

Spark Therapeutics, Inc.  
Form S-1/A  
January 28, 2015  
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As filed with the Securities and Exchange Commission on January 28, 2015

Registration No. 333-201318

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

**Amendment No. 2**  
**to**  
**FORM S-1**  
**REGISTRATION STATEMENT**  
**UNDER**  
**THE SECURITIES ACT OF 1933**

**Spark Therapeutics, Inc.**

(Exact name of registrant as specified in its charter)

**Delaware**  
**(State or other jurisdiction of**  
**incorporation or organization)**

**2836**  
**(Primary Standard Industrial**  
**Classification Code Number)**

**46-2654405**  
**(I.R.S. Employer**  
**Identification No.)**

**3737 Market Street**

**Suite 1300**

**Philadelphia, PA 19104**

**(888) 772-7560**

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

**Jeffrey D. Marrazzo**

**Chief Executive Officer**

**Spark Therapeutics, Inc.**

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**Philadelphia, PA 19104**

**(888) 772-7560**

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**Approximate date of commencement of proposed sale to the public:** As soon as practicable after this Registration Statement is declared effective.

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

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

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

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

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

Large accelerated filer " Accelerated filer "  
 Non-accelerated filer x Smaller reporting company "  
 (Do not check if a smaller reporting company)

### CALCULATION OF REGISTRATION FEE

Title of Each Class of Securities To Be Registered	Amount to be Registered (1)	Proposed Maximum Offering Price Per Share (2)	Proposed Maximum Aggregate Offering Price (2)	Amount of Registration Fee (3)(4)
Common Stock, \$0.001 par value per share	7,475,000	\$21.00	\$156,975,000	\$18,241

(1) Includes 975,000 shares of common stock the underwriters have the option to purchase.

(2)

**Estimated solely for the purpose of calculating the registration fee pursuant to Rule 457(a) under the Securities Act of 1933, as amended.**

- (3) Calculated pursuant to Rule 457(a) based on an estimate of the proposed maximum aggregate offering price.**
- (4) A registration fee of \$12,495 was previously paid in connection with the Registration Statement, and the additional amount of \$5,746 is being paid herewith.**

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

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

Subject to completion, dated January 28, 2015

**6,500,000 shares**

***Common stock***

This is an initial public offering of common stock by Spark Therapeutics, Inc. We are selling 6,500,000 shares of common stock. The estimated initial public offering price is between \$19.00 and \$21.00 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 Select Market under the symbol ONCE.

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 reporting requirements.

	<b>Per share</b>	<b>Total</b>
Initial public offering price	\$	\$
Underwriting discounts and commissions (1)	\$	\$
Proceeds to Spark, before expenses	\$	\$

(1) We have agreed to reimburse the underwriters for certain FINRA-related expenses. See Underwriting beginning on page 166 of this prospectus. Our principal stockholders have indicated an interest in purchasing an aggregate of up to approximately \$15 million in shares of our common stock in this offering at the initial public offering price. However, because indications of interest are not binding agreements or commitments to purchase, these stockholders may determine to purchase fewer shares than they indicate an interest in purchasing or not to purchase any shares in this offering. It also is possible that these stockholders could indicate an interest in purchasing more shares of our common stock. In addition, the underwriters could determine to sell fewer shares to any of these stockholders than the stockholders indicate an interest in purchasing or not to sell any shares to these stockholders.

We have granted the underwriters an option for a period of 30 days to purchase up to an additional 975,000 shares of common stock.

**Investing in our common stock involves risks. See Risk factors beginning on page 12 of this prospectus.**

**Neither the Securities and Exchange Commission nor any other regulatory body 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 investors on or about \_\_\_\_\_, 2015.

**J.P. Morgan**

**Credit Suisse**

**Cowen and Company**

**Sanford C. Bernstein**

The date of this prospectus is \_\_\_\_\_, 2015.

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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. The underwriters and we 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.

**Until \_\_\_\_\_, 2015 (25 days after the commencement of this offering), all dealers that buy, sell or trade shares of our common stock, whether or not participating in this offering, may be required to deliver a prospectus. This delivery requirement is in addition to the obligation of dealers to deliver a prospectus when acting as underwriters and with respect to their unsold allotments or subscription.**

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.



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## **Prospectus summary**

*This summary highlights information contained elsewhere in this prospectus. This summary does not contain all of the information you should consider before investing in our common stock. You should read this entire prospectus carefully, especially the **Risk factors** section beginning on page 12 and our financial statements and the related notes appearing at the end of this prospectus, before making an investment decision.*

### **Overview**

We are a leader in the field of gene therapy, seeking to transform the lives of patients suffering from debilitating genetic diseases by developing one-time, life-altering treatments. Our product candidates have the potential to provide long-lasting effects, dramatically and positively changing the lives of patients with conditions where no, or only palliative, therapies exist. Our initial focus is on treating orphan diseases, and we have demonstrated promising clinical outcomes with our first product candidate targeting rare blinding conditions, which has received both breakthrough therapy and orphan product designation and is in a fully enrolled, pivotal Phase 3 clinical trial with data expected in the second half of 2015. We also have built a pipeline of product candidates targeting additional blinding conditions, hematologic disorders and neurodegenerative diseases, including a second product candidate targeting another rare blinding condition, for which we have initiated enrollment in a clinical trial, and a collaboration with Pfizer Inc., or Pfizer, for the development and commercialization of a gene therapy for the treatment of hemophilia B. Our platform technology is based on more than two decades of gene therapy research, development, manufacturing and clinical trials conducted at The Children's Hospital of Philadelphia, or CHOP.

### **Product candidates**

Our most advanced product candidate, SPK-RPE65, which is in a pivotal Phase 3 clinical trial, targets a group of rare blinding conditions known as inherited retinal dystrophies, or IRDs, caused by non sex-linked, or autosomal recessive, mutations in the RPE65 gene. Patients suffering from RPE65-mediated IRDs are affected by a range of severe visual impairments, which ultimately lead to blindness, that make independent activities of daily living challenging. For example, affected children often depend on visual aids to carry out classroom activities while adults with these diseases may face diminished employment opportunities and may be stripped of some of the rewards of parenting, such as watching a child play his or her favorite sport. We estimate that there are approximately 3,500 individuals with RPE65-mediated IRDs in the United States and the five major European markets.

SPK-RPE65 is engineered using a vector derived from an adeno-associated virus, or AAV, which is a small, non-pathogenic cold virus. To create the vector, DNA encoding the AAV viral genes is removed, disarming the virus, and is replaced with the therapeutic gene sequence for the RPE65 protein, which is then delivered via injection to the retina. Production of RPE65 protein in the retina helps convert light into an electrical signal, and is necessary for vision.

To date, the results of our two Phase 1 clinical trials, along with reports from our clinical study team and other feedback regarding the subjects in the trials, suggest that SPK-RPE65 enables subjects to perform activities of daily living with greater independence than prior to treatment and has long-lasting effects in restoring functional vision, with subjects having been followed for a period of at least five years. Notably, as reported by our clinical study team, following a single injection of SPK-RPE65 in one eye, the children from our initial Phase 1 trial no longer depended on visual aids to carry out classroom activities and were able to walk and play more like normally sighted kids. Furthermore, inclusive of the subjects in our ongoing Phase 3 clinical trial, we have not observed any drug-related serious adverse events to date.

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We are conducting a fully enrolled, pivotal Phase 3 clinical trial of SPK-RPE65 in which we have dosed all subjects in the treatment group and currently are collecting data. We anticipate reporting final results during the second half of 2015. If successful, we plan to submit a biologics license application, or BLA, to the U.S. Food and Drug Administration, or FDA, in 2016. SPK-RPE65 has the potential to be the first gene therapy approved in the United States for the treatment of a genetic disease and the first approved pharmacologic treatment for any IRD.

