid for in cash or by exchange of securities or other assets, and further for corporations, in accordance with the conditions, specified in Section 275 of the SFA; (2) where no consideration is or will be given for the transfer; or (3) where the transfer is by operation of law.

Saudi Arabia

This prospectus may not be distributed in the Kingdom of Saudi Arabia except to such persons as are permitted under the Offers of Securities Regulations as issued by the board of the Saudi Arabian Capital Market Authority, or the CMA pursuant to resolution number 2-11-2004 dated 4 October 2004 as amended by resolution number 1-28-2008, as amended, or the CMA Regulations. The CMA does not make any representation as to the accuracy or completeness of this prospectus and expressly disclaims any liability whatsoever for any loss arising from, or incurred in reliance upon, any part of this prospectus. Prospective purchasers of the shares offered hereby should conduct their own due diligence on the accuracy of the information relating to the shares. If you do not understand the contents of this prospectus, you should consult an authorized financial adviser.

China

This prospectus does not constitute a public offer of shares, whether by sale or subscription, in the People's Republic of China, or the PRC. The shares are not being offered or sold directly or indirectly in the PRC to or for the benefit of, legal or natural persons of the PRC.

Further, no legal or natural persons of the PRC may directly or indirectly purchase any of the shares or any beneficial interest therein without obtaining all prior PRC's governmental approvals that are

required, whether statutorily or otherwise. Persons who come into possession of this prospectus are required by the issuer and its representatives to observe these restrictions.

Korea

The shares have not been and will not be registered under the Financial Investments Services and Capital Markets Act of Korea and the decrees and regulations thereunder (the "FSCMA"), and the shares have been and will be offered in Korea as a private placement under the FSCMA. None of the shares may be offered, sold or delivered directly or indirectly, or offered or sold to any person for re-offering or resale, directly or indirectly, in Korea or to any resident of Korea except pursuant to the applicable laws and regulations of Korea, including the FSCMA and the Foreign Exchange Transaction Law of Korea and the decrees and regulations thereunder, or the FETL. The shares have not been listed on any of securities exchanges in the world including, without limitation, the Korea Exchange in Korea. Furthermore, the purchaser of the shares shall comply with all applicable regulatory requirements (including, but not limited to, requirements under the FETL) in connection with the purchase of the shares. By the purchase of the shares, the relevant holder thereof will be deemed to represent and warrant that if it is in Korea or is a resident of Korea, it purchased the shares pursuant to the applicable laws and regulations of Korea.

Taiwan

The shares have not been and will not be registered with the Financial Supervisory Commission of Taiwan pursuant to relevant securities laws and regulations and may not be sold, issued or offered within Taiwan through a public offering or in circumstances which constitutes an offer within the meaning of the Securities and Exchange Act of Taiwan that requires a registration or approval of the Financial Supervisory Commission of Taiwan. No person or entity in Taiwan has been authorized to offer, sell, give advice regarding or otherwise intermediate this offering and sale of the shares in Taiwan.

LEGAL MATTERS

The validity of the shares of common stock offered hereby is being passed upon for us by Wilmer Cutler Pickering Hale and Dorr LLP, Boston, Massachusetts. Ropes & Gray LLP, Boston, Massachusetts is acting as counsel for the underwriters in connection with this offering.

EXPERTS

Ernst & Young LLP, independent registered public accounting firm, has audited our consolidated financial statements at December 31, 2017 and 2018, and for each of the two years in the period ended December 31, 2018, as set forth in their report (which contains an explanatory paragraph describing conditions that raise substantial doubt about the company's ability to continue as a going concern as described in Note 1 to the consolidated financial statements). We have included our financial statements in the prospectus and elsewhere in the registration statement in reliance on Ernst & Young LLP's report, given on their authority as experts in accounting and auditing.

WHERE YOU CAN FIND MORE INFORMATION

We have filed with the SEC a registration statement on Form S-1 under the Securities Act with respect to the shares of common stock we are offering to sell. This prospectus, which constitutes part of the registration statement, does not include all of the information contained in the registration statement and the exhibits, schedules and amendments to the registration statement. For further information with respect to us and our common stock, we refer you to the registration statement and to the exhibits and schedules to the registration statement. Statements contained in this prospectus about the contents of any contract, agreement or other document are not necessarily complete, and, in each instance, we refer you to the copy of the contract, agreement or other document filed as an exhibit to the registration statement. Each of these statements is qualified in all respects by this reference to such contract, agreement or document.

The SEC maintains an Internet website, which is located at <http://www.sec.gov>, that contains reports, proxy and information statements and other information regarding issuers that file electronically with the SEC. You may access the registration statement of which this prospectus is a part at the SEC's Internet website. Upon completion of this offering, we will be subject to the information reporting requirements of the Securities Exchange Act of 1934, as amended, and we will file reports, proxy statements and other information with the SEC. We plan to fulfill our obligations with respect to such requirements by filing periodic reports and other information with the SEC. We intend to furnish our stockholders with annual reports containing financial statements certified by an independent registered public accounting firm. Our website address is www.fulcrumtx.com. The information contained on, or that can be accessed through, our website is not a part of this prospectus. We have included our website address in this prospectus solely as an inactive textual reference.

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Report of Independent Registered Public Accounting Firm

To the Stockholders and the Board of Directors of Fulcrum Therapeutics, Inc.

Opinion on the Financial Statements

We have audited the accompanying consolidated balance sheets of Fulcrum Therapeutics, Inc. (the Company) as of December 31, 2018 and 2017, the related consolidated statements of operations and comprehensive loss, convertible preferred stock and stockholders' (deficit) equity and cash flows for the years then ended, and the related notes (collectively referred to as the "consolidated financial statements"). In our opinion, the consolidated financial statements present fairly, in all material respects, the financial position of the Company at December 31, 2018 and 2017, and the results of its operations and its cash flows for the years then ended, in conformity with U.S. generally accepted accounting principles.

The Company's Ability to Continue as a Going Concern

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

Basis for Opinion

These financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on the Company's financial statements based on our audits. We are a public accounting firm registered with the Public Company Accounting Oversight Board (United States) (PCAOB) and are required to be independent with respect to the Company in accordance with the U.S. federal securities laws and the applicable rules and regulations of the Securities and Exchange Commission and the PCAOB.

We conducted our audits in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement, whether due to error or fraud. The Company is not required to have, nor were we engaged to perform, an audit of its internal control over financial reporting. As part of our audits we are required to obtain an understanding of internal control over financial reporting but not for the purpose of expressing an opinion on the effectiveness of the Company's internal control over financial reporting. Accordingly, we express no such opinion.

Our audits included performing procedures to assess the risks of material misstatement of the financial statements, whether due to error or fraud, and performing procedures that respond to those risks. Such procedures included examining, on a test basis, evidence regarding the amounts and disclosures in the financial statements. Our audits also included evaluating the accounting principles used and significant estimates made by management, as well as evaluating the overall presentation of the financial statements. We believe that our audits provide a reasonable basis for our opinion.

/s/ Ernst & Young LLP

We have served as the Company's auditor since 2017.

Boston, Massachusetts
May 1, 2019, except for Note 14(c),
as to which the date is July 8, 2019

Fulcrum Therapeutics, Inc.

Consolidated Balance Sheets

(In thousands, except share and per share amounts)

	December 31, 2017	December 31, 2018	Pro Forma December 31, 2018 (Unaudited)
Assets			
Current assets:			
Cash and cash equivalents	\$ 407	\$ 72,797	\$ 72,797
Prepaid expenses and other current assets	931	1,298	1,298
Total current assets	1,338	74,095	74,095
Property and equipment, net	2,942	10,546	10,546
Restricted cash	—	1,092	1,092
Other assets	60	38	38
Total assets	<u>\$ 4,340</u>	<u>\$ 85,771</u>	<u>\$ 85,771</u>
Liabilities, convertible preferred stock, and stockholders' (deficit) equity			
Current liabilities:			
Accounts payable	\$ 1,673	\$ 1,263	\$ 1,263
Accrued expenses and other current liabilities	1,112	2,497	2,497
Deferred lease incentive, current portion	—	469	469
Total current liabilities	2,785	4,229	4,229
Deferred rent, excluding current portion	199	1,402	1,402
Deferred lease incentive, excluding current portion	—	3,990	3,990
Other liabilities, excluding current portion	34	150	150
Total liabilities	3,018	9,771	9,771
Commitments and contingencies (Note 9)			
Series A convertible preferred stock, \$0.001 par value; 60,000,000 shares authorized as of December 31, 2017 and 2018; 34,666,666 and 60,000,000 shares issued and outstanding as of December 31, 2017 and 2018, respectively (liquidation preference of \$67,187 as of December 31, 2018); no shares issued or outstanding, pro forma as of December 31, 2018 (unaudited)			
	34,587	59,909	—
Series B convertible preferred stock, \$0.001 par value; no shares and 40,000,000 shares authorized as of December 31, 2017 and 2018, respectively; no shares and 40,000,000 shares issued and outstanding as of December 31, 2017 and 2018, respectively (liquidation preference of \$82,261 as of December 31, 2018); no shares issued or outstanding, pro forma as of December 31, 2018 (unaudited)			
	—	79,761	—
Stockholders' (deficit) equity:			
Common stock, \$0.001 par value; 80,000,000 and 135,000,000 shares authorized as of December 31, 2017 and 2018, respectively; 2,628,759 and 2,791,764 shares issued as of December 31, 2017 and 2018, respectively; 972,266 and 1,587,953 shares outstanding as of December 31, 2017 and 2018, respectively; 17,077,468 and 15,873,657 shares issued and outstanding, pro forma as of December 31, 2018 (unaudited)			
	1	2	16
Treasury stock, at cost; 8,036 and 67,024 shares as of December 31, 2017 and 2018, respectively; 67,024 shares, pro forma as of December 31, 2018 (unaudited)			
	—	—	—
Additional paid-in capital	2,270	4,452	144,108
Accumulated deficit	(35,536)	(68,124)	(68,124)
Total stockholders' (deficit) equity	(33,265)	(63,670)	76,000
Total liabilities, convertible preferred stock, and stockholders' (deficit) equity	<u>\$ 4,340</u>	<u>\$ 85,771</u>	<u>\$ 85,771</u>

The accompanying notes are an integral part of these financial statements.

Fulcrum Therapeutics, Inc.

Consolidated Statements of Operations and Comprehensive Loss

(In thousands, except per share data)

	Year Ended December 31,	
	2017	2018
Operating expenses:		
Research and development	\$ 18,494	\$ 25,184
General and administrative	4,499	8,314
Total operating expenses	22,993	33,498
Loss from operations	(22,993)	(33,498)
Other income, net:		
Interest income, net	1	518
Other income	28	392
Net loss and comprehensive loss	\$ (22,964)	\$ (32,588)
Cumulative convertible preferred stock dividends	(2,407)	(6,559)
Net loss attributable to common stockholders	\$ (25,371)	\$ (39,147)
Net loss per share attributable to common stockholders, basic and diluted	\$ (35.68)	\$ (31.14)
Weighted average number of common shares used in net loss per share attributable to common stockholders, basic and diluted	711	1,257
Pro forma net loss per share attributable to common stockholders, basic and diluted (unaudited)		\$ (2.98)
Pro forma weighted average number of common shares used in net loss per share attributable to common stockholders, basic and diluted (unaudited)		10,951

The accompanying notes are an integral part of these financial statements.

Fulcrum Therapeutics, Inc.

Consolidated Statements of Convertible Preferred Stock and Stockholders' (Deficit) Equity

(In thousands, except share amounts)

	Series A Convertible Preferred Stock		Series B Convertible Preferred Stock		Common Stock		Treasury Stock		Additional Paid-In Capital	Accumulated Deficit	Total Stockholders' (Deficit) Equity
	Shares	Amount	Shares	Amount	Shares	Amount	Shares	Amount			
Balance at December 31, 2016	17,000,000	\$ 16,962	—	\$ —	508,488	\$ 1	—	\$ —	890	\$ (12,572)	\$ (11,681)
Issuance of Series A convertible preferred stock at \$1.00 per share, net of issuance costs of \$42	17,666,666	17,625	—	—	—	—	—	—	—	—	—
Issuance of common stock	—	—	—	—	463,778	—	—	—	9	—	9
Repurchase of unvested restricted stock awards	—	—	—	—	—	—	8,036	—	—	—	—
Stock-based compensation expense	—	—	—	—	—	—	—	—	1,371	—	1,371
Net loss	—	—	—	—	—	—	—	—	—	(22,964)	(22,964)
Balance at December 31, 2017	<u>34,666,666</u>	<u>\$ 34,587</u>	<u>—</u>	<u>\$ —</u>	<u>972,266</u>	<u>\$ 1</u>	<u>8,036</u>	<u>\$ —</u>	<u>2,270</u>	<u>\$ (35,536)</u>	<u>\$ (33,265)</u>
Issuance of Series A convertible preferred stock at \$1.00 per share, net of issuance costs of \$11	25,333,334	25,322	—	—	—	—	—	—	—	—	—
Issuance of Series B convertible preferred stock at \$2.00 per share, net of issuance costs of \$239	—	—	40,000,000	79,761	—	—	—	—	—	—	—
Issuance of common stock	—	—	—	—	615,687	1	—	—	23	—	24
Repurchase of unvested restricted stock awards	—	—	—	—	—	—	93,711	—	—	—	—
Retirement of treasury shares	—	—	—	—	—	—	(34,723)	—	—	—	—
Stock-based compensation expense	—	—	—	—	—	—	—	—	2,159	—	2,159
Net loss	—	—	—	—	—	—	—	—	—	(32,588)	(32,588)
Balance at December 31, 2018	<u>60,000,000</u>	<u>\$ 59,909</u>	<u>40,000,000</u>	<u>\$ 79,761</u>	<u>1,587,953</u>	<u>\$ 2</u>	<u>67,024</u>	<u>\$ —</u>	<u>4,452</u>	<u>\$ (68,124)</u>	<u>\$ (63,670)</u>
Pro forma convertible preferred stock and stockholders' equity (unaudited):											
Conversion of convertible preferred stock into common stock (unaudited)	(60,000,000)	(59,909)	(40,000,000)	(79,761)	14,285,704	14	—	—	139,656	—	139,670
Pro forma balance at December 31, 2018 (unaudited)	<u>—</u>	<u>\$ —</u>	<u>—</u>	<u>\$ —</u>	<u>15,873,657</u>	<u>\$ 16</u>	<u>67,024</u>	<u>\$ —</u>	<u>\$ 144,108</u>	<u>\$ (68,124)</u>	<u>\$ 76,000</u>

The accompanying notes are an integral part of these financial statements.

Fulcrum Therapeutics, Inc.
Consolidated Statements of Cash Flows
(In thousands)

	Year Ended December 31,	
	2017	2018
Operating activities		
Net loss	\$ (22,964)	\$ (32,588)
Adjustments to reconcile net loss to net cash used in operating activities:		
Depreciation expense	715	1,345
Stock-based compensation expense	1,371	2,159
Changes in operating assets and liabilities:		
Prepaid expenses and other current assets	(334)	(40)
Other assets	61	22
Accounts payable	208	(20)
Accrued expenses and other current liabilities	713	1,223
Deferred rent and deferred lease incentive	156	5,337
Net cash used in operating activities	(20,074)	(22,562)
Investing activities		
Purchases of property and equipment	(1,908)	(8,981)
Net cash used in investing activities	(1,908)	(8,981)
Financing activities		
Proceeds from issuance of Series A convertible preferred stock, net of issuance costs	17,621	25,322
Proceeds from issuance of Series B convertible preferred stock, net of issuance costs	—	79,761
Principal payments on capital lease obligations	—	(70)
Proceeds from issuance of common stock	41	12
Net cash provided by financing activities	17,662	105,025
Net increase (decrease) in cash, cash equivalents and restricted cash	(4,320)	73,482
Cash, cash equivalents, and restricted cash, beginning of period	4,727	407
Cash, cash equivalents, and restricted cash, end of period	\$ 407	\$ 73,889
Supplemental cash flow information		
Cash paid for interest	\$ —	\$ 10
Non-cash investing and financing activities:		
Property and equipment purchases unpaid at end of period	\$ 390	\$ 174

The following table provides a reconciliation of the cash, cash equivalents, and restricted cash balances as of each of the periods shown above:

	December 31,	
	2017	2018
Cash and cash equivalents	\$ 407	\$ 72,797
Restricted cash	—	1,092
Total cash, cash equivalents, and restricted cash	\$ 407	\$ 73,889

The accompanying notes are an integral part of these financial statements.