RPE65-mediated IRDs historically have been characterized most frequently as Leber's congenital amaurosis, or LCA, and retinitis pigmentosa, or RP. LCA is a rare, inherited eye disease that results in severe visual impairment and, ultimately, blindness that typically is diagnosed in childhood. RP also is a rare, inherited eye disease that results in severe visual impairment and, ultimately, blindness but that typically is diagnosed in the teenage years or later. According to key opinion leaders, over the past decade, the diagnosis of IRDs has begun to shift from clinical classifications to a diagnosis of disease based on the specific underlying causal gene. To date, across all of our clinical trials, SPK-RPE65 has been studied in subjects with LCA due to RPE65 mutations, as confirmed by genetic testing. However, with the broad availability of genetic testing and this corresponding shift from clinical to genetic diagnosis, we believe SPK-RPE65 will have broad application to all IRDs caused by autosomal recessive RPE65 gene mutations.

We have received both breakthrough therapy and orphan product designation for SPK-RPE65. Breakthrough therapy designation is granted by FDA with the intention of expediting the development and regulatory review of a product candidate intended to treat a serious or life-threatening condition when preliminary clinical evidence, which in our case were the data from our two Phase 1 clinical trials of SPK-RPE65, indicates the potential for substantial improvement over existing therapies. SPK-RPE65 also has received orphan product designation in both the United States and the European Union for the treatment of patients with a diagnosis of LCA due to RPE65 mutations. FDA may designate a biologic product as an orphan product if it is intended to treat a rare disease or condition, which generally is defined as having a patient population of fewer than 200,000 individuals in the United States. Orphan product designation, subject to limited exceptions, can provide a period of market exclusivity for a product that is the first to receive marketing approval for the designated indication. We are seeking expansion of our orphan product designation for SPK-RPE65 to other IRDs caused by RPE65 mutations, in addition to LCA. We believe that the potential one-time nature of a gene therapy treatment could enable a company that receives the first FDA approval for a disease or condition, and which also has obtained orphan product exclusivity for such disease or condition, to treat a substantial portion of the addressable patient population during the period of orphan product exclusivity.

The RPE65 gene is one of more than 220 genes that have been identified to cause IRDs. We are expanding our portfolio of product candidates to target additional IRDs caused by gene mutations for which we believe we will be able to leverage our experience with SPK-RPE65. Our first such follow-on product candidate is SPK-CHM for the treatment of choroideremia, or CHM.

CHM is an IRD linked to the X-chromosome, or X-linked, which manifests in affected males in childhood as night blindness and a reduction of visual field, followed by progressive constriction of visual fields. For CHM patients, it is often in middle age, when people typically are at or near their greatest income-earning potential, that visual impairment begins to limit independent activities of daily living leading to a severe decrease in vision and, eventually, blindness. We estimate that CHM affects approximately 12,500 males in the United States and the five major European markets.

We use the same vector design, administration method and manufacturing process for SPK-CHM that we use for SPK-RPE65. We recently initiated enrollment in a dose-escalating, Phase 1/2 clinical trial of SPK-CHM, in which we currently expect to enroll up to 10 subjects. We expect to begin dosing subjects in this trial in the first quarter of 2015. We have received orphan product designation for SPK-CHM for the treatment of choroideremia in both the United States and the European Union.

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We have established human proof-of-concept in using gene therapy to deliver and express a therapeutic gene in the liver as part of our SPK-FIX program for the treatment of hemophilia B. Hemophilia B is a serious and rare inherited hematologic disorder, characterized by a mutation in the Factor IX, or FIX, gene which leads to deficient blood coagulation and an increased risk of bleeding or hemorrhaging. According to the 2012 World Federation of Hemophilia Annual Global Survey, approximately 28,000 people worldwide suffer from hemophilia B.

In December 2014, we entered into a global collaboration agreement with Pfizer for the development and commercialization of product candidates in our SPK-FIX program for the treatment of hemophilia B. Under the terms of the agreement, we received a \$20.0 million upfront payment and are eligible to receive up to \$260.0 million in aggregate milestone payments, as well as royalties calculated as a low-teen percentage of net product sales. Pfizer and we are developing proprietary, bio-engineered AAV vectors utilizing a high-activity transgene and a treatment protocol designed to mitigate immune responses seen in other hemophilia B gene therapy trials, including our own, that have limited the duration of efficacy. We intend to initiate a Phase 1/2 trial in the first half of 2015.

We have preclinical programs in development for the treatment of hemophilia A and neurodegenerative diseases. We have exclusively in-licensed a broad range of rights for these preclinical programs.

From time to time, we may evaluate collaboration opportunities for our product candidates, as we have with Pfizer. We also expect to work opportunistically with pharmaceutical and biotechnology companies, as we are with Genable Technologies Limited, or Genable, seeking to utilize our technology and know-how for developing additional gene therapy products.

The following table summarizes information regarding our product candidates and development programs.

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### **Technology**

We are building a fully integrated gene therapy platform to accelerate the development of product candidates across multiple therapeutic areas. Our platform technology, which leverages two decades of gene therapy research, development, manufacturing and clinical trials conducted at CHOP, enables us to pursue multiple therapeutic targets. Our scientists and scientific advisors have accumulated over 150 years of collective experience in the field of gene therapy, contributing key insights and significant developments that have coincided with a resurgence of interest in gene-based medicines.

Our proprietary manufacturing processes produce consistent yields of highly pure and stable gene therapy product candidates. Gene therapies made using our platform technology, including AAV vectors and vectors derived from the lentivirus family of viruses, or lentiviral vectors, have been, or are being, used by several biopharmaceutical companies in clinical trials of their own gene therapy product candidates, as well as in multiple clinical trials sponsored by the U.S. National Institutes of Health.

### **Our strategy**

Our goal is to transform the lives of patients by being the leading, fully-integrated gene therapy company. We are seeking to develop, manufacture and commercialize multiple product candidates targeting orphan genetic diseases across multiple tissue types and therapeutic areas. To achieve our goal, we are pursuing the following strategies:

Successfully complete clinical development and obtain marketing approval for SPK-RPE65 in the United States and the European Union.

Establish a global commercial and medical affairs infrastructure for SPK-RPE65.

Establish a franchise of gene therapies for additional IRDs, focusing next on the treatment of choroideremia with SPK-CHM.

Continue to build a liver-directed gene therapy platform, with an initial focus on our SPK-FIX program for the treatment of hemophilia B in collaboration with Pfizer.

Advance preclinical neurodegenerative programs into clinical development.

Leverage our proprietary manufacturing platform to partner selectively with other pharmaceutical and biotechnology companies.

### **Series B financing**

In May 2014, we completed a \$72.7 million private placement of shares of Series B convertible preferred stock, or our Series B financing. Investors in our Series B financing include investment funds managed by, or affiliated with, Sofinnova Ventures, Brookside Capital, Deerfield Management Company, Rock Springs Capital, T. Rowe Price Associates, Wellington Management Company and two other healthcare investment funds. CHOP also participated in our Series B financing.

### **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 immediately following this prospectus summary. These risks include the following:

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We have incurred net losses since inception. As of September 30, 2014, we had an accumulated deficit of \$72.6 million. We expect to incur losses for the foreseeable future and may never achieve or maintain profitability.

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Our gene therapy product candidates are based on a novel technology, which makes it difficult to predict the time and cost of development and of subsequently obtaining regulatory approval. At the moment, no gene therapy product has been approved in the United States and only one such product has been approved in the European Union.

Because we are developing product candidates for the treatment of diseases in which there is little clinical experience and, in some cases, using new endpoints or analytical methodologies, there is increased risk that FDA or other regulatory authorities may not consider the endpoints of our pivotal Phase 3 clinical trial to provide clinically meaningful results and that these results may be difficult to analyze.

While we believe SPK-RPE65 should be applicable for the treatment of patients with any IRD mediated by an RPE65 mutation, the results from our pivotal Phase 3 clinical trial for SPK-RPE65, which included only subjects diagnosed with LCA due to RPE65 mutations, may not support as broad a marketing approval as we seek, and FDA and the European Medicines Agency, or EMA, may require us to conduct additional clinical trials or evaluate subjects for an additional follow-up period.

Gene therapies are novel, complex and difficult to manufacture. We could experience problems that result in delays in validating our manufacturing processes or delays in the development or production of our product candidates, that could adversely affect our business. To date, no current Good Manufacturing Practices, or cGMP, gene therapy manufacturing facility in the United States has received approval from FDA for the manufacture of an approved gene therapy product.

We have entered into, and may in the future enter into additional, collaborations with third parties to develop product candidates. If these collaborations are not successful, our business could be adversely affected.

We face significant competition in an environment of rapid technological change. We are aware of at least 12 other companies and academic institutions that currently are developing AAV-based gene therapies. There is a possibility that one or more of our competitors may develop therapies that are more effective than ours or may obtain regulatory approval prior to us.

To the extent we rely on CHOP's manufacturing facility for commercial supply, CHOP will be subject to significant regulatory oversight with respect to manufacturing our products. CHOP's manufacturing facilities may not meet regulatory requirements.

If we are unable to establish sales and marketing capabilities or enter into agreements with third parties to market and sell any approved product candidates, we may be unable to generate any product revenue.

If the market opportunities for our product candidates are smaller than we believe they are, or if we do not maintain orphan product designation or receive market exclusivity, our product revenues may be adversely affected and our business may suffer.

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

Our gene therapy approach utilizes vectors derived from viruses, which may be perceived as unsafe or may result in unforeseen adverse events. Negative public opinion and increased regulatory scrutiny of gene therapy may damage public perception of the safety of our product candidates and adversely affect our ability to conduct clinical trials or obtain regulatory approvals for our product candidates.



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We may not be successful in our efforts to identify or discover additional product candidates and may fail to capitalize on programs or product candidates that may be a greater commercial opportunity or for which there is a greater likelihood of success.

If we are not able to obtain or maintain adequate intellectual property protection covering our product candidates and manufacturing technologies, our competitors could develop and commercialize products and manufacturing technologies similar or identical to ours, and our ability to successfully commercialize our product candidates and manufacturing technologies may be impaired.

Our rights to develop and commercialize our product candidates are subject, in part, to the terms and conditions of licenses granted to us by others. For example, we have a co-exclusive license to patent rights that relate to methods for treating patients with LCA due to RPE65 mutations, under which one licensor, on behalf of the other co-licensors, has the right to license the same patent rights to one additional party.

After this offering, our executive officers, directors and principal stockholders will maintain the ability to control all matters submitted to stockholders for approval.

## **Our corporate information**

Our company was formed as AAvenue Therapeutics, LLC, a Delaware limited liability company, on March 13, 2013. On October 14, 2013, we acquired or exclusively in-licensed the commercial and development rights to certain clinical and preclinical programs and intellectual property from CHOP and the University of Iowa Research Foundation, or UIRF, and in-licensed additional intellectual property from the University of Pennsylvania, or Penn. On October 15, 2013, we changed our name to Spark Therapeutics, LLC. On May 2, 2014, we converted from a Delaware limited liability company into a Delaware corporation, at which time we changed our name to Spark Therapeutics, Inc.

Our executive offices are located at 3737 Market Street, Suite 1300, Philadelphia, PA 19104 and our telephone number is (888) 772-7560. Our website address is <http://www.sparktx.com>. The information contained in, or accessible through, our website does not constitute part of this prospectus, and the inclusion of our website address in this prospectus is an inactive textual reference only.

In this prospectus, unless otherwise stated or the context otherwise requires:

references to Spark LLC refer to Spark Therapeutics, LLC only (which was previously known as AAvenue Therapeutics, LLC);

references to Spark Inc. refer to Spark Therapeutics, Inc. only;

references to Spark, we, us, our and similar references refer to Spark Inc., together with Spark LLC;

references to the corporate conversion refer to all of the transactions related to the conversion of Spark LLC into Spark Inc., including the conversion of all of the outstanding membership interests of Spark LLC into shares of capital stock of Spark Inc.;

references to (i) common stock refer to the common stock of Spark Inc. or, as applicable, to the common units of Spark LLC and (ii) preferred stock refer to the preferred stock of Spark Inc. or, as applicable, to the preferred units of Spark LLC;

references to Spark's clinical trials and similar references regarding clinical trials relating to our product candidates and the associated data (including the use of we, us and our) include the applicable rights to clinical and preclinical programs assigned or licensed to us by CHOP or the University of Iowa Research Foundation;





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references to Spark's intellectual property and similar references regarding intellectual property relating to our product candidates (including the use of we, us and our) include the applicable rights to intellectual property assigned or licensed to us by CHOP, UIRF or Penn; and

references to Spark's manufacturing platform and similar references regarding manufacturing of gene therapy product candidates (including the use of we, us and our) include the applicable know-how assigned or licensed to us by CHOP.

SPARK and the Spark logo are trademarks of Spark Therapeutics, Inc. The other trademarks, trade names and service marks appearing in this prospectus are the property of their respective owners.

## **Implications of being an emerging growth company**

As a company with less than \$1 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 until the end of the 2020 fiscal year. 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 other public companies that are not emerging growth companies. In particular, in this prospectus, we 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.

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<b>Common stock offered by us</b>	6,500,000 shares
<b>Common stock to be outstanding after this offering</b>	22,990,367 shares
<b>Option to purchase additional shares</b>	The underwriters have an option for a period of 30 days to purchase up to 975,000 additional shares of our common stock.
<b>Use of proceeds</b>	We intend to use the net proceeds from this offering as follows: approximately \$11.0 million to fund external research and development expenses for SPK-RPE65; approximately \$8.0 million to fund external research and development expenses for SPK-CHM; approximately \$5.0 million to fund external research and development expenses for our SPK-FIX program; approximately \$14.0 million to fund external research and development expenses for preclinical product candidates; and the remainder for working capital, general and administrative expenses, internal research and development expenses and other general corporate purposes, including pre-commercial activities, in-licenses or potential acquisitions. See <a href="#">Use of proceeds</a> for more information.
<b>Risk factors</b>	You should read the <a href="#">Risk factors</a> section of this prospectus for a discussion of factors to consider carefully before deciding to invest in shares of our common stock.
<b>Directed shares</b>	At our request, the underwriters have reserved for sale, at the initial public offering price, up to 2% of the shares offered hereby for employees, directors and other persons associated with us who have expressed an interest in purchasing common stock in the offering. See <a href="#">Underwriting</a> for more information.
<b>NASDAQ Global Select Market symbol</b>	ONCE

The number of shares of our common stock to be outstanding after this offering is based on the 6,290,317 shares of our common stock outstanding as of January 15, 2015 and the 10,200,050 shares of our common stock issuable upon the automatic conversion, upon the closing of this offering, of all outstanding shares of our preferred stock, including shares of preferred stock that are issuable as accrued dividends, assuming the closing of this offering occurs on February 4, 2015. The number of shares of common stock issuable upon the automatic conversion of the outstanding shares of our preferred stock will continue to increase if the closing occurs after February 4, 2015 as a result of the issuance of additional shares of preferred stock accruing as preferred stock dividends at a rate of 8% per annum. For each day occurring between February 4, 2015 and the closing of this offering, if any, the number of shares of common stock issuable upon the automatic conversion of the outstanding shares of our preferred stock will increase by approximately 2,200 shares.



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

2,264,497 shares of common stock issuable upon exercise of stock options outstanding as of January 15, 2015 at a weighted-average exercise price of \$4.52 per share;

209,500 shares of common stock reserved as of January 15, 2015 for future issuance under our 2014 equity incentive plan, which shares, upon the effectiveness of the registration statement for this offering, will be available for future issuance under our 2015 stock incentive plan;

1,830,000 additional shares of common stock that will be available for future issuance, as of the effectiveness of the registration statement for this offering, under our 2015 stock incentive plan, of which we expect to grant options to purchase an aggregate of 146,000 shares to our recently appointed director and certain recently hired employees upon the commencement of trading of our common stock on the NASDAQ Global Select Market; and

220,000 additional shares of common stock that will be available for future issuance, as of the closing of this offering, under our 2015 employee stock purchase plan.

Unless otherwise indicated, this prospectus reflects and assumes the following:

the conversion of all outstanding shares of our preferred stock into 10,200,050 shares of our common stock, which will occur automatically upon the closing of this offering, assuming the closing occurs on February 4, 2015;

no exercise of outstanding stock options described above;

the filing of our restated certificate of incorporation and the adoption of our amended and restated by-laws upon the closing of this offering; and

no exercise by the underwriters of their option to purchase additional shares.

In addition, unless otherwise indicated, all information in this prospectus gives effect to a one-for-five reverse stock split of our common stock that became effective on January 16, 2015. Information related to the common units of Spark LLC, which were converted into shares of stock in May 2014, does not give effect to such reverse split.