Fulcrum Therapeutics, Inc.

Notes to Consolidated Financial Statements

1. Nature of the Business and Basis of Presentation

Fulcrum Therapeutics, Inc. (the "Company" or "Fulcrum") was incorporated in Delaware on August 18, 2015. The Company is focused on improving the lives of patients with genetically defined diseases in areas of high unmet medical need, with an initial focus on rare diseases.

The Company is subject to a number of risks similar to other companies in the biotechnology industry, including, but not limited to, risks of failure of preclinical studies and clinical trials, dependence on key personnel, protection of proprietary technology, reliance on third party organizations, risks of obtaining regulatory approval for any product candidate that it may develop, development by competitors of technological innovations, compliance with government regulations, and the need to obtain additional financing. Product candidates currently under development will require significant additional research and development efforts, including extensive preclinical and clinical testing and regulatory approval, prior to commercialization. These efforts require significant amounts of additional capital, adequate personnel infrastructure and extensive compliance-reporting capabilities. Even if the Company's development efforts are successful, it is uncertain when, if ever, the Company will realize significant revenue from product sales.

Basis of Presentation

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

Going Concern

The Company has incurred recurring losses and negative cash flows from operations since inception and has primarily funded its operations with proceeds from the issuance of convertible notes and convertible preferred stock. As of December 31, 2018, the Company had an accumulated deficit of \$68.1 million. The Company expects its operating losses and negative operating cash flows to continue into the foreseeable future as it continues to expand its research and development efforts. As of May 1, 2019, the issuance date of the consolidated financial statements for the year ended December 31, 2018, the Company expected that its cash and cash equivalents as of December 31, 2018 will be sufficient to fund its operating expenses and capital expenditure requirements into the first quarter of 2020. The future viability of the Company beyond that point is dependent on its ability to raise additional capital to finance its operations.

If the Company is unable to obtain additional funding, the Company could be forced to delay, reduce or eliminate some or all of its research and development programs, product portfolio expansion, or commercialization efforts, which could adversely affect its business prospects, or the Company may be unable to continue operations. The Company is seeking to complete an initial public offering ("IPO") of its common stock ("Common Stock"). In the event the Company does not complete an IPO, the Company expects to seek additional funding through private equity financings, debt financings, or other capital sources, including collaborations with other companies or other strategic transactions. Although management plans to pursue additional funding, there is no assurance that the Company will be successful in obtaining sufficient funding on terms acceptable to the Company to fund continuing operations, if at all.

Fulcrum Therapeutics, Inc.

Notes to Consolidated Financial Statements (Continued)

1. Nature of the Business and Basis of Presentation (Continued)

Based on its recurring losses and negative cash flows from operations since inception, expectation of continuing operating losses and negative cash flows from operations for the foreseeable future, and the need to raise additional capital to finance its future operations, management concluded that there is substantial doubt about the Company's ability to continue as a going concern within one year after the date that the consolidated financial statements for the year ended December 31, 2018 were issued.

The accompanying consolidated financial statements do not include any adjustments that might result from the outcome of this uncertainty. Accordingly, the consolidated financial statements have been prepared on a basis that assumes the Company will continue as a going concern and which contemplates the realization of assets and satisfaction of liabilities and commitments in the ordinary course of business.

2. Summary of Significant Accounting Policies

Principles of Consolidation

The accompanying consolidated financial statements include the accounts of the Company and its wholly owned subsidiary, Fulcrum Therapeutics Securities Corp., which is a Massachusetts subsidiary created to buy, sell, and hold securities. All intercompany transactions and balances have been eliminated.

Use of Estimates

The preparation of financial statements in accordance with GAAP requires management to make certain estimates and assumptions that affect the reported amounts of assets and liabilities and disclosure of contingent assets and liabilities as of the date of the financial statements, and the reported amount of expenses during the reported periods. Estimates inherent in the preparation of these consolidated financial statements include, but are not limited to, estimates related to accrued expenses, stock-based compensation expense, the fair value of the Common Stock and convertible preferred stock, and income taxes. The Company bases its estimates on historical experience and other market specific or other relevant assumptions it believes to be reasonable under the circumstances. On an ongoing basis, management evaluates its estimates as there are changes in circumstances, facts and experience. Actual results could differ from those estimates or assumptions.

Unaudited Pro Forma Financial Information

The accompanying unaudited pro forma balance sheet and statement of stockholders' (deficit) equity as of December 31, 2018 has been prepared to give effect, upon the closing of a qualified IPO, to the automatic conversion of all shares of convertible preferred stock outstanding as of December 31, 2018 into 14,285,704 shares of Common Stock. In the accompanying consolidated statements of operations and comprehensive loss, the unaudited pro forma basic and diluted net loss per share attributable to common stockholders for the year ended December 31, 2018 have been prepared to give effect, upon the closing of a qualified IPO, to the automatic conversion of all outstanding shares of convertible preferred stock as if the proposed IPO had occurred on the later of January 1, 2018 or the issuance date of the convertible preferred stock (see Note 12).

Cash and Cash Equivalents

Cash equivalents are highly liquid investments that are readily convertible into cash with original maturities of three months or less when purchased. These assets include investments in money market

Fulcrum Therapeutics, Inc.**Notes to Consolidated Financial Statements (Continued)****2. Summary of Significant Accounting Policies (Continued)**

funds that invest in U.S. Treasury obligations. The Company maintains its bank accounts at major financial institutions. The Company had no cash equivalents as of December 31, 2017.

Restricted Cash

Restricted cash represents the cash held to secure a letter of credit associated with the Company's facility lease.

Fair Value of Financial Instruments

The fair value of the Company's financial assets and liabilities reflects the Company's estimate of amounts that it would have received in connection with the sale of the assets or paid in connection with the transfer of the liabilities in an orderly transaction between market participants at the measurement date. In connection with measuring the fair value of its assets and liabilities, the Company seeks to maximize the use of observable inputs (market data obtained from sources independent from the Company) and to minimize the use of unobservable inputs (the Company's assumptions about how market participants would price assets and liabilities). The following fair value hierarchy is used to classify assets and liabilities based on the observable inputs and unobservable inputs used in order to value the assets and liabilities:

Level 1: Quoted prices in active markets for identical assets or liabilities. An active market for an asset or liability is a market in which transactions for the asset or liability occur with sufficient frequency and volume to provide pricing information on an ongoing basis.

Level 2: Observable inputs other than Level 1 inputs. Examples of Level 2 inputs include quoted prices in active markets for similar assets or liabilities and quoted prices for identical assets or liabilities in markets that are not active.

Level 3: Unobservable inputs based on the Company's assessment of the assumptions that market participants would use in pricing the asset or liability.

The Company's cash equivalents are carried at fair value, determined according to the fair value hierarchy described above (see Note 3).

Property and Equipment

Property and equipment are recorded at cost, net of accumulated depreciation. Maintenance and repairs to an asset that do not improve or extend its life are charged to operations. Depreciation expense is recorded using the straight-line method over the estimated useful life of the related asset as follows:

	Estimated Useful Life (in years)
Lab equipment	5
Furniture and fixtures	4
Computer equipment	3
Software	3
Leasehold improvements	Shorter of useful life or remaining lease term

Construction-in-progress is stated at cost, which includes direct costs attributable to the setup or construction of the related asset. Depreciation expense is not recorded on construction-in-progress until

Fulcrum Therapeutics, Inc.**Notes to Consolidated Financial Statements (Continued)****2. Summary of Significant Accounting Policies (Continued)**

the relevant assets are completed and put into use. When assets are retired or otherwise disposed of, the assets and related accumulated depreciation are eliminated from the accounts and any resulting gain or loss is reflected in the Company's consolidated statements of operations and comprehensive loss.

Impairment of Long-Lived Assets

Long-lived assets consist of property and equipment. The Company continually evaluates whether events or circumstances have occurred that indicate that the estimated remaining useful life of its long-lived assets may warrant revision or that the carrying value of these assets may be impaired. An impairment loss would be recognized when estimated undiscounted future cash flows expected to result from the use or disposition of an asset group are less than its carrying amount. The impairment loss would be based on the excess of the carrying value of the impaired asset group over its fair value, determined based on discounted cash flows. The Company did not record any impairment losses on long-lived assets during the years ended December 31, 2017 or 2018.

Deferred Issuance Costs

The Company capitalizes certain legal, professional, accounting and other third-party fees that are directly associated with in-process equity issuances as deferred issuance costs until such equity issuances are consummated. After consummation of the equity issuance, these costs are recorded as a reduction in the capitalized amount associated with the equity issuance. Should the planned financing be abandoned, the deferred issuance costs will be expensed immediately as a charge to operating expenses in the consolidated statement of operations and comprehensive loss. Deferred issuance costs as of December 31, 2018 were less than \$0.1 million. No deferred issuance costs were capitalized as of December 31, 2017.

Leases

Leases are classified at their inception as either operating or capital leases. The Company recognizes rent expense for its facility lease, which is classified as an operating lease, on a straight-line basis over the respective lease term, inclusive of rent escalation provisions and rent holidays. The difference between rent payments made and straight-line rent expense is recorded as deferred rent. Additionally, the Company recognizes tenant improvement allowances for its operating leases as a deferred lease incentive and amortizes the lease incentive as a reduction to rent expense on a straight-line basis over the respective lease term.

Research and Development Expenses

Research and development expenses include costs directly attributable to the conduct of research and development programs, including personnel-related expenses such as salaries, payroll taxes, benefits, and stock-based compensation expense, manufacturing and external costs related to outside vendors engaged to conduct both preclinical studies and clinical trials, laboratory supplies, depreciation on and maintenance of research equipment, and the allocable portions of facility costs, such as rent, utilities, repairs and maintenance, depreciation, and general support services. Expenditures relating to research and development are expensed in the period incurred. Nonrefundable advance payments for goods and services that will be used in future research and development activities are expensed when the activity has been performed or when the goods have been received rather than when the payment is made.

Fulcrum Therapeutics, Inc.**Notes to Consolidated Financial Statements (Continued)****2. Summary of Significant Accounting Policies (Continued)*****Research Contract Costs and Accruals***

The Company has entered into various research and development contracts with research institutions and other companies. The Company records accruals for estimated ongoing research costs. When evaluating the adequacy of the accrued liabilities, the Company analyzes progress of the studies or trials, including invoices received and contracted costs. Significant judgments and estimates are made in determining the accrued balances at each reporting period. Actual results could differ from the Company's estimates.

Patent-Related Costs

Patent-related costs incurred in connection with patent applications are expensed as incurred due to the uncertainty about the recovery of the expenditure. Amounts incurred are classified as general and administrative expenses in the accompanying statements of operations.

Fair Value of Common Stock and Series B Convertible Preferred Stock

The Company determined the estimated fair value of Common Stock and Series B convertible preferred stock (the "Series B Preferred Stock") based on a number of objective and subjective factors, including, but not limited to, external market conditions affecting the biotechnology industry sector, the prices at which the Company sold shares of convertible preferred stock and the superior rights and preferences of securities senior to the Company's Common Stock at the time, and the likelihood and potential timing of achieving a liquidity event, such as an IPO, in light of prevailing market conditions. The Company utilized valuation methodologies in accordance with the guidance outlined in the American Institute of Certified Public Accountants' Accounting and Valuation Guide, Valuation of Privately-Held-Company Equity Securities Issued as Compensation, to estimate the fair value of Common Stock and the Series B Preferred Stock. The methodologies utilized to estimate the fair value of Common Stock included the guideline public company method and/or the precedent transaction method to estimate the equity value, and the option-pricing method ("OPM") or the hybrid method, which is a probability-weighted expected return method ("PWERM"), to allocate equity value to the Common Stock and Preferred Stock. The Company utilized the hybrid method to estimate the fair value of the Series B Preferred Stock. Significant changes to the key assumptions used in the valuations could result in different fair values of Common Stock and the Series B Preferred Stock.

Stock-Based Compensation

The Company measures stock-based awards based on the fair value on the date of grant. Compensation expense of those awards is recognized over the requisite service period, which is generally the vesting period of the respective award. Generally, the Company issues awards with only service-based vesting conditions and records the expense for these awards using the straight-line method. The Company has also granted certain stock-based awards with performance-based vesting conditions. The Company records the expense for stock-based awards with performance-based vesting conditions over the remaining service period using an accelerated attribution method when management determines that achievement of the performance condition is probable. At each reporting date, the Company evaluates if the achievement of a performance-based milestone is probable based on the expected satisfaction of the performance conditions.

Fulcrum Therapeutics, Inc.**Notes to Consolidated Financial Statements (Continued)****2. Summary of Significant Accounting Policies (Continued)**

The fair value of each restricted stock award is based on the fair value of the Company's Common Stock on the grant date, less any applicable purchase price. The fair value of each stock option is estimated on the grant date using the Black-Scholes option-pricing model, which requires inputs based on certain subjective assumptions, including the fair value of the Company's Common Stock, the expected stock price volatility, the expected term of the award, the risk-free interest rate, and expected dividends. Expected volatility is calculated based on reported volatility data for a representative group of publicly traded companies for which historical information is available. The historical volatility is calculated based on a period of time commensurate with the assumption used for the expected term. The risk-free interest rate is based on the U.S. Treasury yield curve in effect at the time of grant commensurate with the expected term assumption. The Company uses the simplified method, under which the expected term is presumed to be the midpoint between the vesting date and the end of the contractual term. The Company utilizes this method due to the lack of historical exercise data and the plain nature of its stock-based awards. The expected dividend yield is assumed to be zero as the Company has never paid dividends and has no current plans to pay any dividends on Common Stock.

The Company accounts for forfeitures as they occur (refer to the "Recently Adopted Accounting Pronouncements" below). The Company classifies stock-based compensation expense in its statements of operations in the same manner in which the award recipient's payroll or service costs are classified.

Income Taxes

The Company accounts for income taxes using the asset and liability method, which requires the recognition of deferred tax assets and liabilities for the expected future tax consequences of events that have been recognized in the consolidated financial statements or in the Company's tax returns. Under this method, deferred tax assets and liabilities are determined based on differences between the financial statement carrying amounts and the tax bases of the assets and liabilities using the enacted tax rates in effect in the years in which the differences are expected to reverse. A valuation allowance against deferred tax assets is recorded if, based on the weight of the available evidence, it is more likely than not that some or all of the deferred tax assets will not be realized. Potential for recovery of deferred tax assets is evaluated by considering several factors, including estimating the future taxable profits expected, estimating future reversals of existing taxable temporary differences, considering taxable profits in carryback periods, and considering prudent and feasible tax planning strategies.

The Company accounts for uncertain tax positions using a more-likely-than-not threshold for recognizing and resolving uncertain tax positions. The evaluation of uncertain tax positions is based on factors including, but not limited to, changes in the law, the measurement of tax positions taken or expected to be taken in tax returns, the effective settlement of matters subject to audit, new audit activity, and changes in facts or circumstances related to a tax position.