Our principal stockholders have indicated an interest in purchasing an aggregate of up to approximately \$15 million in shares of our common stock in this offering at the initial public offering price. Assuming an initial public offering price of \$20.00 per share, which is the midpoint of the price range set forth on the cover page of this prospectus, these stockholders would purchase up to an aggregate of approximately 750,000 of the 6,500,000 shares offered in this offering based on these indications of interest. However, because indications of interest are not binding agreements or commitments to purchase, these stockholders may determine to purchase fewer shares than they indicate an interest in purchasing or not to purchase any shares in this offering. It also is possible that these stockholders could indicate an interest in purchasing more shares of our common stock. In addition, the underwriters could determine to sell fewer shares to any of these stockholders than the stockholders indicate an interest in purchasing or not to sell any shares to these stockholders.

Table of Contents**Summary financial data**

The following tables set forth, for the periods and at the dates indicated, our summary financial data. Historical results are not indicative of the results to be expected in the future and results of interim periods are not necessarily indicative of results for the entire year. You should read the following information together with the more detailed information contained in Selected financial data, Management's discussion and analysis of financial condition and results of operations and our financial statements and the accompanying notes thereto appearing elsewhere in this prospectus.

	Period from March 13, 2013 (inception) to December 31, 2013	Period from March 13, 2013 (inception) to September 30, 2013 (unaudited)	Nine months ended September 30, 2014
	(in thousands, except unit/share and per unit/share amounts)		
<b>Statements of Operations Data:</b>			
Revenues	\$	\$	\$ 20
Operating expenses:			
Research and development	4,897	2,968	10,169
Acquired in-process research and development	50,000		
General and administrative	2,381	661	5,162
Total operating expenses	57,278	3,629	15,331
Loss from operations	(57,278)	(3,629)	(15,311)
Interest income			2
Net loss	\$ (57,278)	\$ (3,629)	\$ (15,309)
Basic and diluted net loss per common unit/share(1)	\$ (8.44)(2)		\$ (2.87)
Weighted average basic and diluted common units/shares outstanding(1)	6,788,396 (2)		5,334,610
Unaudited pro forma net loss	\$ (57,278)		\$ (15,309)
Unaudited pro forma basic and diluted net loss per common share(1)	\$ (35.27)		\$ (1.44)
Unaudited pro forma weighted average basic and diluted common shares outstanding(1)	1,623,891		10,638,070

(1) See Note 3(f) to our audited financial statements and Note 3(i) to our unaudited financial statements included elsewhere in this prospectus for an explanation of the method used to calculate (a) basic and diluted net loss per common unit/share and weighted average basic and diluted common units/shares outstanding used to calculate the per common unit/share amounts and (b) unaudited pro forma net loss per common share and the unaudited pro forma weighted average

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basic and diluted common shares outstanding used to calculate the pro forma per common share amounts. The unaudited pro forma information for the nine-month period ended September 30, 2014 does not give effect to the issuance of any shares after such date.

- (2) Basic and diluted net loss per common unit and weighted average basic and diluted common units outstanding for the period from March 13, 2013 (inception) to December 31, 2013 do not give effect to the one-for-five reverse stock split that became effective on January 16, 2015 as only units of Spark LLC were outstanding during 2013 and the reverse split was not applicable to the units.

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	As of September 30, 2014		
	Actual	Pro forma(1) (unaudited) (in thousands)	Pro forma as adjusted(2)
<b>Balance Sheet Data:</b>			
Cash and cash equivalents	\$ 67,273	\$ 67,273	\$ 185,446
Working capital	\$ 62,281	\$ 62,281	\$ 180,181
Total assets	\$ 80,914	\$ 80,914	\$ 197,753
Total preferred stock(3)	\$ 82,437	\$	\$
Total stockholders' equity	\$ 62,725	\$ 62,725	\$ 180,625

- (1) The pro forma balance sheet data give effect to (a) the issuance of 200,000 shares of restricted stock that are subject to certain milestone-based vesting conditions and were issued to Penn in connection with entry into our license agreement in December 2014 and (b) the automatic conversion of all outstanding shares of our preferred stock, including shares of preferred stock issuable as accrued dividends, into an aggregate of 10,200,050 shares of common stock upon the closing of this offering assuming the closing occurs on February 4, 2015.
- (2) The pro forma as adjusted balance sheet data give further effect to our issuance and sale of 6,500,000 shares of common stock in this offering (assuming no exercise by the underwriters of their option to purchase additional shares) at an assumed initial public offering price of \$20.00 per share, the midpoint of the price range listed on the cover page of this prospectus, after deducting the estimated underwriting discounts and commissions and estimated offering expenses payable by us.
- (3) The balance of total preferred stock is included in total stockholders' equity. A \$1.00 increase (decrease) in the assumed initial public offering price of \$20.00 per share, which is the midpoint of the range listed on the cover page of this prospectus, would increase (decrease) the pro forma as adjusted amount of each of cash and cash equivalents and working capital, total assets and total stockholders' equity by approximately \$6.0 million, assuming that the number of shares offered by us, as set forth on the cover page of this prospectus, remains the same and after deducting estimated underwriting discounts and commissions and estimated offering expenses payable by us.



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## **Risk factors**

*Investing in our common stock involves a high degree of risk. Before investing in our common stock, you should consider carefully the risks described below, together with the other information contained in this prospectus, including our financial statements and the related notes appearing at the end of this prospectus. If any of the following risks occur, our business, financial condition, results of operations and prospects could be materially and adversely affected. In these circumstances, the market price of our common stock could decline, and you may lose all or part of your investment.*

### **Risks related to our financial position**

***We have incurred net losses since inception. We expect to incur losses for the foreseeable future and may never achieve or maintain profitability.***

Since inception, we have incurred net losses. Our net loss was \$15.3 million for the nine months ended September 30, 2014. As of September 30, 2014, we had an accumulated deficit of \$72.6 million. We historically have financed our operations primarily through private placements of our preferred stock. We have devoted substantially all of our efforts to research and development, including clinical and preclinical development of our product candidates, as well as to building out our team. We expect that it could be several years, if ever, before we have a commercialized product candidate. We expect to continue to incur significant expenses and increasing operating losses for the foreseeable future. The net losses we incur may fluctuate significantly from quarter to quarter. We anticipate that our expenses will increase substantially if, and as, we:

continue our clinical development of our product candidates, including our ongoing pivotal Phase 3 clinical trial for SPK-RPE65 and our Phase 1/2 clinical trial for SPK-CHM;

initiate additional clinical trials and preclinical studies for our other product candidates;

seek to identify additional product candidates;

prepare our BLA and marketing authorization application, or MAA, for SPK-RPE65 and seek marketing approvals for any of our other product candidates that successfully complete clinical trials;

validate a commercial-scale cGMP manufacturing facility;

further develop our gene therapy platform;

establish a sales, marketing and distribution infrastructure to commercialize any product candidates for which we may obtain marketing approval;

maintain, expand and protect our intellectual property portfolio; and

acquire or in-license other product candidates and technologies.

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To become and remain profitable, we must develop and eventually commercialize product candidates with significant market potential. This will require us to be successful in a range of challenging activities, including completing preclinical testing and clinical trials of our product candidates, obtaining marketing approval for these product candidates, manufacturing, marketing and selling those products for which we may obtain marketing approval and satisfying any post-marketing requirements. We may never succeed in any or all of these activities and, even if we do, we may never generate revenues that are significant or large enough to achieve profitability. 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 decrease the value of our

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company and could impair our ability to raise capital, maintain our research and development efforts, expand our business or continue our operations. A decline in the value of our company also could cause you to lose all or part of your investment.

*We have never generated revenue from product sales and may never be profitable.*

Our ability to generate revenue from product sales and achieve profitability depends on our ability, alone or with collaborative partners, to successfully complete the development of, and obtain the regulatory approvals necessary to commercialize, our product candidates. We do not anticipate generating revenues from product sales for the next several years, if ever. Our ability to generate future revenues from product sales depends heavily on our, or our collaborators', success in:

completing research and preclinical and clinical development of our product candidates and identifying new gene therapy product candidates;

seeking and obtaining regulatory and marketing approvals for product candidates for which we complete clinical trials;

launching and commercializing product candidates for which we obtain regulatory and marketing approval by establishing a sales force, marketing and distribution infrastructure or, alternatively, collaborating with a commercialization partner;

qualifying for adequate coverage and reimbursement by government and third-party payors for our product candidates;

maintaining and enhancing a sustainable, scalable, reproducible and transferable manufacturing process for our vectors and product candidates;

establishing and maintaining supply and manufacturing relationships with third parties that can provide adequate, in both amount and quality, products and services to support clinical development and the market demand for our product candidates, if approved;

obtaining market acceptance of our product candidates as a viable treatment option;

addressing any competing technological and market developments;

implementing additional internal systems and infrastructure, as needed;

negotiating favorable terms in any collaboration, licensing or other arrangements into which we may enter and performing our obligations in such collaborations;

maintaining, protecting and expanding our portfolio of intellectual property rights, including patents, trade secrets and know-how;

avoiding and defending against third-party interference or infringement claims; and

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attracting, hiring and retaining qualified personnel.

Even if one or more of the product candidates that we develop is approved for commercial sale, we anticipate incurring significant costs associated with commercializing any approved product candidate. Our expenses could increase beyond expectations if we are required by FDA, EMA or other regulatory authorities to perform clinical and other studies in addition to those that we currently anticipate. Even if we are able to generate revenues from the sale of any approved products, we may not become profitable and may need to obtain additional funding to continue operations.

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*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 are a development-stage company founded in March 2013. Our operations to date have been limited to organizing and staffing our company, business planning, raising capital, acquiring our technology, identifying potential product candidates and undertaking preclinical studies and clinical trials of our most advanced product candidates and establishing collaborations. We have not yet demonstrated the ability to complete Phase 3 trials of our product candidates, obtain marketing approvals, manufacture a commercial-scale product or conduct sales and marketing activities necessary for successful 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.

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

*Even if this offering is successful, we will need to raise additional funding, which may not be available on acceptable terms, or at all. Failure to obtain this necessary capital when needed may force us to delay, limit or terminate certain of our product development efforts or other operations.*

We expect our expenses to increase in connection with our ongoing activities, particularly as we continue the research and development of, initiate further clinical trials of and seek marketing approval for, our product candidates. In addition, if we obtain marketing approval for any of our product candidates, we expect to incur significant expenses related to product sales, medical affairs, marketing, manufacturing 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 attractive terms, we would be forced to delay, reduce or eliminate certain of our research and development programs.

Our operations have consumed significant amounts of cash since inception. As of September 30, 2014, our cash and cash equivalents were \$67.3 million. Our research and development expenses increased from \$4.9 million for the period from March 31, 2013 (inception) to December 31, 2013 to \$10.2 million for the nine months ended September 30, 2014. We estimate that the net proceeds from this offering will be approximately \$117.9 million, based on the assumed initial public offering price of \$20.00 per share, which is the midpoint of the price range set forth on the cover page of this prospectus, after deducting underwriting discounts and commissions and estimated offering expenses payable by us. We expect that the net proceeds from this offering, together with our existing cash and cash equivalents, along with the \$20.0 million upfront payment received under the Pfizer collaboration, will enable us to fund our operating expenses and capital expenditure requirements into late 2017. See Use of proceeds.

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

the results of our Phase 3 trial for SPK-RPE65, and whether additional clinical testing is required to secure regulatory approvals for all intended or desired indications;

the scope, progress, results and costs of drug discovery, laboratory testing, preclinical development and clinical trials for our other product candidates;

the costs, timing and outcome of regulatory review of our product candidates;

the costs of future activities, including product sales, medical affairs, marketing, manufacturing and distribution, for any of our product candidates for which we receive marketing approval;

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revenue, if any, received from commercial sale of our products, should any of our product candidates receive marketing approval;

the costs of preparing, filing and prosecuting patent applications, maintaining and enforcing our intellectual property rights and defending intellectual property-related claims;

our current collaboration agreements remaining in effect and our achievement of milestones under those agreements;

our ability to establish and maintain additional collaborations on favorable terms, if at all; and

the extent to which we acquire or in-license other product candidates and technologies.

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 marketing approval and achieve product sales. In addition, our product candidates, if approved, may not achieve commercial success. Our product revenues, if any, and any commercial milestones or royalty payments under our collaboration agreements, will be derived from or based on sales of products that may not be commercially available for many years, if at all. Accordingly, we will need to continue to rely on additional financing to achieve our business objectives. To the extent that additional capital is raised through the sale of equity or equity-linked securities, the issuance of those securities could result in substantial dilution for our current stockholders and the terms may include liquidation or other preferences that adversely affect the rights of our current stockholders. Furthermore, the issuance of additional securities, whether equity or debt, by us, or the possibility of such issuance, may cause the market price of our common stock to decline and existing stockholders may not agree with our financing plans or the terms of such financings. Adequate additional financing may not be available to us on acceptable terms, or at all.

## **Risks related to the development of our product candidates**

*Our gene therapy product candidates are based on a novel technology, which makes it difficult to predict the time and cost of development and of subsequently obtaining regulatory approval. At the moment, no gene therapy product has been approved in the United States and only one such product has been approved in the European Union.*

We have concentrated our research and development efforts on our gene therapy platform, and our future success depends on our successful development of viable gene therapy product candidates. There can be no assurance that we will not experience problems or delays in developing new product candidates and that such problems or delays will not cause unanticipated costs, or that any such development problems can be solved. Although we intend to leverage our experience with SPK-RPE65, we may be unable to reduce development timelines and costs for our other IRD gene therapy development programs. We also may experience unanticipated problems or delays in expanding our manufacturing capacity, which may prevent us from completing our clinical trials, meeting the obligations of our collaborations or commercializing our products on a timely or profitable basis, if at all. For example, we, a collaborator or another group may uncover a previously unknown risk associated with AAV, and this may prolong the period of observation required for obtaining regulatory approval or may necessitate additional clinical testing.

In addition, the clinical trial requirements of FDA, EMA and other regulatory authorities and the criteria these regulators use to determine the safety and efficacy of a product candidate vary substantially according to the type, complexity, novelty and intended use and market of such product candidates. The regulatory approval process for novel product candidates such as ours can be more expensive and take longer than for other, better known or more extensively studied product candidates. Only one gene therapy product, uniQure N.V.'s Glybera,

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has received marketing authorization from the European Commission. It is difficult to determine how long it will take or how much it will cost to obtain regulatory approvals for our product candidates in either the United States or the European Union or how long it will take to commercialize our product candidates. Approvals by the European Commission may not be indicative of what FDA may require for approval.

Regulatory requirements governing gene and cell therapy products have changed frequently and may continue to change in the future. FDA has established the Office of Cellular, Tissue and Gene Therapies within its Center for Biologics Evaluation and Research, or CBER, to consolidate the review of gene therapy and related products, and has established the Cellular, Tissue and Gene Therapies Advisory Committee to advise CBER in its review. Gene therapy clinical trials conducted at institutions that receive funding for recombinant DNA research from the United States National Institutes of Health, or NIH, also are potentially subject to review by the NIH Office of Biotechnology Activities' Recombinant DNA Advisory Committee, or the RAC; however, NIH recently announced that the RAC will soon only publicly review clinical trials if the trials cannot be evaluated by standard oversight bodies and pose unusual risks. Although FDA decides whether individual gene therapy protocols may proceed, the RAC public review process, if undertaken, can delay the initiation of a clinical trial, even if FDA has reviewed the trial design and details and approved its initiation. Conversely, FDA can put an IND on a clinical hold even if the RAC has provided a favorable review or an exemption from in-depth, public review. If we were to engage an NIH-funded institution, such as CHOP, to conduct a clinical trial, that institution's institutional biosafety committee as well as its institutional review board, or IRB, would need to review the proposed clinical trial to assess the safety of the trial. In addition, adverse developments in clinical trials of gene therapy products conducted by others may cause FDA or other oversight bodies to change the requirements for approval of any of our product candidates. Similarly, EMA may issue new guidelines concerning the development and marketing authorization for gene therapy medicinal products and require that we comply with these new guidelines.