Comprehensive Loss

Comprehensive loss is defined as the change in equity of a business enterprise during a period from transactions and other events and circumstances from non-owner sources. For the years ended December 31, 2017 and 2018, comprehensive loss was equal to net loss.

Fulcrum Therapeutics, Inc.**Notes to Consolidated Financial Statements (Continued)****2. Summary of Significant Accounting Policies (Continued)*****Net Income (Loss) Per Share***

The Company applies the two-class method to compute basic and diluted net income (loss) per share attributable to common stockholders when it has issued shares that meet the definition of participating securities. The two-class method determines net income (loss) per share for each class of common and participating securities according to dividends declared or accumulated and participation rights in undistributed earnings. The two-class method requires income (loss) available to common stockholders for the period to be allocated between common and participating securities based upon their respective rights to share in the earnings as if all income (loss) for the period had been distributed. The Company's convertible preferred stock participates in any dividends declared by the Company and are therefore considered to be participating securities. The participating securities are not required to participate in the losses of the Company, and therefore during periods of loss there is no allocation required under the two-class method.

Basic net income (loss) per share attributable to common stockholders is computed by dividing the net income (loss) attributable to common stockholders by the weighted average number of shares of common stock outstanding for the period. Diluted net income (loss) attributable to common stockholders is computed by adjusting net income (loss) per share attributable to common stockholders to reallocate undistributed earnings based on the potential impact of dilutive securities. Diluted net income (loss) per share attributable to common stockholders is computed by dividing the diluted net income (loss) attributable to common stockholders by the weighted average number of shares of common stock outstanding for the period, including potential dilutive common shares. For purpose of this calculation, outstanding options to purchase Common Stock, unvested restricted stock awards, and shares of convertible preferred stock are considered potential dilutive common shares. The Company has generated a net loss in all periods presented, and therefore the basic and diluted net loss per share attributable to common stockholders are the same as the inclusion of the potentially dilutive securities would be anti-dilutive.

Off-Balance Sheet Risk and Concentrations of Credit Risk

The Company has no significant off-balance sheet risk such as foreign exchange contracts, option contracts, or other foreign hedging arrangements. Financial instruments that potentially expose the Company to concentrations of credit risk consist primarily of cash, cash equivalents, and restricted cash. The Company's cash, cash equivalents, and restricted cash are deposited in accounts at large financial institutions. The Company believes it is not exposed to significant credit risk due to the financial strength of the depository institutions in which the cash, cash equivalents and restricted cash are held. The Company maintains its cash equivalents in money market funds that invest in U.S. Treasury securities.

Segment Information

Operating segments are defined as components of an enterprise about which separate discrete financial information is available for evaluation by the chief operating decision-maker in making decisions regarding resource allocation and assessing performance. The Company and the Company's chief operating decision-maker, the Company's chief executive officer, view the Company's operations and manage its business as a single operating segment.

Fulcrum Therapeutics, Inc.**Notes to Consolidated Financial Statements (Continued)****2. Summary of Significant Accounting Policies (Continued)*****Emerging Growth Company Status***

The Company is an emerging growth company ("EGC"), as defined in the Jumpstart Our Business Startups Act (the "JOBS Act"), and may take advantage of certain exemptions from various reporting requirements that are applicable to other public companies that are not EGCs. The Company may take advantage of these exemptions until it is no longer an EGC under Section 107 of the JOBS Act, which provides that an EGC can take advantage of the extended transition period afforded by the JOBS Act for the implementation of new or revised accounting standards. The Company has elected to use the extended transition period for complying with new or revised accounting standards, and as a result of this election, its consolidated financial statements may not be comparable to companies that comply with public company effective dates for ASUs. The Company may take advantage of these exemptions up until the last day of the fiscal year following the fifth anniversary of an offering or such earlier time that it is no longer an EGC.

Recently Adopted Accounting Pronouncements

In May 2014, the FASB issued ASU No. 2014-09, *Revenue from Contracts with Customers (Topic 606)* ("ASU 2014-09"). The standard replaces existing revenue recognition standards and significantly expands the disclosure requirements for revenue arrangements. The standard must be adopted using either a modified retrospective approach or a full retrospective approach for all periods presented. The Company adopted the standard as of January 1, 2017 under the full retrospective method. The Company does not have and has never had any contracts that are within the scope of ASU 2014-09 or its predecessor guidance, ASC 605, *Revenue Recognition*. Accordingly, adoption of the standard did not have an impact on the Company's financial position, results of operations or cash flows. However, the adoption of this standard will impact the accounting for potential future revenue transactions.

In March 2016, the FASB issued ASU No. 2016-09, *Compensation—Stock Compensation* ("ASU 2016-09"), which amends ASC Topic 718, *Compensation—Stock Compensation* ("Topic 718"). The standard is intended to simplify various aspects of the accounting for share-based payments, including the income tax consequences, classification of awards as either equity or liabilities, an option to recognize gross share compensation expense with actual forfeitures recognized as they occur, as well as certain classifications on the statement of cash flows. The Company adopted ASU 2016-09 effective as of January 1, 2016. The Company elected to account prospectively for forfeitures as they occur rather than apply an estimated forfeiture rate to stock-based compensation expense. The adoption of the standard did not have a material impact on the Company's consolidated financial statements or footnote disclosures.

In August 2016, the FASB issued ASU No. 2016-15, *Statement of Cash Flows (Topic 230): Classification of Certain Cash Receipts and Cash Payments* ("ASU 2016-15"), which simplifies certain elements of cash flow classification. The standard is intended to reduce diversity in practice in how certain transactions are classified in the statement of cash flows. The Company adopted the standard effective as of January 1, 2016. The adoption of the standard did not have a material impact on the Company's consolidated financial statements or footnote disclosures.

In November 2016, the FASB issued ASU 2016-18, *Statement of Cash Flows (Topic 230): Restricted Cash* ("ASU 2016-18"). The standard requires that amounts generally described as restricted cash be included within cash and cash equivalents when reconciling the beginning-of-period and end-of-period total amounts shown on the statement of cash flows. The Company adopted ASU 2016-18 effective as of

Fulcrum Therapeutics, Inc.**Notes to Consolidated Financial Statements (Continued)****2. Summary of Significant Accounting Policies (Continued)**

January 1, 2016 using a full retrospective approach. The adoption of the standard did not have a material impact on the Company's consolidated financial statements or footnote disclosures.

In January 2017, the FASB issued ASU 2017-01, *Business Combinations (Topic 805): Clarifying the Definition of a Business* ("ASU 2017-01"). The standard clarifies the framework for determining whether an integrated set of assets and activities meets the definition of a business. The revised framework establishes a screen for determining whether an integrated set of assets and activities is a business and narrows the definition of a business. The screen requires that when substantially all of the fair value of the gross assets acquired (or disposed of) is concentrated in a single identifiable asset or a group of similar identifiable assets, the set is not a business. This screen reduces the number of transactions that need to be further evaluated. The Company adopted ASU 2017-01 effective as of January 1, 2018. The adoption of this standard did not have a material impact on the Company's consolidated financial statements or footnote disclosures.

In May 2017, the FASB issued ASU No. 2017-09, *Compensation—Stock Compensation (Topic 718): Scope of Modification Accounting* ("ASU 2017-09"). The standard is intended to reduce the diversity in practice and cost and complexity when applying the guidance in Topic 718 to a change to the terms or conditions of a share-based payment award. Under the guidance, modification accounting is required only if the fair value, the vesting conditions or the classification of the award (as equity or liability) changes as a result of the change in terms or conditions. The Company adopted ASU 2017-09 effective as of January 1, 2016. The adoption of this standard did not have a material impact on the Company's consolidated financial statements or footnote disclosures.

In June 2018, the FASB issued ASU No. 2018-07, *Compensation—Stock Compensation (Topic 718): Improvements to Nonemployee Share-Based Payment* ("ASU 2018-07"). The standard is intended to simplify the accounting for share-based payments to non-employees by aligning it with the accounting for share-based payments to employees, with certain exceptions. Under the guidance, the measurement of equity-classified non-employee awards will be fixed at the grant date, which may lower their cost and reduce volatility in the income statement. The Company adopted ASU 2018-07 as of January 1, 2017. The adoption of this standard did not have a material impact on the Company's consolidated financial statements or footnote disclosures.

In August 2018, the FASB issued ASU No. 2018-13, *Fair Value Measurement (Topic 820): Disclosure Framework—Changes to the Disclosure Requirements for Fair Value Measurement* ("ASU 2018-13"). The standard eliminates, adds and modifies certain disclosure requirements for fair value measurements. The Company adopted ASU 2018-13 as of January 1, 2018. The adoption of this standard did not have a material impact on the Company's consolidated financial statements or footnote disclosures.

Recent Accounting Pronouncements—To Be Adopted

In February 2016, the FASB issued ASU No. 2016-02, *Leases (Topic 842)* ("ASU 2016-02"), as amended by various subsequently issued ASUs. The standard requires lessees to recognize an operating lease with a term greater than one year on their balance sheets as a right-of-use asset and corresponding lease liability, measured at the present value of the lease payments. Lessees are required to classify leases as either finance or operating leases. If the lease is effectively a financed-purchase by the lessee, it is classified as a financing lease, otherwise it is classified as an operating lease. This classification will determine whether lease expense is recognized based on an effective interest method or on a straight-line basis over the term of the lease. In July 2018, the FASB also issued ASU 2018-11, *Leases (Topic 842)*:

Fulcrum Therapeutics, Inc.**Notes to Consolidated Financial Statements (Continued)****2. Summary of Significant Accounting Policies (Continued)**

Targeted Improvements ("ASU 2018-11"), which permits entities to continue applying legacy guidance in ASC 840, *Leases*, including its disclosure requirements, in the comparative periods presented in the year that the entity adopts the new leasing standard. The new standard will be effective for the Company on January 1, 2020 (refer to previous discussion under "Emerging Growth Company Status"). The Company will apply the transition method permitted by ASU 2018-11. The Company is currently evaluating the effect that adoption of the standard is expected to have on the Company's consolidated financial statements and related disclosures. The Company expects to take advantage of certain available expedients by electing the transition package of practical expedients permitted within ASU 2016-02, which allows the Company to not reassess previous accounting conclusions around whether arrangements are, or contain, leases, the classification of leases, and the treatment of initial direct costs. The Company also expects to make an accounting policy election to exclude leases with an initial term of twelve months or less from the balance sheet.

In June 2016, the FASB issued ASU No. 2016-13, *Financial Instruments—Credit Losses (Topic 326): Measurement of Credit Losses on Financial Instruments* ("ASU 2016-13"). The standard requires that credit losses be reported using an expected losses model rather than the incurred losses model that is currently used, and establishes additional disclosures related to credit risks. For available-for-sale debt securities with unrealized losses, this standard requires allowances to be recorded instead of reducing the amortized cost of the investment. The new standard will be effective for the Company on January 1, 2021. The Company is currently evaluating the potential impact that this standard may have on its consolidated financial position and results of operations.

In July 2017, the FASB issued ASU No. 2017-11, *Earnings Per Share (Topic 260), Distinguishing Liabilities from Equity (Topic 480), Derivatives and Hedging (Topic 815) I. Accounting for Certain Financial Instruments with Down Round Features II. Replacement of the Indefinite Deferral for Mandatorily Redeemable Financial Instruments of Certain Nonpublic Entities and Certain Mandatorily Redeemable Noncontrolling Interests with a Scope Exception* ("ASU 2017-11"). Part I of the standard applies to entities that issue financial instruments such as warrants, convertible debt or convertible preferred stock that contain down-round features. Part II of the standard replaces the indefinite deferral for certain mandatorily redeemable noncontrolling interests and mandatorily redeemable financial instruments of nonpublic entities contained within ASC Topic 480 with a scope exception and does not impact the accounting for these mandatorily redeemable instruments. The new standard will be effective for the Company on January 1, 2020 (refer to previous discussion under "Emerging Growth Company Status"). The Company is currently evaluating the impact that the adoption of ASU 2017-11 will have on its consolidated financial statements.

3. Fair Value Measurements

The following table presents information about the Company's financial assets measured at fair value on a recurring basis and indicate the level of the fair value hierarchy utilized to determine such fair values as of December 31, 2018 (in thousands):

	Total	Level 1	Level 2	Level 3
Cash equivalents:				
Money market funds	\$ 72,797	\$ 72,797	\$ —	\$ —
Total	\$ 72,797	\$ 72,797	\$ —	\$ —

The Company had no cash equivalents as of December 31, 2017. There have been no transfers between fair value levels during the year ended December 31, 2018.

Fulcrum Therapeutics, Inc.**Notes to Consolidated Financial Statements (Continued)****4. Property and Equipment, Net**

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

	December 31, 2017	December 31, 2018
Lab equipment	\$ 3,018	\$4,847
Furniture and fixtures	—	542
Computer equipment	281	517
Software	90	90
Leasehold improvements	280	6,174
Construction in process	166	334
Total property and equipment	3,835	12,504
Less: accumulated depreciation	(893)	(1,958)
Property and equipment, net	\$ 2,942	\$ 10,546

Depreciation expense for the years ended December 31, 2017 and 2018 was \$0.7 million and \$1.3 million, respectively. Total property and equipment, gross, as of December 31, 2017 and 2018 included zero and \$0.2 million, respectively, of property and equipment recorded under capital leases. Accumulated depreciation, as of December 31, 2017 and 2018, included zero and less than \$0.1 million, respectively, for property and equipment recorded under capital leases.

5. Additional Balance Sheet Detail

Prepaid expenses and other current assets consisted of the following (in thousands):

	December 31, 2017	December 31, 2018
Prepaid expenses	\$ 422	\$460
Prepaid sign-on bonuses subject to vesting provisions	222	99
Security deposits	90	—
Leasehold improvement allowance receivable	39	366
Interest income receivable	—	135
Other	158	238
Total prepaid expenses and other current assets	\$ 931	\$ 1,298

Fulcrum Therapeutics, Inc.**Notes to Consolidated Financial Statements (Continued)****5. Additional Balance Sheet Detail (Continued)**

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

	December 31, 2017	December 31, 2018
External research and development	\$ 8	\$ 437
Payroll and benefits	1,004	1,448
Professional services	80	254
Capital lease obligation, current portion	—	46
Restricted stock liability, current portion	18	18
Property and equipment purchases	—	174
Other	2	120
Total accrued expenses and other current liabilities	<u>\$ 1,112</u>	<u>\$ 2,497</u>

Future minimum lease payments associated with the Company's capital lease obligations are less than \$0.1 million in each of the years ending December 31, 2019, 2020 and 2021. No minimum lease payments associated with the Company's capital lease obligations are due after December 31, 2021.

6. Convertible Preferred Stock

In July 2016, the Company entered into a Series A convertible preferred stock purchase agreement (the "2016 Stock Purchase Agreement"), which provided for the issuance and sale of up to 55,000,000 shares of Series A convertible preferred stock (the "Series A Preferred Stock") at a price of \$1.00 per share in three tranches, each of which could occur in multiple closings. Included in the terms of the Series A Preferred Stock purchase agreement were tranche rights. The tranche rights obligated the investors in the Series A Preferred Stock to purchase, and the Company to sell, shares of Series A Preferred Stock at \$1.00 per share, subject to the achievement of certain milestones related to the Company's research platform and organizational development. The specified milestones were waivable with the consent of the holders of a majority of the shares of Series A Preferred Stock.

During the year ended December 31, 2017, the Company sold 12,666,666 shares of Series A Preferred Stock under the 2016 Stock Purchase Agreement for aggregate proceeds of approximately \$12.7 million. During the year ended December 31, 2018, the Company sold the remaining 25,333,334 shares of Series A Preferred Stock under the 2016 Stock Purchase Agreement for aggregate proceeds of approximately \$25.3 million.