These regulatory review committees and advisory groups and the new guidelines they promulgate may lengthen the regulatory review process, require us to perform additional studies, increase our development costs, lead to changes in regulatory positions and interpretations, delay or prevent approval and commercialization of these product candidates or lead to significant post-approval limitations or restrictions. As we advance our product candidates, we will be required to consult with these regulatory and advisory groups, and comply with applicable guidelines. If we fail to do so, we may be required to delay or discontinue development of certain of our product candidates. These additional processes may result in a review and approval process that is longer than we otherwise would have expected. Delay or failure to obtain, or unexpected costs in obtaining, the regulatory approval necessary to bring a potential product to market could decrease our ability to generate sufficient product revenue, and our business, financial condition, results of operations and prospects would be materially and adversely affected.

***Because we are developing product candidates for the treatment of diseases in which there is little clinical experience and, in some cases, using new endpoints or methodologies, there is increased risk that FDA or other regulatory authorities may not consider the endpoints of our pivotal Phase 3 clinical trial to provide clinically meaningful results and that these results may be hard to analyze.***

There are no pharmacologic therapies approved to treat the underlying causes of any IRD, including those caused by autosomal recessive mutations to the RPE65 gene or mutations to the CHM gene. In addition, there has been limited clinical trial experience for the development of pharmaceuticals to treat IRDs. Certain aspects of IRDs render efficacy endpoints historically used for vision clinical trials less applicable as clinical endpoints. As a result, the design and conduct of clinical trials for these disorders is subject to increased risk.

FDA described, in general terms, the criteria by which it will judge the validity of the primary efficacy endpoint we chose for our pivotal Phase 3 clinical trial of SPK-RPE65. FDA has communicated that guidance through comments on our request for a Special Protocol Assessment, or SPA, which was submitted in 2009, and during

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subsequent regulatory meetings. FDA stated that the primary endpoint should be clinically meaningful, reflecting a tangible benefit to patients. Further, FDA stated that, preferably, the benefit would improve quality of life, a standard that can be difficult to validate. We voluntarily withdrew our SPA submission at FDA's request to allow FDA more time for a comprehensive assessment of the Phase 3 trial design. A subsequent Advisory Committee in June 2011 addressed a number of these elements. Although EMA's only comment on the validity of the primary endpoint for our pivotal Phase 3 clinical trial was to use only the binocular testing condition, there can be no assurances that it may not have additional questions or comments on the primary endpoint in the future.

We developed a mobility test that measures subjects' ability to navigate a specially designed course at incrementally reduced lighting conditions. The subjects follow black arrows on white tiles on the floor around the course, while avoiding common obstacles such as waste baskets. This mobility test is designed to measure improvements in peripheral vision and improvements in night blindness. These are two predominant visual deficits in patients with RPE65-mediated IRDs. The mobility test for our pivotal Phase 3 clinical trial of SPK-RPE65 uses seven decreasing increments of light designed to correspond to light conditions encountered during daily activities and in common environments, such as the interior of a shopping mall, the inside of a stairwell and an outdoor parking lot at night. We defined our primary efficacy endpoint as the ability to navigate the course accurately within a given timeframe, at one or more lighting levels lower than the level at which a subject previously had been able to complete the course.

At an FDA advisory committee meeting on gene therapy products for the treatment of retinal disorders convened by CBER in June 2011, we presented a summary of our clinical data to date, as well as our then-proposed Phase 3 trial design. In May 2012, reviewers from FDA, CBER and several ophthalmologists from FDA provided feedback on our proposed mobility test stating that improvement in the ability to navigate at a lower lighting condition may represent an improvement in visual function. FDA requested that we justify a change score on the endpoint that would reliably confer clinical benefit and power our trial accordingly. In the protocol for the Phase 3 trial submitted to FDA, we described in detail our primary endpoint based on a change score of positive one or more light levels. FDA allowed our clinical trial to proceed using that endpoint, even though FDA has authority to place a clinical trial on hold if the protocol for an investigation is clearly deficient in design to meet its stated objectives. FDA has discretion, however, to reserve judgment on whether the endpoint and the change scores seen in our trial sufficiently demonstrate clinical meaningfulness until FDA reviews our BLA. FDA has not communicated further with us its views about the clinical meaningfulness of the proposed change score. Consequently, FDA may decide that achieving a change score of positive one, as we have defined that score, is not clinically meaningful and, therefore, that meeting our primary endpoint does not demonstrate that SPK-RPE65 is effective.

Moreover, even if FDA does find our success criteria to be sufficiently validated and clinically meaningful, we may not achieve the pre-specified endpoint to a degree of statistical significance. Further, even if we do achieve the pre-specified criteria, we may produce results that are unpredictable or inconsistent with the results of the secondary efficacy endpoints in the trial. FDA also could give overriding weight to other efficacy endpoints over the mobility test endpoint, even if we achieve statistically significant results on the mobility test, if we do not achieve statistically significant or clinically meaningful results on any of our secondary efficacy endpoints. FDA also weighs the benefits of a product against its risks and FDA may view the efficacy results in the context of safety as not being supportive of regulatory approval. Other regulatory authorities in the European Union and other countries may make similar comments with respect to these endpoints.

Additionally, for the Phase 3 trial, we enrolled subjects as young as four years of age (compared to subjects as young as eight years of age in our earlier Phase 1 trials). Even though both arms of the Phase 3 trial are balanced as to age, there is a risk that regulators may question whether subjects at this age could demonstrate



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improvement in the mobility trial as a result of their cognitive development, and not due to SPK-RPE65. The mobility test is not designed to detect the extent to which improvement is a result of cognitive development versus the impact of SPK-RPE65, therefore potentially calling into question efficacy results for younger age subjects.

Further, while certain of our secondary endpoints, such as measuring visual acuity, traditionally have been used in clinical settings, due to the unique deficits faced by subjects with IRDs, these traditional tests may not adequately assess patients' ability to independently carry out activities of daily living. Moreover, quantifying pupillary responses to light, a traditionally qualitative evaluation, in patients with IRDs may be difficult or may yield unreliable quantitative results which could delay or prevent approval of SPK-RPE65, and could result in FDA or other regulatory authorities requiring us to conduct additional clinical trials.

In addition, the treatment of certain IRDs, such as CHM, may require assessment of clinical endpoints that reflect a stabilization, as opposed to an improvement, of functional vision. Assessing these endpoints may require longer periods of observation and may delay the completion of any trials we may undertake.

***The results from our pivotal Phase 3 clinical trial for SPK-RPE65 may not support as broad a marketing approval as we seek and FDA and EMA may require us to conduct additional clinical trials, or evaluate subjects for an additional follow-up period.***

While we believe SPK-RPE65 should be applicable for the treatment of patients with any IRD mediated by an RPE65 mutation, the results from our pivotal phase 3 clinical trial for SPK-RPE65, which included only subjects diagnosed with LCA due to RPE65 mutations, may not support as broad a marketing approval as we seek. Even if we obtain regulatory approval for SPK-RPE65, we might obtain marketing approval only to treat patients diagnosed with LCA due to RPE65 mutations, based on the inclusion criteria of the Phase 3 trial and the absence of data for patients diagnosed with RPE65-mediated IRDs other than LCA. If SPK-RPE65 is not approved for RPE65-mediated IRDs other than LCA, we may be required by FDA and EMA to conduct additional clinical trials to support approval of SPK-RPE65 for patients with patients diagnosed with RP due to RPE65 mutations or other RPE65-mediated IRDs. This could result in our experiencing substantial delays in obtaining, or never obtaining, marketing approval for SPK-RPE65 to treat patients diagnosed with RP due to RPE65 mutations or other RPE65-mediated IRDs. The inability to market SPK-RPE65 to treat patients with these other clinical classifications would have a material adverse effect on our projected revenues from SPK-RPE65 and our business, financial condition, results of operations and prospects.

***Success in preclinical studies or early clinical trials may not be indicative of results obtained in later trials.***

Results from preclinical studies or previous clinical trials are not necessarily predictive of future clinical trial results, and interim results of a clinical trial are not necessarily indicative of final results. Our product candidates may fail to show the desired safety and efficacy in clinical development despite demonstrating positive results in preclinical studies or having successfully advanced through initial clinical trials. For example, after multiple successful preclinical studies using gene therapy to treat hemophilia B, several hemophilia B product candidates, including product candidates we previously evaluated, have produced sub-optimal durability in Phase 1 trials.