In April 2017, the Company increased the number of shares of Series A Preferred Stock authorized for issuance to 60,000,000 shares and entered into an additional Series A Preferred Stock purchase agreement (the "2017 Stock Purchase Agreement", and together with the 2016 Stock Purchase Agreement, the "Stock Purchase Agreements"), pursuant to which the Company sold 5,000,000 shares of Series A Preferred Stock for aggregate proceeds of \$5.0 million. The Company incurred issuance costs associated with the Stock Purchase Agreements of less than \$0.1 million during each of the years ended December 31, 2017 and 2018.

The Company determined that the tranche rights did not meet the definition of a freestanding financial instrument because, while separately exercisable, they were not legally detachable. Further, the Company determined that the embedded future tranche rights did not require bifurcation as they were

Fulcrum Therapeutics, Inc.

Notes to Consolidated Financial Statements (Continued)

6. Convertible Preferred Stock (Continued)

clearly and closely related to the economic characteristics and risks of the Series A Preferred Stock and did not meet the definition of a derivative on a standalone basis.

In August 2018, the Company entered into a Series B convertible preferred stock purchase agreement (the "Series B Stock Purchase Agreement"), pursuant to which the Company sold 40,000,000 shares of Series B Preferred Stock at a purchase price of \$2.00 per share for gross proceeds of \$80,000,000. In connection with the Series B Stock Purchase Agreement, the Company's Certificate of Incorporation was amended and restated to authorize the Company to issue 40,000,000 shares of Series B Preferred Stock. Refer to Note 14 for information regarding the issuance of Series B Preferred Stock subsequent to December 31, 2018.

The Company assessed the Series A Preferred Stock and the Series B Preferred Stock (together, the "Preferred Stock") for any beneficial conversion features or embedded derivatives, including the conversion option, that would require bifurcation from the Preferred Stock and receive separate accounting treatment. Based on the Company's determination that the Preferred Stock is an "equity host," the Company determined that all features of the Preferred Stock were either clearly and closely related to the equity host or did not meet the definition of a derivative, and therefore do not require bifurcation as a derivative liability. On the date of issuance, the estimated fair value of Common Stock into which the Preferred Stock was convertible was less than the effective conversion price of the Preferred Stock, and as such, there was no beneficial conversion feature at the commitment dates.

As the Preferred Stock may become redeemable upon the occurrence of a Deemed Liquidation Event (as defined below), the Preferred Stock has been classified outside of stockholders' deficit. Since the Preferred Stock is not initially redeemable and the Company has determined that it is not probable that it will become redeemable, the carrying value of the Preferred Stock has not been adjusted.

No dividends have been declared since inception. Aggregate cumulative dividends associated with the Series A Preferred Stock and the Series B Preferred Stock as of December 31, 2018 were \$7.2 million and \$2.3 million, respectively.

The holders of the Preferred Stock have the following rights, privileges, and preferences:

Voting Rights

The holders of the Preferred Stock are entitled to vote on all matters submitted to stockholders for a vote and have the right to vote the number of shares equal to the number of shares of Common Stock into which such shares of Preferred Stock could convert on the record date for determination of stockholders entitled to vote. The holders of Preferred Stock will vote together with the holders of Common Stock as a single class, on an as-converted basis, unless otherwise specified by law or the Certificate of Incorporation. For example, the holders of Series A Preferred Stock, exclusively and as a separate class, are entitled to elect one director of the Company and the holders of Series B Preferred Stock, exclusively and as a separate class, are entitled to elect one director of the Company.

Conversion

Each share of Preferred Stock is convertible, at the option of the holder, at any time, and without the payment of additional consideration by the holder, into such number of fully paid and nonassessable shares of Common Stock as is determined by dividing the Original Issue Price (as defined below) applicable to such series of Preferred Stock by the Conversion Price (as defined below) applicable to such series of

Fulcrum Therapeutics, Inc.**Notes to Consolidated Financial Statements (Continued)****6. Convertible Preferred Stock (Continued)**

Preferred Stock in effect at the time of conversion. The Original Issue Price is \$1.00 per share for Series A Preferred Stock and \$2.00 per share for Series B Preferred Stock, each subject to appropriate adjustment in the event of any stock dividend, stock split, combination or other similar recapitalization with respect to the Preferred Stock. The Conversion Price is \$7.00 per share for Series A Preferred Stock and \$14.00 per share for Series B Preferred Stock, each subject to appropriate adjustment in the event of any stock dividend, stock split, combination or other similar recapitalization and other adjustments, as set forth in the Company's Certificate of Incorporation, as amended and/or restated.

Each share of Preferred Stock will automatically convert into shares of Common Stock at the then-effective conversion ratio upon either (i) the closing of the sale of shares of Common Stock to the public in a firm-commitment underwritten public offering pursuant to an effective registration statement under the Securities Act of 1933, as amended (the "Securities Act"), provided that such offering results in at least \$45 million of gross proceeds to the Company and, following such offering, the Common Stock is listed on the New York Stock Exchange or Nasdaq or (ii) the date and time, or the occurrence of an event, specified by the vote or written consent of the holders of at least 65% of the outstanding shares of Preferred Stock. If the holders of at least 65% of the outstanding shares of Preferred Stock approve such a mandatory conversion in connection with a proposed Deemed Liquidation Event in which the holders of Series B Preferred Stock would receive less than the full liquidation preference applicable to the Series B Preferred Stock (as discussed below), then the mandatory conversion will also require the consent of the holders of a majority of the outstanding shares of Series B Preferred Stock, voting together as a separate class.

Dividends

From the date of issuance of the Series B Preferred Stock, dividends at an annual rate of \$0.16 per share will accrue on such shares of Series B Preferred Stock, subject to adjustment in the event of any stock split, stock dividend, or other similar recapitalization with respect to the Series B Preferred Stock (the "Series B Accruing Dividends"). From the date of issuance of the Series A Preferred Stock, dividends at an annual rate of \$0.08 per share will accrue on such shares of Series A Preferred Stock, subject to adjustment in the event of any stock split, stock dividend, or other similar recapitalization with respect to the Series A Preferred Stock (the "Series A Accruing Dividends", and together with the Series B Accruing Dividends, the "Accruing Dividends"). The Accruing Dividends are cumulative and are payable only when and if declared by the board of directors of the Company or in the event of a liquidation, dissolution or winding up of the Company or a Deemed Liquidation Event. The Company cannot declare dividends on the Common Stock unless the holders of Preferred Stock first receive, or simultaneously receive, a dividend on each outstanding share of Preferred Stock. No dividends have been declared since inception.

Liquidation Preference

In the event of any voluntary or involuntary liquidation, dissolution or winding up of the Company or Deemed Liquidation Event, the holders of shares of Preferred Stock then outstanding will be entitled to be paid out of the assets of the Company available for distribution to its stockholders before any payment will be made to the holders of Common Stock by reason of their ownership thereof, an amount per share equal to the greater of (i) the applicable Original Issue Price, plus any applicable Accruing Dividends accrued but unpaid thereon, whether or not declared, together with any other dividends declared but unpaid thereon or (ii) such amount per share as would have been payable had all shares of Preferred Stock been

Fulcrum Therapeutics, Inc.**Notes to Consolidated Financial Statements (Continued)****6. Convertible Preferred Stock (Continued)**

converted into Common Stock immediately prior to such liquidation, dissolution, winding up or Deemed Liquidation Event.

After the payment of all preferential amounts required to be paid to the holders of shares of Preferred Stock, the remaining assets of the Company available for distribution to its stockholders will be distributed among the holders of the shares of Common Stock, pro rata based on the number of shares held by each such holder.

Unless the holders of at least 65% of the outstanding shares of Preferred Stock, voting together as a single class, elect otherwise, a "Deemed Liquidation Event" will include (i) a merger or consolidation (other than one in which stockholders of the Company owning a majority by voting power of the outstanding shares of the Company prior to the merger or consolidation continue to own a majority by voting power of the outstanding shares of the surviving or acquiring corporation) or (ii) a sale, lease, transfer, exclusive license, or other disposition by the Company or its subsidiaries of all or substantially all of the assets of the Company and its subsidiaries, taken as a whole, or the sale or disposition of one or more subsidiaries of the Company if substantially all of the assets of the Company and its subsidiaries, taken as a whole, are held by such subsidiaries.

7. Common Stock

Each share of Common Stock entitles the holder to one vote on all matters submitted to a vote of the Company's stockholders provided, however, that, except as otherwise required by law, holders of Common Stock will not be entitled to vote on any amendment to the Company's Certificate of Incorporation that relates solely to the terms of one or more outstanding series of Preferred Stock if the holders of such affected series are entitled, either separately or together with the holders of one or more other such series, to vote thereon pursuant to the Certificate of Incorporation or pursuant to the Delaware General Corporation Law. Common stockholders are entitled to receive dividends, as may be declared by the Company's board of directors, if any, subject to the preferential dividend rights of the Preferred Stock. No dividends have been declared or paid during the years ended December 31, 2017 or 2018.

During the year ended December 31, 2018, the Company's Certificate of Incorporation was amended and restated to increase the number of authorized shares of Common Stock from 80,000,000 to 135,000,000 shares.

The Company had reserved the following shares of Common Stock for the potential conversion of Preferred Stock and for the future issuance of Common Stock pursuant to the Company's 2016 Stock Incentive Plan, as amended from time to time (the "2016 Plan"):

	December 31, 2017	December 31, 2018
Shares reserved for conversion of outstanding Series A Preferred Stock	8,571,427	8,571,427
Shares reserved for conversion of outstanding Series B Preferred Stock	—	5,714,277
Shares reserved for future issuance under the 2016 Stock Incentive Plan	220,343	919,030
	<u>8,791,770</u>	<u>15,204,734</u>

Fulcrum Therapeutics, Inc.

Notes to Consolidated Financial Statements (Continued)

8. Stock-based Compensation Expense

Grants Under the 2016 Stock Incentive Plan

In July 2016, the Company adopted the 2016 Plan, under which it may grant restricted stock awards, restricted stock units, incentive stock options, non-statutory stock options and other stock-based awards to eligible employees, officers, directors, consultants and advisors.

The 2016 Plan is administered by the board of directors or, at the discretion of the board of directors, by a subcommittee of the board of directors. The exercise prices, vesting and other restrictions are determined at the discretion of the board of directors, or their subcommittee if so delegated, except that the exercise price per share of the stock options may not be less than 100% of the fair market value of a share of the Company's Common Stock on the date of grant and the term of the stock options may not be greater than ten years.

During the year ended December 31, 2018, the Company granted restricted stock awards and stock options. As of December 31, 2017, the Company had only granted restricted stock awards since its inception. The dates of the Company's valuations of Common Stock have not always coincided with the dates of the restricted stock awards. For financial reporting purposes, the Company performed Common Stock valuations with the assistance of a third-party specialist as of November 30, 2018, August 24, 2018, June 1, 2018, December 31, 2017 and December 31, 2016 to determine stock-based compensation expense for restricted stock awards and stock options.

The total number of shares of Common Stock that were authorized for issuance under the 2016 Plan was 1,780,714 as of December 31, 2017. In January 2018, the 2016 Plan was amended to increase the number of shares of Common Stock reserved for issuance under the 2016 Plan by 428,571 shares. In August 2018, the 2016 Plan was amended to increase the number of shares of Common Stock reserved for issuance under the 2016 Plan by 1,000,000 shares. The total number of shares of Common Stock that were authorized for issuance under the 2016 Plan was 3,209,285 as of December 31, 2018. Refer to Note 14 for an additional increase to the number of shares issuable under the 2016 Plan that occurred subsequent to December 31, 2018.

During the year ended December 31, 2017, the Company issued 518,387 shares and 5,714 shares of Common Stock to employees and non-employees, respectively, under the 2016 Plan. During the year ended December 31, 2018, the Company issued 256,716 shares of Common Stock to employees under the 2016 Plan. The Company may repurchase unvested shares at the original purchase price if employees or non-employees are terminated or cease their employment or service relationship with the Company. The shares typically vest over a one-year or four-year period. The shares are recorded in stockholders' (deficit) equity as they vest.

Fulcrum Therapeutics, Inc.

Notes to Consolidated Financial Statements (Continued)

8. Stock-based Compensation Expense (Continued)

The following table summarizes the Company's restricted stock activity under the 2016 Plan:

	Number of Shares	Weighted Average Grant Date Fair Value
Unvested at December 31, 2016	947,418	\$ 2.94
Granted	524,101	3.09
Vested	(365,922)	2.94
Repurchased	(8,036)	2.94
Unvested at December 31, 2017	1,097,561	\$ 3.01
Granted	256,716	3.33
Vested	(503,544)	3.05
Repurchased	(93,711)	3.24
Unvested at December 31, 2018	<u>757,022</u>	\$ 3.07

Shares of Common Stock repurchased from employees and non-employees are shares held in the Company's treasury ("Treasury Shares"). The board of directors may, at its discretion, authorize that the Treasury Shares be returned to the pool of authorized but unissued Common Stock.

Stock options granted by the Company typically vest over a four year period and have a ten year contractual term. The following table summarizes the Company's stock option activity under the 2016 Plan since December 31, 2017:

	Number of Shares	Weighted Average Exercise Price	Weighted Average Remaining Contractual Term (in years)	Aggregate Intrinsic Value
Outstanding at December 31, 2017	—	\$ —	—	\$ —
Granted	507,891	7.12		
Exercised	—	—		
Cancelled	—	—		
Outstanding at December 31, 2018	<u>507,891</u>	\$ 7.12	9.84	\$ 367,427
Exercisable at December 31, 2018	<u>14,667</u>	\$ 4.83	9.48	\$ 44,158

The aggregate intrinsic value of stock options is calculated as the difference between the exercise price of the stock options and the fair value of the Company's Common Stock as of the balance sheet date for those options that had exercise prices lower than the fair value of the Company's Common Stock.

The weighted average grant date fair value of stock options granted in the year ended December 31, 2018 was \$5.06 per share. As of December 31, 2018, no stock options have been exercised since inception.

Fulcrum Therapeutics, Inc.**Notes to Consolidated Financial Statements (Continued)****8. Stock-based Compensation Expense (Continued)**

The fair value of stock options granted during the year ended December 31, 2018 under the 2016 Plan has been calculated on the date of grant using the following weighted average assumptions:

	<u>Year Ended</u> <u>December 31, 2018</u>
Risk-free interest rate	2.8%
Expected dividend yield	0.0%
Expected term (years)	6.1
Expected stock price volatility	81.6%

Grants Outside the 2016 Stock Incentive Plan

During July 2016, the Company issued 724,997 shares and 65,713 shares of Common Stock outside of the Company's 2016 Plan to non-employee founders and certain advisors, respectively. The shares were issued under the terms of restricted stock agreements between the Company and such holders, and the unvested shares are subject to repurchase by the Company upon the termination of the holder's relationship with the Company. Of the total shares issued to non-employee founders, 82,141 vested immediately upon grant; 357,141 vest quarterly over a four-year period based on each holder's continued service relationship with the Company; and 285,715 vest in equal quarterly installments over a period of one year, commencing with the first quarter after the four-year anniversary of the date of the respective non-employee founder's agreement, based on each holder's continued service relationship with the Company. Of the shares issued to non-employee advisors, 34,285 shares vest in equal quarterly installments over four years, 28,571 of the shares vest in equal quarterly installments over a period of two years upon the achievement of certain performance-based milestones, and 2,857 shares vested immediately upon grant. Stock-based compensation expense associated with the performance-based awards is recognized if the performance condition is considered probable of achievement using management's best estimates.

During the year ended December 31, 2017, management concluded that the milestone associated with 28,571 shares of performance-based restricted stock was probable of achievement, and therefore the Company began to record stock-based compensation expense using the accelerated attribution method. The milestone was subsequently achieved during the year ended December 31, 2018. The Company recorded \$0.1 million and less than \$0.1 million of stock-based compensation expense for non-employee performance-based awards during the years ended December 31, 2017 and 2018, respectively. The shares are recorded in stockholders' (deficit) equity as they vest.

Fulcrum Therapeutics, Inc.**Notes to Consolidated Financial Statements (Continued)****8. Stock-based Compensation Expense (Continued)**

The following table summarizes the Company's restricted stock activity outside of the 2016 Plan:

	Number of Shares	Weighted Average Grant Date Fair Value
Unvested at December 31, 2016	656,788	\$ 2.94
Granted	—	—
Vested	(97,856)	2.94
Repurchased	—	—
Unvested at December 31, 2017	558,932	\$ 2.94
Granted	—	—
Vested	(112,143)	2.94
Repurchased	—	—
Unvested at December 31, 2018	<u>446,789</u>	\$ 2.94

The aggregate intrinsic value of all restricted stock awards that vested during the years ended December 31, 2017 and 2018 was \$1.5 million and \$3.4 million, respectively.

Stock-based Compensation Expense

The total compensation cost recognized in the statements of operations associated with all stock-based compensation awards granted by the Company is as follows (in thousands):

	Year Ended December 31, 2017	Year Ended December 31, 2018
Research and development	\$ 804	\$ 1,124
General and administrative	567	1,035
Total stock-based compensation expense	<u>\$ 1,371</u>	<u>\$ 2,159</u>

As of December 31, 2018, the Company had an aggregate of \$5.6 million of unrecognized stock-based compensation expense, which is expected to be recognized over a weighted average period of 2.94 years.

9. Commitments and Contingencies**Operating Leases**

In May 2016, the Company entered into a sublease agreement for approximately 8,143 square feet of office and laboratory space at its prior corporate headquarters in Cambridge, Massachusetts. The sublease commenced during June 2016. The Company had the option to extend the sublease until June 30, 2019, subject to the landlord's own need for the space. During June 2017, the Company exercised its option to extend the sublease through June 30, 2019. During February 2018, the Company amended its sublease agreement to reduce the term of the sublease to June 30, 2018. The Company recorded rent expense for this sublease on a straight-line basis. Rent expense associated with this sublease for the years ended December 31, 2017 and 2018 was \$0.5 million and \$0.3 million, respectively. The sublease for this space terminated on June 30, 2018.

Fulcrum Therapeutics, Inc.**Notes to Consolidated Financial Statements (Continued)****9. Commitments and Contingencies (Continued)**

In November 2017, the Company entered into a lease agreement for its current corporate headquarters for approximately 28,731 square feet of office and laboratory space in Cambridge, Massachusetts, commencing December 2017. The Company began recognizing rent expense associated with this lease during December 2017. The Company began to occupy and use the leased space for its intended purpose in June 2018. The lease ends on June 30, 2028. The Company has the option to extend the term of the lease for an additional five-year period, at the market rate, by giving the landlord written notice of its election to exercise the extension at least nine months prior to the original expiration of the lease term. The lease has a total commitment of \$25.1 million over the ten year term, and includes escalating rent payments. The lease provides the Company with an allowance for normal leasehold improvements of \$5.0 million. The Company accounts for leasehold improvement incentives as a reduction to rent expense ratably over the lease term. The balance from the leasehold improvement incentives is classified as a deferred lease incentive on the balance sheet. As of December 31, 2017, the Company had not incurred leasehold improvement costs that are subject to reimbursement by the landlord, and therefore no lease incentive obligation was recorded on the balance sheet. The lease agreement requires the Company to either pay a security deposit or maintain a letter of credit of \$1.1 million. The Company obtained a letter of credit for this lease in April 2018 and has recorded the cash held to secure the letter of credit as restricted cash on the consolidated balance sheet as of December 31, 2018. The Company records rent expense for this lease on a straight-line basis. Rent expense associated with this lease for the years ended December 31, 2017 and 2018 was approximately \$0.2 million and \$1.9 million, respectively.

The future minimum lease payments associated with the lease for the Company's current headquarters as of December 31, 2018 are as follows (in thousands):

2019	\$ 2,219
2020	2,285
2021	2,354
2022	2,424
2023	2,497
Thereafter	12,187
Total minimum lease payments	<u>\$ 23,966</u>

Other Agreements

The Company has agreements with third parties in the normal course of business under which it can license certain developed technologies. If the Company exercises its rights to license the technologies it may be subject to additional fees and milestone payments. As of December 31, 2018, the Company has not exercised its rights to license such technologies.

Indemnification Agreements

In the ordinary course of business, the Company may provide indemnification of varying scope and terms to vendors, lessors, business partners and other parties with respect to certain matters arising out of the relationship between such parties and the Company. In addition, the Company has entered into indemnification agreements with members of its board of directors and senior management that will require the Company, among other things, to indemnify them against certain liabilities that may arise by reason of their status or service as directors or officers. The maximum potential amount of future

Fulcrum Therapeutics, Inc.**Notes to Consolidated Financial Statements (Continued)****9. Commitments and Contingencies (Continued)**

payments the Company could be required to make under these indemnification agreements is, in many cases, unlimited. To date, the Company has not incurred any material costs as a result of such indemnifications. The Company is not aware of any claims under indemnification arrangements, and it has not accrued any liabilities related to such obligations as of December 31, 2017 or 2018.

Legal Proceedings

The Company is not currently a party to any material legal proceedings. At each reporting date, the Company evaluates whether or not a potential loss amount or a potential range of loss is probable and reasonably estimable under the provisions of the authoritative guidance that addresses accounting for contingencies. The Company expenses the costs related to its legal proceedings as they are incurred. No such costs have been incurred for the years ended December 31, 2017 and 2018.

10. Income Taxes

A reconciliation of the U.S. federal statutory income tax rate to the Company's effective income tax rate is as follows:

	Year Ended December 31, 2017	Year Ended December 31, 2018
Federal income tax (benefit) at statutory rate	34.00%	21.00%
Permanent differences	(3.64)	(1.37)
Federal and state research and development credits	4.81	3.15
State income tax, net of federal benefit	4.88	5.77
Impact of U.S. tax reform	(16.25)	—
Change in valuation allowance	(23.80)	(28.55)
Effective income tax rate	—%	—%

During the years ended December 31, 2017 and 2018, the Company incurred book and tax losses and, because it maintains a full valuation allowance on its net deferred tax assets, did not recognize federal or state income tax expense or benefit.

Fulcrum Therapeutics, Inc.**Notes to Consolidated Financial Statements (Continued)****10. Income Taxes (Continued)**

The Company's deferred tax assets and liabilities consist of the following (in thousands):

	<u>December 31, 2017</u>	<u>December 31, 2018</u>
Deferred tax assets:		
Net operating loss carryforwards	\$ 8,493	\$ 16,566
Research and development credit carryforwards	1,475	2,503
Accrued expenses and other	336	457
Deferred lease incentive	—	1,218
Deferred rent	54	383
Gross deferred tax assets	10,358	21,127
Valuation allowance	(10,293)	(19,592)
Net deferred tax assets	65	1,535
Deferred tax liability	(65)	(1,535)
Net deferred tax assets	\$ —	\$ —

The Company has evaluated the positive and negative evidence bearing upon its ability to realize the deferred tax assets. The Company considered its history of cumulative net losses incurred since inception and its lack of commercialization of any products since inception and has concluded that it is more likely than not that the Company will not realize the benefits of the deferred tax assets. Accordingly, a full valuation allowance has been established against the net deferred tax assets as of December 31, 2017 and 2018. The Company reevaluates the positive and negative evidence at each reporting period.

As of December 31, 2018, the Company had federal net operating loss carryforwards of approximately \$60.7 million which begin to expire in 2035. Approximately \$29.7 million of the federal net operating losses can be carried forward indefinitely. As of December 31, 2018, the Company also had state net operating loss carryforwards of approximately \$60.5 million, which begin to expire in 2035.

As of December 31, 2018, the Company had federal research and development tax credit carryforwards of approximately \$1.5 million, which begin to expire in 2035. As of December 31, 2018, the Company also had state research and development tax credit carryforwards of approximately \$1.3 million, which begin to expire in 2035.

Utilization of the net operating loss carryforwards and research and development tax credit carryforwards may be subject to an annual limitation under Section 382 of the Internal Revenue Code of 1986, as amended (the "Internal Revenue Code"), and corresponding provisions of state law, due to ownership changes that have occurred previously or that could occur in the future. These ownership changes may limit the amount of carryforwards that can be utilized annually to offset future taxable income. In general, an ownership change, as defined by Section 382, results from transactions increasing the ownership of certain shareholders or public groups in the stock of a corporation by more than 50% over a three-year period. The Company has not conducted a study to assess whether a change of control has occurred or whether there have been multiple changes of control since inception due to the significant complexity and cost associated with such a study. If the Company has experienced a change of control, as defined by Section 382, at any time since inception, utilization of the net operating loss carryforwards or research and development tax credit carryforwards would be subject to an annual limitation under Section 382, which is determined by first multiplying the value of the Company's stock at the time of the ownership change by the applicable long-term tax-exempt rate, and then could be subject to additional

Fulcrum Therapeutics, Inc.

Notes to Consolidated Financial Statements (Continued)

10. Income Taxes (Continued)

adjustments, as required. Any limitation may result in expiration of a portion of the net operating loss carryforwards or research and development tax credit carryforwards before utilization. Further, until a study is completed and any limitation is known, no amounts are being presented as an uncertain tax position.

The Company files tax returns as prescribed by the tax laws of the jurisdictions in which it operates. In the normal course of business, the Company is subject to examination by federal and state jurisdictions, where applicable. There are currently no pending tax examinations. As of December 31, 2018, the Company's tax years are still open under statute from 2015 to the present.

It is the Company's policy to include penalties and interest expense related to income taxes as a component of the provision for income taxes. As of December 31, 2017 and 2018, the Company had no accrued interest or penalties related to uncertain tax positions and no amounts have been recognized in the Company's statements of operations. For the year ended December 31, 2018, the Company generated research credits but has not conducted a study to document the qualified activities. This study may result in an adjustment to the Company's research and development credit carryforwards; however, until a study is completed and any adjustment is known, no amounts are being presented as an uncertain tax position. A full valuation allowance has been provided against the Company's research and development credits and, if an adjustment is required, this adjustment would result in an adjustment to the deferred tax asset established for the research and development credit carryforwards and the valuation allowance.

On December 22, 2017, the Tax Cuts and Jobs Act (the "Tax Reform Act") was enacted, which significantly reforms the Internal Revenue Code. The Tax Reform Act, among other things, contains significant changes to corporate taxation, including reduction of the corporate tax rate from a top marginal rate of 35% to a flat rate of 21%, effective as of January 1, 2018; limitation of the tax deduction for interest expense; limitation of the deduction for net operating losses to 80% of annual taxable income and elimination of net operating loss carrybacks, in each case, for losses arising in taxable years beginning after December 31, 2017 (though any such tax losses may be carried forward indefinitely); and modifying or repealing many business deductions and credits, including reducing the business tax credit for certain clinical testing expenses incurred in the testing of certain drugs for rare diseases or conditions generally referred to as "orphan drugs."

The staff of the Securities and Exchange Commission issued Staff Accounting Bulletin No. 118 ("SAB 118") to address the application of GAAP in situations when a registrant does not have the necessary information available, prepared, or analyzed (including computations) in reasonable detail to complete the accounting for certain income tax effects of the Tax Reform Act. The Company is applying the provisions of SAB 118. In connection with the initial analysis of the impact of the Tax Reform Act for the year ended December 31, 2017, the Company remeasured certain deferred tax assets and liabilities based on the revised U.S. federal corporate tax rate of 21%. The remeasurement of the Company's deferred tax assets and liabilities was offset by a corresponding change in the Company's valuation allowance.

As permitted by SAB 118, the Company recorded provisional estimates during the year ended December 31, 2017 and has subsequently finalized its accounting analysis based on the guidance, interpretations, and data available as of December 31, 2018. Adjustments made in the fourth quarter of 2018 upon finalization of the Company's accounting analysis were not material to the Company's consolidated financial statements.

Fulcrum Therapeutics, Inc.**Notes to Consolidated Financial Statements (Continued)****11. Defined Contribution Plan**

The Company has a defined contribution savings plan under Section 401(k) of the Internal Revenue Code (the "401(k) Plan"). The 401(k) Plan covers all employees who meet defined minimum age and service requirements, and allows participants the option to elect to defer a portion of their annual compensation on a pretax basis. As currently established, the Company is not required to make and has not made any contributions to the 401(k) Plan.

12. Net Loss per Share and Unaudited Pro Forma Net Loss per Share***Net Loss per Share***

Basic net loss per share attributable to common stockholders is calculated by dividing net loss attributable to common stockholders by the weighted average shares outstanding during the period, without consideration for Common Stock equivalents. Net loss attributable to common stockholders is calculated by adjusting the net loss of the Company for cumulative preferred stock dividends. Diluted net loss per share attributable to common stockholders is calculated by adjusting weighted average shares outstanding for the dilutive effect of Common Stock equivalents outstanding for the period. For purposes of the diluted net loss per share attributable to common stockholders calculation, Preferred Stock, stock options, and unvested restricted stock are considered to be Common Stock equivalents but are excluded from the calculation of diluted net loss per share attributable to common stockholders, as their effect would be anti-dilutive. Therefore, basic and diluted net loss per share attributable to common stockholders were the same for all periods presented as a result of the Company's net loss.

The following Common Stock equivalents were excluded from the calculation of diluted net loss per share attributable to common stockholders for the periods indicated because including them would have had an anti-dilutive effect:

	<u>Year Ended December 31, 2017</u>	<u>Year Ended December 31, 2018</u>
Series A Preferred Stock	4,952,379	8,571,427
Series B Preferred Stock	—	5,714,277
Outstanding stock options	—	507,891
Unvested restricted stock awards	1,656,493	1,203,811
Total	<u>6,608,872</u>	<u>15,997,406</u>

In February 2019, the Company issued 12,500,000 shares of Series B Preferred Stock as consideration for the GSK Agreement (as defined in Note 14).

Unaudited Pro Forma Net Loss per Share

The unaudited pro forma basic and diluted net loss per share attributable to common stockholders for the year ended December 31, 2018 give effect to adjustments arising upon the closing of a qualified IPO. The unaudited pro forma basic and diluted weighted average common shares outstanding used in the calculation of unaudited pro forma basic and diluted net loss per share attributable to common stockholders for the year ended December 31, 2018 give effect to the automatic conversion upon a qualified IPO of all outstanding shares of Preferred Stock into shares of Common Stock as if the conversion had occurred on the later of January 1, 2018 or the issuance date of the Preferred Stock. Accordingly, the pro forma basic and diluted net loss per share attributable to stockholders does not include the effects of the cumulative preferred stock dividends. Shares to be sold in the offering are

Fulcrum Therapeutics, Inc.**Notes to Consolidated Financial Statements (Continued)****12. Net Loss per Share and Unaudited Pro Forma Net Loss per Share (Continued)**

excluded from the unaudited pro forma basic and diluted loss per share attributable to common stockholders calculations.