We have no clinical data demonstrating either the safety or efficacy of SPK-CHM in humans. In addition, we have no clinical data demonstrating either the safety or efficacy of our current SPK-FIX product candidates in humans, as our current SPK-FIX product candidates are different than what was utilized in our prior Phase 1 hemophilia B trials. There can be no assurance that the success we achieved in the preclinical studies for SPK-CHM or for our current SPK-FIX product candidates ultimately will result in success in our planned clinical trials. In addition, we cannot assure you that we will be able to achieve the same or similar success in our preclinical studies and clinical trials of our other product candidates.

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There is a high failure rate for drugs and biologic products proceeding through clinical trials. 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. Data obtained from preclinical and clinical activities are subject to varying interpretations, which may delay, limit or prevent regulatory approval. In addition, we may experience regulatory delays or rejections as a result of many factors, including due to changes in regulatory policy during the period of our product candidate development. Any such delays could materially and adversely affect our business, financial condition, results of operations and prospects.

***We may find it difficult to enroll patients in our clinical trials, which could delay or prevent us from proceeding with clinical trials of our product candidates.***

Identifying and qualifying patients to participate in clinical trials of our product candidates is critical to our success. The timing of our clinical trials depends on our ability to recruit patients to participate as well as completion of required follow-up periods. For example, hemophilia trials often take longer to enroll than trials for other indications due to the availability of existing treatments. We have experienced slow enrollment in some of our hemophilia trials, and we may experience similar delays in any of our future clinical trials. If patients are unwilling to participate in our gene therapy studies because of negative publicity from adverse events related to the biotechnology or gene therapy fields, competitive clinical trials for similar patient populations, clinical trials in products employing our vectors or our platform or for other reasons, the timeline for recruiting patients, conducting studies and obtaining regulatory approval of our product candidates may be delayed. These delays could result in increased costs, delays in advancing our product candidates, delays in testing the effectiveness of our product candidates or termination of the clinical trials altogether.

We may not be able to identify, recruit and enroll a sufficient number of patients, or those with required or desired characteristics, to complete our clinical trials in a timely manner. Patient enrollment and trial completion is affected by factors including:

size of the patient population and process for identifying subjects;

design of the trial protocol;

eligibility and exclusion criteria;

perceived risks and benefits of the product candidate under study;

perceived risks and benefits of gene therapy-based approaches to treatment of diseases;

availability of competing therapies and clinical trials;

severity of the disease under investigation;

availability of genetic testing for potential patients;

proximity and availability of clinical trial sites for prospective subjects;

ability to obtain and maintain subject consent;

risk that enrolled subjects will drop out before completion of the trial;

patient referral practices of physicians; and

ability to monitor subjects adequately during and after treatment.

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Our current product candidates are being developed to treat rare conditions. We plan to seek initial marketing approvals in the United States and the European Union. We may not be able to initiate or continue clinical trials if we cannot enroll a sufficient number of eligible patients to participate in the clinical trials required by FDA or EMA or other regulatory authorities. Our ability to successfully initiate, enroll and complete a clinical trial in any foreign country is subject to numerous risks unique to conducting business in foreign countries, including:

difficulty in establishing or managing relationships with contract research organizations, or CROs, and physicians;

different standards for the conduct of clinical trials;

absence in some countries of established groups with sufficient regulatory expertise for review of gene therapy protocols;

our inability to locate qualified local consultants, physicians and partners; and

the potential burden of complying with a variety of foreign laws, medical standards and regulatory requirements, including the regulation of pharmaceutical and biotechnology products and treatment.

If we have difficulty enrolling a sufficient number of patients to conduct our clinical trials as planned, we may need to delay, limit or terminate ongoing or planned clinical trials, any of which would have an adverse effect on our business, financial condition, results of operations and prospects.

***We may encounter substantial delays in our clinical trials or we may fail to demonstrate safety and efficacy to the satisfaction of applicable regulatory authorities.***

Before obtaining marketing approval from regulatory authorities for the sale of our product candidates, we must conduct extensive clinical trials to demonstrate the safety and efficacy of the product candidates. Clinical testing is expensive, time-consuming and uncertain as to outcome. We cannot guarantee that any clinical trials will be conducted as planned or completed on schedule, if at all. A failure of one or more clinical trials can occur at any stage of testing. Events that may prevent successful or timely completion of clinical development include:

delays in reaching a consensus with regulatory authorities on trial design;

delays in reaching agreement on acceptable terms with prospective CROs and clinical trial sites;

delays in opening clinical trial sites or obtaining required IRB or independent Ethics Committee approval at each clinical trial site;

delays in recruiting suitable subjects to participate in our clinical trials;

imposition of a clinical hold by regulatory authorities as a result of a serious adverse event or after an inspection of our clinical trial operations or trial sites;

failure by us, any CROs we engage or any other third parties to adhere to clinical trial requirements;

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

delays in the testing, validation, manufacturing and delivery of our product candidates to the clinical sites, including delays by third parties with whom we have contracted to perform certain of those functions;

delays in having subjects complete participation in a trial or return for post-treatment follow-up;

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clinical trial sites or subjects dropping out of a trial;

selection of clinical endpoints that require prolonged periods of clinical observation or analysis of the resulting data;

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

occurrence of serious adverse events in trials of the same class of agents conducted by other sponsors; or

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

Any inability to successfully complete preclinical and clinical development could result in additional costs to us or impair our ability to generate revenues from product sales, regulatory and commercialization milestones and royalties. In addition, if we make manufacturing or formulation changes to our product candidates, we may need to conduct additional studies to bridge our modified product candidates to earlier versions. Clinical trial delays 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, which could impair our ability to successfully commercialize our product candidates and may harm our business, financial condition, results of operations and prospects.

Additionally, if the results of our clinical trials are inconclusive or if there are safety concerns or serious adverse events associated with our product candidates, we may:

be delayed in obtaining marketing approval for our product candidates, if at all;

obtain approval for indications or patient populations that are not as broad as intended or desired;

obtain approval with labeling that includes significant use or distribution restrictions or safety warnings;

be subject to changes in the way the product is administered;

be required to perform additional clinical trials to support approval or be subject to additional post-marketing testing requirements;

have regulatory authorities withdraw, or suspend, their approval of the product or impose restrictions on its distribution in the form of a modified risk evaluation and mitigation strategy;

be subject to the addition of labeling statements, such as warnings or contraindications;

be sued; or

experience damage to our reputation.

***Our product candidates and the process for administering our product candidates may cause undesirable side effects or have other properties that could delay or prevent their regulatory approval, limit the commercial potential or result in significant negative consequences following any potential marketing approval.***

There have been several significant adverse side effects in gene therapy treatments in the past, including reported cases of leukemia and death seen in other trials using other vectors. While new recombinant vectors have been developed to reduce these side effects, gene therapy is still a relatively new approach to disease treatment and additional adverse side effects could develop. There also is the potential risk of delayed adverse events following exposure to gene therapy products due to persistent biologic activity of the genetic material or other components of products used to carry the genetic material.

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Possible adverse side effects that could occur with treatment with gene therapy products include an immunologic reaction early after administration which, while not necessarily adverse to the patient's health, could substantially limit the effectiveness of the treatment. In previous clinical trials involving AAV vectors for gene therapy, some subjects experienced the development of a T-cell response, whereby after the vector is within the target cell, the cellular immune response system triggers the removal of transduced cells by activated T-cells. If our vectors demonstrate a similar effect we may decide or be required to halt or delay further clinical development of our product candidates.

In addition to side effects caused by the product candidate, the administration process or related procedures also can cause adverse side effects. If any such adverse events occur, our clinical trials could be suspended or terminated. For example, FDA placed our second open-label Phase 1 clinical trial, which we refer to as our 102 trial, on a clinical hold temporarily when we voluntarily halted enrollment and reported a serious adverse event arising from a steroid injection given following administration of SPK-RPE65 to manage post-operative inflammation related to the standard vitrectomy procedure subjects undergo prior to administration of SPK-RPE65. We subsequently adjusted the protocol regarding the use of local steroids and FDA released the clinical hold, allowing the trial to proceed.