The following table summarizes the Company's unaudited pro forma net loss per share attributable to common stockholders (in thousands, except per share data):

	<u>Year Ended</u> <u>December 31, 2018</u>
Numerator:	
Net loss attributable to common stockholders	\$ (39,147)
Cumulative convertible preferred stock dividends	6,559
Pro forma net loss attributable to common stockholders	<u>\$ (32,588)</u>
Denominator:	
Weighted average common shares outstanding	1,257
Pro forma weighted average shares outstanding after giving effect to the conversion of Preferred Stock	9,694
Pro forma weighted average shares outstanding	<u>10,951</u>
Pro forma basic and diluted loss per share attributable to common stockholders, basic and diluted	<u>\$ (2.98)</u>

13. Related-Party Transactions

During the years ended December 31, 2017 and 2018, the Company paid fees to Third Rock Ventures, LLC ("TRV"), an affiliate of one of the Company's principal stockholders, in exchange for consulting services. The Company recorded expenses related to such fees of \$0.1 million during each of the years ended December 31, 2017 and 2018. As of both December 31, 2017 and 2018, there was less than \$0.1 million of amounts due to TRV for such services that were included in accounts payable and accrued expenses. Additionally, consultants that provide services to the Company are employees of TRV. The Company has issued an aggregate of 142,284 shares of Common Stock to these consultants in exchange for their continuing consulting services.

During the year ended December 31, 2018, the Company recorded other income of \$0.4 million related to the sale of drug material to an entity affiliated with TRV.

14. Subsequent Events

For its consolidated financial statements as of December 31, 2018 and for the year then ended, the Company evaluated subsequent events through May 1, 2019, the date on which those consolidated financial statements were issued, except for Note 14(c), as to which the date is July 8, 2019.

(a) 2016 Stock Incentive Plan

In January 2019, the 2016 Plan was amended to increase the number of shares of Common Stock reserved for issuance under the 2016 Plan by 357,143 shares. In January 2019 and March 2019, the Company issued stock options to purchase an aggregate of 1,020,496 shares of Common Stock under the 2016 Plan.

Fulcrum Therapeutics, Inc.**Notes to Consolidated Financial Statements (Continued)****14. Subsequent Events (Continued)****(b) GSK Agreement**

In February 2019, the Company entered into a right of reference and license agreement (the "GSK Agreement") with subsidiaries of GlaxoSmithKline plc (collectively referred to as "GSK"), pursuant to which the Company has been granted an exclusive worldwide license to develop and commercialize losmapimod. Under the GSK Agreement, the Company also acquired reference rights to relevant regulatory and manufacturing documents and GSK's existing supply of losmapimod drug substance and product. The Company also has the right to sublicense its rights under the license agreement, subject to certain conditions. The Company is obligated to use commercially reasonable efforts to develop and commercialize losmapimod at its sole cost. The Company is also responsible for costs related to the filing and maintenance of the licensed patent rights.

Under the GSK Agreement, the Company issued 12,500,000 million shares of Series B Preferred Stock to GSK with an estimated fair value of \$25.5 million, or \$2.04 per share, which was determined with the assistance of a third-party specialist contemporaneously with the issuance of the Series B Preferred Stock to GSK. In addition, the Company may owe GSK up to \$37.5 million in certain specified clinical and regulatory milestones, of which \$2.5 million is due upon the initiation of a Phase 2 clinical trial, and up to \$60.0 million in certain specified sales milestones. The Company has agreed to pay tiered royalties on annual net sales of losmapimod that range from mid single-digit percentages to a low double-digit, but less than teens, percentage. The royalties are payable on a product-by-product and country-by-country basis, and may be reduced in specified circumstances. The Company also incurred \$0.1 million of direct expenses related to the transaction, which the Company will include in the total consideration for the transaction.

The GSK Agreement may be terminated by either party for a material breach by the other, subject to notice and cure provisions. Unless earlier terminated, the GSK Agreement will continue in effect until the expiration of the Company's royalty obligations, which expire on a country-by-country basis on the later of (i) ten years after the first commercial sale in the country or (ii) approval of a generic version of losmapimod by the applicable regulatory agency.

The Company concluded the arrangement did not result in the acquisition of a business, as substantially all of the fair value of the gross assets acquired was concentrated in a single in-process research and development asset, losmapimod. In addition, the Company did not obtain any substantive processes in connection to the GSK Agreement and losmapimod was not generating revenue at the time the GSK Agreement was executed. Therefore, the Company accounted for the arrangement as an asset acquisition. The Company also concluded that the acquired assets do not have an alternative future use, and therefore the fair value attributable to the GSK Agreement of \$25.6 million, inclusive of transaction costs, will be recorded as in-process research and development expense in the Company's consolidated statement of operations and comprehensive loss for the three months ended March 31, 2019, which is the period in which the Company obtained (i) the license to losmapimod, (ii) the right to reference relevant regulatory and manufacturing documents, and (iii) GSK's existing supply of losmapimod drug substance and product. Additionally, the Company will recognize clinical and regulatory milestone payments when the underlying contingency is resolved and the consideration is paid or becomes payable. The milestone payments will be capitalized or expensed depending on the nature of the associated asset as of the date of recognition. The Company will record sales milestone payments and royalties as additional expense of the related product sales in the period in which the corresponding sales occur.

In February 2019, in connection with the GSK Agreement, the Company's Certificate of Incorporation was amended and restated to increase the number of authorized shares of Series B

Fulcrum Therapeutics, Inc.

Notes to Consolidated Financial Statements (Continued)

14. Subsequent Events (Continued)

Preferred Stock from 40,000,000 shares to 52,500,000 shares and to increase the number of authorized shares of Common Stock from 135,000,000 shares to 147,500,000 shares.

(c) Other

On July 5, 2019, the Company eliminated the gross proceeds threshold of \$45 million for a firm-commitment underwritten public offering that would result in the automatic conversion of all outstanding shares of Preferred Stock into Common Stock. On July 5, 2019, the Company effected a one-for-seven reverse stock split of the Company's common stock. All share and per share amounts in the financial statements and notes thereto have been retroactively adjusted for all periods presented to give effect to this reverse stock split, including reclassifying an amount equal to the reduction in par value of common stock to additional paid-in capital. Shares of common stock underlying outstanding stock options and other equity instruments were proportionately reduced and the respective exercise prices, if applicable, were proportionately increased in accordance with the terms of the appropriate securities agreements. Shares of common stock reserved for issuance upon the conversion of our convertible preferred stock were proportionately reduced and the respective conversion prices were proportionately increased. Stockholders entitled to fractional shares as a result of the reverse stock split will receive a cash payment in lieu of receiving fractional shares.

Fulcrum Therapeutics, Inc.

Consolidated Balance Sheets

(In thousands, except share and per share amounts)

(Unaudited)

	December 31, 2018	March 31, 2019	Pro Forma March 31, 2019
Assets			
Current assets:			
Cash and cash equivalents	\$ 72,797	\$ 62,452	\$ 62,452
Prepaid expenses and other current assets	1,298	1,544	1,544
Total current assets	74,095	63,996	63,996
Property and equipment, net	10,546	10,225	10,225
Restricted cash	1,092	1,092	1,092
Other assets	38	275	275
Total assets	<u>\$ 85,771</u>	<u>\$ 75,588</u>	<u>\$ 75,588</u>
Liabilities, convertible preferred stock, and stockholders' (deficit) equity			
Current liabilities:			
Accounts payable	\$ 1,263	\$ 2,522	\$ 2,522
Accrued expenses and other current liabilities	2,497	1,699	1,699
Deferred lease incentive, current portion	469	469	469
Total current liabilities	4,229	4,690	4,690
Deferred rent, excluding current portion	1,402	1,450	1,450
Deferred lease incentive, excluding current portion	3,990	3,873	3,873
Other liabilities, excluding current portion	150	126	126
Total liabilities	9,771	10,139	10,139
Commitments and contingencies (Note 10)			
Series A convertible preferred stock, \$0.001 par value; 60,000,000 shares authorized, issued and outstanding as of December 31, 2018 and March 31, 2019 (liquidation preference of \$68,371 as of March 31, 2019); no shares issued or outstanding, pro forma as of March 31, 2019			
	59,909	59,909	—
Series B convertible preferred stock, \$0.001 par value; 40,000,000 and 52,500,000 shares authorized, issued and outstanding as of December 31, 2018 and March 31, 2019, respectively (liquidation preference of \$109,119 as of March 31, 2019); no shares issued or outstanding, pro forma as of March 31, 2019			
	79,761	105,227	—
Stockholders' (deficit) equity:			
Common stock, \$0.001 par value; 135,000,000 and 147,500,000 shares authorized as of December 31, 2018 and March 31, 2019, respectively; 2,791,764 and 2,747,842 shares issued as of December 31, 2018 and March 31, 2019, respectively; 1,587,953 and 1,721,966 shares outstanding as of December 31, 2018 and March 31, 2019, respectively; 18,819,260 and 17,793,384 shares issued and outstanding, pro forma as of March 31, 2019			
	2	2	18
Treasury stock, at cost; 67,024 and no shares as of December 31, 2018 and March 31, 2019, respectively; no shares, pro forma as of March 31, 2019			
	—	—	—
Additional paid-in capital	4,452	5,278	170,398
Accumulated deficit	(68,124)	(104,967)	(104,967)
Total stockholders' (deficit) equity	(63,670)	(99,687)	65,449
Total liabilities, convertible preferred stock, and stockholders' (deficit) equity	<u>\$ 85,771</u>	<u>\$ 75,588</u>	<u>\$ 75,588</u>

The accompanying notes are an integral part of these financial statements.

Fulcrum Therapeutics, Inc.

Consolidated Statements of Operations and Comprehensive Loss

(In thousands, except per share data)

(Unaudited)

	Three Months Ended	
	March 31,	
	2018	2019
Operating expenses:		
Research and development	\$ 5,573	\$ 34,629
General and administrative	1,737	2,598
Total operating expenses	7,310	37,227
Loss from operations	(7,310)	(37,227)
Other income, net:		
Interest income, net	—	377
Other income	370	7
Net loss and comprehensive loss	\$ (6,940)	\$ (36,843)
Cumulative convertible preferred stock dividends	(828)	(3,041)
Net loss attributable to common stockholders	\$ (7,768)	\$ (39,884)
Net loss per share attributable to common stockholders, basic and diluted	\$ (7.62)	\$ (24.29)
Weighted average number of common shares used in net loss per share attributable to common stockholders, basic and diluted	1,019	1,642
Pro forma net loss per share attributable to common stockholders, basic and diluted		\$ (2.17)
Pro forma weighted average number of common shares used in net loss per share attributable to common stockholders, basic and diluted		16,940

The accompanying notes are an integral part of these financial statements.

Fulcrum Therapeutics, Inc.

Consolidated Statements of Convertible Preferred Stock and Stockholders' (Deficit) Equity

(In thousands, except share amounts)

(Unaudited)

	Series A Convertible Preferred Stock		Series B Convertible Preferred Stock		Common Stock		Treasury Stock		Additional Paid-In Capital	Accumulated Deficit	Total Stockholders' (Deficit) Equity
	Shares	Amount	Shares	Amount	Shares	Amount	Shares	Amount			
Balance at December 31, 2017	34,666,666	\$ 34,587	—	\$ —	972,266	\$ 1	8,036	\$ —	2,270	\$ (35,536)	\$ (33,265)
Issuance of Series A convertible preferred stock at \$1.00 per share, net of issuance costs of \$7	12,666,667	12,659	—	—	—	—	—	—	—	—	—
Issuance of common stock	—	—	—	—	125,123	—	—	—	4	—	4
Repurchase of unvested restricted stock awards	—	—	—	—	—	—	12,599	—	—	—	—
Retirement of treasury shares	—	—	—	—	—	—	(20,635)	—	—	—	—
Stock-based compensation expense	—	—	—	—	—	—	—	—	429	—	429
Net loss	—	—	—	—	—	—	—	—	—	(6,940)	(6,940)
Balance at March 31, 2018	47,333,333	\$ 47,246	—	\$ —	1,097,389	\$ 1	—	\$ —	2,703	\$ (42,476)	\$ (39,772)
Balance at December 31, 2018	60,000,000	\$ 59,909	40,000,000	\$ 79,761	1,587,953	\$ 2	67,024	\$ —	4,452	\$ (68,124)	\$ (63,670)
Issuance of Series B convertible preferred stock in connection with asset acquisition, net of issuance costs of \$34	—	—	12,500,000	25,466	—	—	—	—	—	—	—
Issuance of common stock	—	—	—	—	134,013	—	—	—	5	—	5
Repurchase of unvested restricted stock awards	—	—	—	—	—	—	43,922	—	—	—	—
Retirement of treasury shares	—	—	—	—	—	—	(110,946)	—	—	—	—
Stock-based compensation expense	—	—	—	—	—	—	—	—	821	—	821
Net loss	—	—	—	—	—	—	—	—	—	(36,843)	(36,843)
Balance at March 31, 2019	60,000,000	\$ 59,909	52,500,000	\$ 105,227	1,721,966	\$ 2	—	\$ —	5,278	\$ (104,967)	\$ (99,687)
Pro forma convertible preferred stock and stockholders' equity (unaudited):											
Conversion of convertible preferred stock into common stock	(60,000,000)	(59,909)	(52,500,000)	(105,227)	16,071,418	16	—	—	165,120	—	165,136
Pro forma balance at March 31, 2019	—	\$ —	—	\$ —	17,793,384	\$ 18	—	\$ —	170,398	\$ (104,967)	\$ 65,449

The accompanying notes are an integral part of these financial statements.

Fulcrum Therapeutics, Inc.
Consolidated Statements of Cash Flows
(In thousands)
(Unaudited)

	Three Months Ended	
	March 31,	
	2018	2019
Operating activities		
Net loss	\$ (6,940)	\$ (36,843)
Adjustments to reconcile net loss to net cash used in operating activities:		
Depreciation expense	174	504
Stock-based compensation expense	429	821
In-process research and development expenses	—	25,591
Changes in operating assets and liabilities:		
Prepaid expenses and other current assets	(565)	(264)
Other assets	28	(63)
Accounts payable	196	1,233
Accrued expenses and other current liabilities	(430)	(807)
Deferred rent and deferred lease incentive	476	(69)
Net cash used in operating activities	(6,632)	(9,897)
Investing activities		
Purchases of property and equipment	(783)	(310)
Transaction costs associated with asset acquisition	—	(91)
Net cash used in investing activities	(783)	(401)
Financing activities		
Proceeds from issuance of Series A convertible preferred stock, net of issuance costs	12,665	—
Issuance costs associated with issuance of Series B convertible preferred stock	—	(34)
Principal payments on capital lease obligations	(42)	(11)
Proceeds from issuance of common stock (repurchases of common stock)	17	(2)
Net cash provided by (used in) financing activities	12,640	(47)
Net increase (decrease) in cash, cash equivalents and restricted cash	5,225	(10,345)
Cash, cash equivalents, and restricted cash, beginning of period	407	73,889
Cash, cash equivalents, and restricted cash, end of period	\$ 5,632	\$ 63,544
Supplemental cash flow information		
Cash paid for interest	\$ 2	\$ 2
Non-cash investing and financing activities:		
Acquisition of in process research and development through issuance of stock	\$ —	\$ 25,500
Property and equipment purchases unpaid at end of period	\$ 1,778	\$ 47
Deferred offering costs unpaid at end of period	\$ —	\$ 190

The following table provides a reconciliation of the cash, cash equivalents, and restricted cash balances as of each of the periods shown above:

	March 31, 2018	March 31, 2019
Cash and cash equivalents	\$ 5,632	\$ 62,452
Restricted cash	—	1,092
Total cash, cash equivalents, and restricted cash	\$ 5,632	\$ 63,544

The accompanying notes are an integral part of these financial statements.

Fulcrum Therapeutics, Inc.

Notes to Consolidated Financial Statements

1. Nature of the Business and Basis of Presentation

Fulcrum Therapeutics, Inc. (the "Company" or "Fulcrum") was incorporated in Delaware on August 18, 2015. The Company is focused on improving the lives of patients with genetically defined diseases in areas of high unmet medical need, with an initial focus on rare diseases.

The Company is subject to a number of risks similar to other companies in the biotechnology industry, including, but not limited to, risks of failure of preclinical studies and clinical trials, dependence on key personnel, protection of proprietary technology, reliance on third party organizations, risks of obtaining regulatory approval for any product candidate that it may develop, development by competitors of technological innovations, compliance with government regulations, and the need to obtain additional financing. Product candidates currently under development will require significant additional research and development efforts, including extensive preclinical and clinical testing and regulatory approval, prior to commercialization. These efforts require significant amounts of additional capital, adequate personnel infrastructure and extensive compliance-reporting capabilities. Even if the Company's development efforts are successful, it is uncertain when, if ever, the Company will realize significant revenue from product sales.

Basis of Presentation

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

The accompanying unaudited consolidated financial statements and footnotes to the financial statements have been prepared on the same basis as the most recently audited annual financial statements and, in the opinion of management, reflect all normal recurring adjustments necessary for the fair presentation of the Company's financial position as of March 31, 2019 and the results of its operations and its cash flows for the three months ended March 31, 2018 and 2019. The results for the three months ended March 31, 2019 are not necessarily indicative of results to be expected for the year ending December 31, 2019, any other interim periods, or any future year or period. These consolidated financial statements should be read in conjunction with the Company's audited consolidated financial statements.

Going Concern

The Company has incurred recurring losses and negative cash flows from operations since inception and has primarily funded its operations with proceeds from the issuance of convertible notes and convertible preferred stock. As of March 31, 2019, the Company had an accumulated deficit of \$105.0 million. The Company expects its operating losses and negative operating cash flows to continue into the foreseeable future as it continues to expand its research and development efforts. As of June 5, 2019, the issuance date of the consolidated financial statements for the three months ended March 31, 2019, the Company expected that its cash and cash equivalents as of March 31, 2019 will be sufficient to fund its operating expenses and capital expenditure requirements into the first quarter of 2020. The future viability of the Company beyond that point is dependent on its ability to raise additional capital to finance its operations.

If the Company is unable to obtain additional funding, the Company could be forced to delay, reduce or eliminate some or all of its research and development programs, product portfolio expansion, or

Fulcrum Therapeutics, Inc.

Notes to Consolidated Financial Statements (Continued)

1. Nature of the Business and Basis of Presentation (Continued)

commercialization efforts, which could adversely affect its business prospects, or the Company may be unable to continue operations. The Company is seeking to complete an initial public offering ("IPO") of its common stock ("Common Stock"). In the event the Company does not complete an IPO, the Company expects to seek additional funding through private equity financings, debt financings, or other capital sources, including collaborations with other companies or other strategic transactions. Although management plans to pursue additional funding, there is no assurance that the Company will be successful in obtaining sufficient funding on terms acceptable to the Company to fund continuing operations, if at all.

Based on its recurring losses and negative cash flows from operations since inception, expectation of continuing operating losses and negative cash flows from operations for the foreseeable future, and the need to raise additional capital to finance its future operations, management concluded that there is substantial doubt about the Company's ability to continue as a going concern within one year after the date that the consolidated financial statements as of and for the three months ended March 31, 2019 were issued.

The accompanying consolidated financial statements do not include any adjustments that might result from the outcome of this uncertainty. Accordingly, the consolidated financial statements have been prepared on a basis that assumes the Company will continue as a going concern and which contemplates the realization of assets and satisfaction of liabilities and commitments in the ordinary course of business.

2. Summary of Significant Accounting Policies

Principles of Consolidation

The accompanying consolidated financial statements include the accounts of the Company and its wholly owned subsidiary, Fulcrum Therapeutics Securities Corp., which is a Massachusetts subsidiary created to buy, sell, and hold securities. All intercompany transactions and balances have been eliminated.

Summary of Significant Accounting Policies

The significant accounting policies and estimates used in the preparation of the consolidated financial statements are described in the Company's audited financial statements. There have been no material changes in the Company's significant accounting policies during the three months ended March 31, 2019.

Use of Estimates

The preparation of financial statements in accordance with GAAP requires management to make certain estimates and assumptions that affect the reported amounts of assets and liabilities and disclosure of contingent assets and liabilities as of the date of the financial statements, and the reported amount of expenses during the reported periods. Estimates inherent in the preparation of these consolidated financial statements include, but are not limited to, estimates related to accrued expenses, stock-based compensation expense, the fair value of the Common Stock and convertible preferred stock, and income taxes. The Company bases its estimates on historical experience and other market specific or other relevant assumptions it believes to be reasonable under the circumstances. On an ongoing basis, management evaluates its estimates as there are changes in circumstances, facts and experience. Actual results could differ from those estimates or assumptions.

Fulcrum Therapeutics, Inc.**Notes to Consolidated Financial Statements (Continued)****2. Summary of Significant Accounting Policies (Continued)*****Pro Forma Financial Information***

The accompanying pro forma balance sheet and statement of stockholders' (deficit) equity as of March 31, 2019 has been prepared to give effect, upon the closing of a qualified IPO, to the automatic conversion of all shares of convertible preferred stock outstanding as of March 31, 2019 into 16,071,418 shares of Common Stock. In the accompanying consolidated statements of operations and comprehensive loss, the pro forma basic and diluted net loss per share attributable to common stockholders for the three months ended March 31, 2019 have been prepared to give effect, upon the closing of a qualified IPO, to the automatic conversion of all outstanding shares of convertible preferred stock as if the proposed IPO had occurred on the later of January 1, 2019 or the issuance date of the convertible preferred stock (see Note 12).

Deferred Issuance Costs

The Company capitalizes certain legal, professional, accounting and other third-party fees that are directly associated with in-process equity issuances as deferred issuance costs until such equity issuances are consummated. After consummation of the equity issuance, these costs are recorded as a reduction in the capitalized amount associated with the equity issuance. Should the planned financing be abandoned, the deferred issuance costs will be expensed immediately as a charge to operating expenses in the consolidated statement of operations and comprehensive loss. Deferred issuance costs as of December 31, 2018 and March 31, 2019 were less than \$0.1 million and \$0.2 million, respectively.

Research and Development Expenses

Research and development expenses include costs directly attributable to the conduct of research and development programs, including personnel-related expenses such as salaries, payroll taxes, benefits, and stock-based compensation expense, manufacturing and external costs related to outside vendors engaged to conduct both preclinical studies and clinical trials, laboratory supplies, depreciation on and maintenance of research equipment, and the allocable portions of facility costs, such as rent, utilities, repairs and maintenance, depreciation, and general support services. Expenditures relating to research and development are expensed in the period incurred. Nonrefundable advance payments for goods and services that will be used in future research and development activities are expensed when the activity has been performed or when the goods have been received rather than when the payment is made.

Research and development expenses also include in-process research and development ("IPR&D") expenses, which relate to IPR&D acquired as part of an asset acquisition for which there is no alternative future use. Research and development with no future alternative use is expensed as incurred.

Off-Balance Sheet Risk and Concentrations of Credit Risk

The Company has no significant off-balance sheet risk such as foreign exchange contracts, option contracts, or other foreign hedging arrangements. Financial instruments that potentially expose the Company to concentrations of credit risk consist primarily of cash, cash equivalents, and restricted cash. The Company's cash, cash equivalents, and restricted cash are deposited in accounts at large financial institutions. The Company believes it is not exposed to significant credit risk due to the financial strength of the depository institutions in which the cash, cash equivalents and restricted cash are held. The Company maintains its cash equivalents in money market funds that invest in U.S. Treasury securities.

Fulcrum Therapeutics, Inc.**Notes to Consolidated Financial Statements (Continued)****2. Summary of Significant Accounting Policies (Continued)*****Recent Accounting Pronouncements—To Be Adopted***

In February 2016, the FASB issued ASU No. 2016-02, *Leases (Topic 842)* ("ASU 2016-02"), as amended by various subsequently issued ASUs. The standard requires lessees to recognize an operating lease with a term greater than one year on their balance sheets as a right-of-use asset and corresponding lease liability, measured at the present value of the lease payments. Lessees are required to classify leases as either finance or operating leases. If the lease is effectively a financed-purchase by the lessee, it is classified as a financing lease, otherwise it is classified as an operating lease. This classification will determine whether lease expense is recognized based on an effective interest method or on a straight-line basis over the term of the lease. In July 2018, the FASB also issued ASU 2018-11, *Leases (Topic 842): Targeted Improvements* ("ASU 2018-11"), which permits entities to continue applying legacy guidance in ASC 840, *Leases*, including its disclosure requirements, in the comparative periods presented in the year that the entity adopts the new leasing standard. The new standard will be effective for the Company on January 1, 2020. The Company will apply the transition method permitted by ASU 2018-11. The Company is currently evaluating the effect that adoption of the standard is expected to have on the Company's consolidated financial statements and related disclosures. The Company expects to take advantage of certain available expedients by electing the transition package of practical expedients permitted within ASU 2016-02, which allows the Company to not reassess previous accounting conclusions around whether arrangements are, or contain, leases, the classification of leases, and the treatment of initial direct costs. The Company also expects to make an accounting policy election to exclude leases with an initial term of twelve months or less from the balance sheet.

In June 2016, the FASB issued ASU No. 2016-13, *Financial Instruments—Credit Losses (Topic 326): Measurement of Credit Losses on Financial Instruments* ("ASU 2016-13"). The standard requires that credit losses be reported using an expected losses model rather than the incurred losses model that is currently used, and establishes additional disclosures related to credit risks. For available-for-sale debt securities with unrealized losses, this standard requires allowances to be recorded instead of reducing the amortized cost of the investment. The new standard will be effective for the Company on January 1, 2021. The Company is currently evaluating the potential impact that this standard may have on its consolidated financial position and results of operations.

In July 2017, the FASB issued ASU No. 2017-11, *Earnings Per Share (Topic 260), Distinguishing Liabilities from Equity (Topic 480), Derivatives and Hedging (Topic 815) I. Accounting for Certain Financial Instruments with Down Round Features II. Replacement of the Indefinite Deferral for Mandatorily Redeemable Financial Instruments of Certain Nonpublic Entities and Certain Mandatorily Redeemable Noncontrolling Interests with a Scope Exception* ("ASU 2017-11"). Part I of the standard applies to entities that issue financial instruments such as warrants, convertible debt or convertible preferred stock that contain down-round features. Part II of the standard replaces the indefinite deferral for certain mandatorily redeemable noncontrolling interests and mandatorily redeemable financial instruments of nonpublic entities contained within ASC Topic 480 with a scope exception and does not impact the accounting for these mandatorily redeemable instruments. The new standard will be effective for the Company on January 1, 2020. The Company is currently evaluating the impact that the adoption of ASU 2017-11 may have on its consolidated financial statements.

Fulcrum Therapeutics, Inc.

Notes to Consolidated Financial Statements (Continued)

3. Fair Value Measurements

The following tables present information about the Company's financial assets measured at fair value on a recurring basis and indicate the level of the fair value hierarchy utilized to determine such fair values (in thousands):

	Fair Value Measurements at December 31, 2018			
	Total	Level 1	Level 2	Level 3
Cash equivalents:				
Money market funds	\$ 72,797	\$ 72,797	\$ —	\$ —
Total	<u>\$ 72,797</u>	<u>\$ 72,797</u>	<u>\$ —</u>	<u>\$ —</u>

	Fair Value Measurements at March 31, 2019			
	Total	Level 1	Level 2	Level 3
Cash equivalents:				
Money market funds	\$ 62,452	\$ 62,452	\$ —	\$ —
Total	<u>\$ 62,452</u>	<u>\$ 62,452</u>	<u>\$ —</u>	<u>\$ —</u>

There have been no transfers between fair value levels during the three months ended March 31, 2018 or 2019.

4. Property and Equipment, Net

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

	December 31, 2018	March 31, 2019
Lab equipment	\$ 4,847	\$ 5,305
Furniture and fixtures	542	542
Computer equipment	517	512
Software	90	90
Leasehold improvements	6,174	6,174
Construction in process	334	—
Total property and equipment	12,504	12,623
Less: accumulated depreciation	(1,958)	(2,398)
Property and equipment, net	<u>\$ 10,546</u>	<u>\$ 10,225</u>

Depreciation expense for the three months ended March 31, 2018 and 2019 was \$0.2 million and \$0.5 million, respectively.

Fulcrum Therapeutics, Inc.**Notes to Consolidated Financial Statements (Continued)****5. Additional Balance Sheet Detail**

Prepaid expenses and other current assets consisted of the following (in thousands):

	December 31, 2018	March 31, 2019
Prepaid expenses	\$ 460	\$ 508
Prepaid sign-on bonuses subject to vesting provisions	99	229
Leasehold improvement allowance receivable	366	366
Interest income receivable	135	123
Other	238	318
Total prepaid expenses and other current assets	<u>\$ 1,298</u>	<u>\$ 1,544</u>

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

	December 31, 2018	March 31, 2019
External research and development	\$ 437	\$ 889
Payroll and benefits	1,448	527
Professional services	254	170
Capital lease obligation, current portion	46	47
Restricted stock liability, current portion	18	15
Property and equipment purchases	174	—
Other	120	51
Total accrued expenses and other current liabilities	<u>\$ 2,497</u>	<u>\$ 1,699</u>

6. Convertible Preferred Stock

As of December 31, 2018, 100,000,000 shares of convertible preferred stock were authorized, issued, and outstanding, of which 60,000,000 shares were designated as \$0.001 par value Series A convertible preferred stock (the "Series A Preferred Stock"), and 40,000,000 shares were designated as \$0.001 par value Series B convertible preferred stock (the "Series B Preferred Stock", and together with the Series A Preferred Stock, the "Preferred Stock"). As of March 31, 2019, 112,500,000 shares of Preferred Stock were authorized, issued, and outstanding, of which 60,000,000 shares were designated as \$0.001 par value Series A Preferred Stock, and 52,500,000 shares were designated as \$0.001 par value Series B Preferred Stock.

During the three months ended March 31, 2019, the Company issued 12,500,000 shares of Series B Preferred Stock in connection with the GSK Agreement (Note 9). The rights, privileges, and preferences of the Series B Preferred Stock issued in connection with the GSK Agreement are consistent with the rights, privileges, and preferences of the Series B Preferred Stock issued during the year ended December 31, 2018.

No dividends have been declared since inception. Aggregate cumulative dividends associated with the Series A Preferred Stock and the Series B Preferred Stock as of December 31, 2018 were \$7.2 million and \$2.3 million, respectively. Aggregate cumulative dividends associated with the Series A Preferred Stock and the Series B Preferred Stock as of March 31, 2019 were \$8.4 million and \$4.1 million, respectively.

Fulcrum Therapeutics, Inc.**Notes to Consolidated Financial Statements (Continued)****7. Common Stock**

Common stockholders are entitled to receive dividends, as may be declared by the Company's board of directors, if any, subject to the preferential dividend rights of the Preferred Stock. No dividends have been declared or paid during the three months ended March 31, 2018 or 2019.

During the three months ended March 31, 2019, the Company's Certificate of Incorporation was amended and restated to increase the number of authorized shares of Common Stock from 135,000,000 to 147,500,000 shares.

The Company had reserved the following shares of Common Stock for the potential conversion of Preferred Stock and for the future issuance of Common Stock pursuant to the Company's 2016 Stock Incentive Plan, as amended from time to time (the "2016 Plan"):

	<u>December 31,</u> <u>2018</u>	<u>March 31,</u> <u>2019</u>
Shares reserved for conversion of outstanding Series A Preferred Stock	8,571,427	8,571,427
Shares reserved for conversion of outstanding Series B Preferred Stock	5,714,277	7,499,991
Shares reserved for future issuance under the 2016 Stock Incentive Plan	919,030	366,623
	<u>15,204,734</u>	<u>16,438,041</u>

8. Stock-based Compensation Expense***Grants Under the 2016 Stock Incentive Plan***

In July 2016, the Company adopted the 2016 Plan, under which it may grant restricted stock awards, restricted stock units, incentive stock options, non-statutory stock options, and other stock-based awards to eligible employees, officers, directors, consultants, and advisors. The total number of shares of Common Stock that were authorized for issuance under the 2016 Plan was 3,209,285 as of December 31, 2018. In January 2019, the 2016 Plan was amended to increase the number of shares of Common Stock reserved for issuance under the 2016 Plan by 357,143 shares. The total number of shares of Common Stock that were authorized for issuance under the 2016 Plan was 3,566,428 as of March 31, 2019.

For financial reporting purposes, the Company performed Common Stock valuations with the assistance of a third-party specialist as of March 15, 2019, November 30, 2018, August 24, 2018, June 1, 2018, December 31, 2017, and December 31, 2016 to determine stock-based compensation expense for restricted stock awards and stock options.

Shares of Common Stock repurchased from employees and non-employees are shares held in the Company's treasury ("Treasury Shares"). The board of directors may, at its discretion, authorize that the Treasury Shares be returned to the pool of authorized but unissued Common Stock.

Fulcrum Therapeutics, Inc.

Notes to Consolidated Financial Statements (Continued)

8. Stock-based Compensation Expense (Continued)

The following table summarizes the Company's restricted stock activity under the 2016 Plan since December 31, 2018:

	Number of Shares	Weighted Average Grant Date Fair Value
Unvested at December 31, 2018	757,022	\$ 3.07
Granted	—	—
Vested	(105,980)	3.04
Repurchased	(43,922)	3.06
Unvested at March 31, 2019	<u>607,120</u>	<u>\$ 3.07</u>

The following table summarizes the Company's stock option activity under the 2016 Plan since December 31, 2018:

	Number of Shares	Weighted Average Exercise Price	Weighted Average Remaining Contractual Term (in years)	Aggregate Intrinsic Value
Outstanding at December 31, 2018	507,891	\$ 7.12	9.84	\$ 367,427
Granted	1,020,496	7.85		
Exercised	—	—		
Cancelled	—	—		
Outstanding at March 31, 2019	<u>1,528,387</u>	\$ 7.60	9.74	\$ 1,109,354
Exercisable at March 31, 2019	<u>74,680</u>	\$ 6.82	9.62	\$ 113,092

The aggregate intrinsic value of stock options is calculated as the difference between the exercise price of the stock options and the fair value of the Company's Common Stock as of the balance sheet date for those options that had exercise prices lower than the fair value of the Company's Common Stock.

The weighted average grant date fair value of stock options granted during the three months ended March 31, 2019 was \$5.56 per share. As of March 31, 2019, no stock options have been exercised since inception. The fair value of stock options granted during the three months ended March 31, 2019 under the 2016 Plan has been calculated on the date of grant using the following weighted average assumptions:

	Three Months Ended March 31, 2019
Risk-free interest rate	2.6%
Expected dividend yield	0.0%
Expected term (years)	6.0
Expected stock price volatility	81.4%

Fulcrum Therapeutics, Inc.**Notes to Consolidated Financial Statements (Continued)****8. Stock-based Compensation Expense (Continued)****Grants Outside the 2016 Stock Incentive Plan**

The following table summarizes the Company's restricted stock activity outside of the 2016 Plan since December 31, 2018:

	Number of Shares	Weighted Average Grant Date Fair Value
Unvested at December 31, 2018	446,789	\$ 2.94
Granted	—	—
Vested	(28,033)	2.94
Repurchased	—	—
Unvested at March 31, 2019	<u>418,756</u>	<u>\$ 2.94</u>

The aggregate intrinsic value of all restricted stock awards that vested during the three months ended March 31, 2019 was \$1.4 million.

Stock-based Compensation Expense

The total compensation cost recognized in the statements of operations associated with all stock-based compensation awards granted by the Company is as follows (in thousands):

	Three Months Ended March 31, 2018	Three Months Ended March 31, 2019
Research and development	\$ 256	\$ 406
General and administrative	173	415
Total stock-based compensation expense	<u>\$ 429</u>	<u>\$ 821</u>

As of March 31, 2019, the Company had an aggregate of \$10.5 million of unrecognized stock-based compensation expense, which is expected to be recognized over a weighted average period of 3.26 years.

9. Asset Acquisition

In February 2019, the Company entered into a right of reference and license agreement (the "GSK Agreement") with subsidiaries of GlaxoSmithKline plc (collectively referred to as "GSK"), pursuant to which the Company has been granted an exclusive worldwide license to develop and commercialize losmapimod. Under the GSK Agreement, the Company also acquired reference rights to relevant regulatory and manufacturing documents and GSK's existing supply of losmapimod drug substance and product. The Company also has the right to sublicense its rights under the license agreement, subject to certain conditions. The Company is obligated to use commercially reasonable efforts to develop and commercialize losmapimod at its sole cost. The Company is also responsible for costs related to the filing and maintenance of the licensed patent rights.

Under the GSK Agreement, the Company issued 12,500,000 million shares of Series B Preferred Stock to GSK with an estimated fair value of \$25.5 million, or \$2.04 per share, which was determined with the assistance of a third-party specialist contemporaneously with the issuance of the Series B Preferred Stock to GSK. In addition, the Company may owe GSK up to \$37.5 million in certain specified clinical and

Fulcrum Therapeutics, Inc.**Notes to Consolidated Financial Statements (Continued)****9. Asset Acquisition (Continued)**

regulatory milestones, of which \$2.5 million is due upon the initiation of a Phase 2 clinical trial, and up to \$60.0 million in certain specified sales milestones. The Company has agreed to pay tiered royalties on annual net sales of losmapimod that range from mid single-digit percentages to a low double-digit, but less than teens, percentage. The royalties are payable on a product-by-product and country-by-country basis, and may be reduced in specified circumstances. The Company also incurred \$0.1 million of direct expenses related to the transaction, which the Company included in the total consideration for the transaction.

The GSK Agreement may be terminated by either party for a material breach by the other, subject to notice and cure provisions. Unless earlier terminated, the GSK Agreement will continue in effect until the expiration of the Company's royalty obligations, which expire on a country-by-country basis on the later of (i) ten years after the first commercial sale in the country or (ii) approval of a generic version of losmapimod by the applicable regulatory agency.

The Company concluded the arrangement did not result in the acquisition of a business, as substantially all of the fair value of the gross assets acquired was concentrated in a single in-process research and development asset, losmapimod. In addition, the Company did not obtain any substantive processes in connection to the GSK Agreement and losmapimod was not generating revenue at the time the GSK Agreement was executed. Therefore, the Company accounted for the arrangement as an asset acquisition. The Company also concluded that the acquired assets do not have an alternative future use, and therefore the fair value attributable to the GSK Agreement of \$25.6 million, inclusive of transaction costs, was recorded as in-process research and development expense (a component of research and development expenses) in the Company's consolidated statement of operations and comprehensive loss for the three months ended March 31, 2019, which is the period in which the Company obtained (i) the license to losmapimod, (ii) the right to reference relevant regulatory and manufacturing documents, and (iii) GSK's existing supply of losmapimod drug substance and product. Additionally, the Company will recognize clinical and regulatory milestone payments when the underlying contingency is resolved and the consideration is paid or becomes payable. The milestone payments will be capitalized or expensed depending on the nature of the associated asset as of the date of recognition. The Company will record sales milestone payments and royalties as additional expense of the related product sales in the period in which the corresponding sales occur.

10. Commitments and Contingencies***Operating Leases***

In May 2016, the Company entered into a sublease agreement for approximately 8,143 square feet of office and laboratory space at its prior corporate headquarters in Cambridge, Massachusetts. The sublease for this space terminated on June 30, 2018. Rent expense associated with this sublease for the three months ended March 31, 2018 was \$0.1 million.

In November 2017, the Company entered into a lease agreement for its current corporate headquarters for approximately 28,731 square feet of office and laboratory space in Cambridge, Massachusetts. The lease has a total commitment of \$25.1 million over the ten year term, and includes escalating rent payments. The lease agreement requires the Company to either pay a security deposit or maintain a letter of credit of \$1.1 million. The Company maintains a letter of credit for this lease and has recorded the cash held to secure the letter of credit as restricted cash on the consolidated balance sheet as of December 31, 2018 and March 31, 2019. Rent expense associated with this lease for the three months ended March 31, 2018 and 2019 was approximately \$0.5 million and \$0.5 million, respectively.

Fulcrum Therapeutics, Inc.**Notes to Consolidated Financial Statements (Continued)****10. Commitments and Contingencies (Continued)**

The future minimum lease payments associated with the lease for the Company's current headquarters as of March 31, 2019, are as follows (in thousands):

2019 ⁽¹⁾	\$ 1,673
2020	2,285
2021	2,354
2022	2,424
2023	2,497
Thereafter	12,187
Total minimum lease payments	<u>\$ 23,420</u>

(1) Amounts are for the nine months ending December 31, 2019.

Other Agreements

The Company has agreements with third parties in the normal course of business under which it can license certain developed technologies. If the Company exercises its rights to license the technologies it may be subject to additional fees and milestone payments. As of March 31, 2019, the Company has not exercised its rights to license such technologies.

Indemnification Agreements

In the ordinary course of business, the Company may provide indemnification of varying scope and terms to vendors, lessors, business partners and other parties with respect to certain matters arising out of the relationship between such parties and the Company. In addition, the Company has entered into indemnification agreements with members of its board of directors and senior management that will require the Company, among other things, to indemnify them against certain liabilities that may arise by reason of their status or service as directors or officers. The maximum potential amount of future payments the Company could be required to make under these indemnification agreements is, in many cases, unlimited. To date, the Company has not incurred any material costs as a result of such indemnifications. The Company is not aware of any claims under indemnification arrangements, and it has not accrued any liabilities related to such obligations as of December 31, 2018 or March 31, 2019.

Legal Proceedings

The Company is not currently a party to any material legal proceedings. At each reporting date, the Company evaluates whether or not a potential loss amount or a potential range of loss is probable and reasonably estimable under the provisions of the authoritative guidance that addresses accounting for contingencies. The Company expenses the costs related to its legal proceedings as they are incurred. No such costs have been incurred during the three months ended March 31, 2018 or 2019.

11. Defined Contribution Plan

The Company has a defined contribution savings plan under Section 401(k) of the Internal Revenue Code (the "401(k) Plan"). The 401(k) Plan covers all employees who meet defined minimum age and service requirements, and allows participants the option to elect to defer a portion of their annual

Fulcrum Therapeutics, Inc.**Notes to Consolidated Financial Statements (Continued)****11. Defined Contribution Plan (Continued)**

compensation on a pretax basis. As currently established, the Company is not required to make and has not made any contributions to the 401(k) Plan.

12. Net Loss per Share and Pro Forma Net Loss per Share***Net Loss per Share***

The following common stock equivalents were excluded from the calculation of diluted net loss per share attributable to common stockholders for the periods indicated because including them would have had an anti-dilutive effect:

	Three Months Ended March 31, 2018	Three Months Ended March 31, 2019
Series A Preferred Stock	6,761,903	8,571,427
Series B Preferred Stock	—	7,499,991
Outstanding stock options	—	1,528,387
Unvested restricted stock awards	1,768,750	1,025,876
Total	8,530,653	18,625,681

Pro Forma Net Loss per Share

The pro forma basic and diluted net loss per share attributable to common stockholders for the three months ended March 31, 2019 give effect to adjustments arising upon the closing of a qualified IPO. The pro forma basic and diluted weighted average common shares outstanding used in the calculation of pro forma basic and diluted net loss per share attributable to common stockholders for the three months ended March 31, 2019 give effect to the automatic conversion upon a qualified IPO of all outstanding shares of Preferred Stock into shares of Common Stock as if the conversion had occurred on the later of January 1, 2019 or the issuance date of the Preferred Stock. Accordingly, the pro forma basic and diluted net loss per share attributable to stockholders does not include the effects of the cumulative preferred stock dividends. Shares to be sold in the offering are excluded from the pro forma basic and diluted loss per share attributable to common stockholders calculations.

Fulcrum Therapeutics, Inc.**Notes to Consolidated Financial Statements (Continued)****12. Net Loss per Share and Pro Forma Net Loss per Share (Continued)**

The following table summarizes the Company's pro forma net loss per share attributable to common stockholders (in thousands, except per share data):

	<u>Three Months Ended</u> <u>March 31, 2019</u>
Numerator:	
Net loss attributable to common stockholders	\$ (39,884)
Cumulative convertible preferred stock dividends	3,041
Pro forma net loss attributable to common stockholders	<u>\$ (36,843)</u>
Denominator:	
Weighted average common shares outstanding	1,642
Pro forma weighted average shares outstanding after giving effect to the conversion of Preferred Stock	15,298
Pro forma weighted average shares outstanding	<u>16,940</u>
Pro forma basic and diluted loss per share attributable to common stockholders, basic and diluted	<u>\$ (2.17)</u>

13. Related-Party Transactions

During the three months ended March 31, 2018 and 2019, the Company paid fees to Third Rock Ventures, LLC ("TRV"), an affiliate of one of the Company's principal stockholders, in exchange for consulting services. The Company recorded expenses related to such fees of less than \$0.1 million during each of the three months ended March 31, 2018 and 2019. As of both December 31, 2018 and March 31, 2019, there was less than \$0.1 million of amounts due to TRV for such services that were included in accounts payable and accrued expenses. Additionally, consultants that provide services to the Company are employees of TRV. The Company has issued an aggregate of 142,284 shares of Common Stock to these consultants in exchange for their continuing consulting services.

During the three months ended March 31, 2018, the Company recorded other income of \$0.4 million related to the sale of drug material to an entity affiliated with TRV.

14. Subsequent Events

For its consolidated financial statements as of March 31, 2019 and for the three months then ended, the Company evaluated subsequent events through June 5, 2019, the date on which those consolidated financial statements were issued, except for Note 14(a), as to which the date is July 8, 2019.

(a) Other

On July 5, 2019, the Company eliminated the gross proceeds threshold of \$45 million for a firm-commitment underwritten public offering that would result in the automatic conversion of all outstanding shares of Preferred Stock into Common Stock. On July 5, 2019, the Company effected a one-for-seven reverse stock split of the Company's common stock. All share and per share amounts in the financial statements and notes thereto have been retroactively adjusted for all periods presented to give effect to this reverse stock split, including reclassifying an amount equal to the reduction in par value of common

Fulcrum Therapeutics, Inc.

Notes to Consolidated Financial Statements (Continued)

14. Subsequent Events (Continued)

stock to additional paid-in capital. Shares of common stock underlying outstanding stock options and other equity instruments were proportionately reduced and the respective exercise prices, if applicable, were proportionately increased in accordance with the terms of the appropriate securities agreements. Shares of common stock reserved for issuance upon the conversion of our convertible preferred stock were proportionately reduced and the respective conversion prices were proportionately increased. Stockholders entitled to fractional shares as a result of the reverse stock split will receive a cash payment in lieu of receiving fractional shares.

4,500,000 Shares



Common Stock

Prospectus

MORGAN STANLEY

BofA MERRILL LYNCH

SVB LEERINK

July 17, 2019

Until August 11, 2019 (25 days after the date of this prospectus), all dealers that effect transactions in these securities, whether or not participating in this offering, may be required to deliver a prospectus. This delivery requirement is in addition to the dealers' obligation to deliver a prospectus when acting as underwriters and with respect to their unsold allotments or subscriptions.