If in the future we are unable to demonstrate that such adverse events were caused by the administration process or related procedures, FDA, the European Commission, EMA or other regulatory authorities could order us to cease further development of, or deny approval of, our product candidates for any or all targeted indications. Even if we are able to demonstrate that all future serious adverse events are not product-related, such occurrences could affect patient recruitment or the ability of enrolled patients to complete the trial. Moreover, if we elect, or are required, to delay, suspend or terminate any clinical trial of any of our product candidates, the commercial prospects of such product candidates may be harmed and our ability to generate product revenues from any of these product candidates may be delayed or eliminated. Any of these occurrences may harm our ability to develop other product candidates, and may harm our business, financial condition and prospects significantly.

Additionally, if any of our product candidates receives marketing approval, FDA could require us to adopt a Risk Evaluation and Mitigation Strategy, or REMS, to ensure that the benefits outweigh its risks, which may include, among other things, a medication guide outlining the risks of the product for distribution to patients and a communication plan to health care practitioners. Furthermore, if we or others later identify undesirable side effects caused by our product candidate, several potentially significant negative consequences could result, including:

regulatory authorities may suspend or withdraw approvals of such product candidate;

regulatory authorities may require additional warnings on the label;

we may be required to change the way a product candidate is administered or conduct additional clinical trials;

we could be sued and held liable for harm caused to patients; and

our reputation may suffer.

Any of these events could prevent us from achieving or maintaining market acceptance of our product candidates and could significantly harm our business, prospects, financial condition and results of operations.



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***We may be unable to obtain orphan drug designation or exclusivity. If our competitors are able to obtain orphan drug exclusivity for products that constitute the same drug and treat the same indications as our product candidates, we may not be able to have competing products approved by the applicable regulatory authority for a significant period of time.***

Regulatory authorities in some jurisdictions, including the United States and the European Union, may designate drugs for relatively small patient populations as orphan drugs. Under the Orphan Drug Act of 1983, FDA may designate a product candidate as an orphan drug if it is intended to treat a rare disease or condition, which is generally defined as having a patient population of fewer than 200,000 individuals in the United States, or a patient population greater than 200,000 in the United States where there is no reasonable expectation that the cost of developing the drug will be recovered from sales in the United States. In the European Union, EMA's Committee for Orphan Medicinal Products grants orphan drug designation to promote the development of products that are intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting not more than 5 in 10,000 persons in the European Union. Additionally, orphan designation is granted for products intended for the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition and when, without incentives, it is unlikely that sales of the drug in the European Union would be sufficient to justify the necessary investment in developing the drug or biologic product.

SPK-RPE65 has been granted orphan drug designation by FDA and the European Commission for the treatment of LCA due to RPE65 mutations, and we are seeking expansion of the orphan drug designation for SPK-RPE65 for the treatment of other IRDs caused by RPE65 mutations. SPK-CHM has also been granted orphan drug designation by FDA and the European Commission for the treatment of choroideremia. If we request orphan drug designation for our other product candidates, there can be no assurances that FDA or the European Commission will grant any of our product candidates such designation. Additionally, the designation of any of our product candidates as an orphan product does not guarantee that any regulatory agency will accelerate regulatory review of, or ultimately approve, that product candidate, nor does it limit the ability of any regulatory agency to grant orphan drug designation to product candidates of other companies that treat the same indications as our product candidates prior to our product candidates receiving exclusive marketing approval. For example, we are aware that NightstaRx Ltd. also has been granted orphan product designation by the European Commission for its product candidate for the treatment of choroideremia and that a Phase 1/2 clinical trial is being conducted in Europe for this product candidate.

Generally, if a product candidate with an orphan drug designation 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 FDA or the European Commission from approving another marketing application for a product that constitutes the same drug treating the same indication for that marketing exclusivity period, except in limited circumstances. If another sponsor receives such approval before we do (regardless of our orphan drug designation), we will be precluded from receiving marketing approval for our product for the applicable exclusivity period. The applicable period is seven years in the United States and 10 years in the European Union. The exclusivity period in the United States can be extended by six months if the BLA sponsor submits pediatric data that fairly respond to a written request from FDA for such data. The exclusivity period in the European Union can be reduced to six years if a product no longer meets the criteria for orphan drug designation or if the product is sufficiently profitable so that market exclusivity is no longer justified. Orphan drug exclusivity may be revoked if any regulatory agency determines that the request for designation was materially defective or if the manufacturer is unable to assure sufficient quantity of the product to meet the needs of patients with the rare disease or condition.

Even if we obtain orphan drug exclusivity for a product candidate, that exclusivity may not effectively protect the product candidate from competition because different drugs can be approved for the same condition. In the

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United States, even after an orphan drug is approved, FDA may subsequently approve another drug for the same condition if FDA concludes that the latter drug is not the same drug or is clinically superior in that it is shown to be safer, more effective or makes a major contribution to patient care. In the European Union, marketing authorization may be granted to a similar medicinal product for the same orphan indication if:

The second applicant can establish in its application that its medicinal product, although similar to the orphan medicinal product already authorized, is safer, more effective or otherwise clinically superior;

The holder of the marketing authorization for the original orphan medicinal product consents to a second orphan medicinal product application; or

The holder of the marketing authorization for the original orphan medicinal product cannot supply sufficient quantities of orphan medicinal product.

***Breakthrough therapy designation by FDA may not lead to a faster development, regulatory review or approval process, and it does not increase the likelihood that any of our product candidates will receive marketing approval in the United States.***

We have received breakthrough therapy designation for SPK-RPE65 for nyctalopia in patients with LCA due to RPE65 mutations, as confirmed by genetic testing, and may, in the future, apply for breakthrough therapy designation for other product candidates in the United States. A breakthrough therapy product candidate is defined as a product candidate 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 such product candidate may demonstrate substantial improvement on one or more clinically significant endpoints over existing therapies. FDA will seek to ensure the sponsor of a breakthrough therapy product candidate receives: (i) intensive guidance on an efficient drug development program; (ii) intensive involvement of senior managers and experienced staff on a proactive, collaborative and cross-disciplinary review; and (iii) a rolling review process whereby FDA may consider reviewing portions of a BLA before the sponsor submits the complete application. Product candidates designated as breakthrough therapies by FDA may be eligible for priority review if supported by clinical data.

Designation as a breakthrough therapy is within the discretion of FDA. Accordingly, even if we believe one of our product candidates meets the criteria for designation as a breakthrough therapy, FDA may disagree. In any event, the receipt of a breakthrough therapy designation for a product candidate may not result in a faster development process, review or approval compared to products considered for approval under conventional FDA procedures and, in any event, does not assure ultimate approval by FDA. In addition, even though SPK-RPE65 has been designated as a breakthrough therapy product candidate, FDA may later decide that it no longer meets the conditions for designation or decide that the time period for FDA review or approval will not be shortened.

***Even if we complete the necessary clinical trials, we cannot predict when, or if, we will obtain regulatory approval to commercialize a product candidate and the approval may be for a more narrow indication than we seek.***

We cannot commercialize a product candidate until the appropriate regulatory authorities have reviewed and approved the product candidate. Even if our product candidates meet their safety and efficacy endpoints in clinical trials, the regulatory authorities may not complete their review processes in a timely manner, or we may not be able to obtain regulatory approval. Additional delays may result if an FDA Advisory Committee or other regulatory authority recommends non-approval or restrictions on approval. In addition, we may experience delays or rejections based upon additional government regulation from future legislation or administrative action, or changes in regulatory authority policy during the period of product development, clinical trials and the review process.

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Regulatory authorities also may approve a product candidate for more limited indications than requested (such as approving SPK-RPE65 for the treatment of patients diagnosed with LCA due to RPE65 mutations but not for the treatment of patients with RP due to RPE65 mutations or other RPE65-mediated IRDs) or they may impose significant limitations in the form of narrow indications, warnings or a REMS. These regulatory authorities may require precautions or contra-indications with respect to conditions of use or they may grant approval subject to the performance of costly post-marketing clinical trials. In addition, regulatory authorities may not approve the labeling claims that are necessary or desirable for the successful commercialization of our product candidates. Any of the foregoing scenarios could materially harm the commercial prospects for our product candidates and materially and adversely affect our business, financial condition, results of operations and prospects.

Further, the regulatory authorities may require concurrent approval or the CE mark of a companion diagnostic device. For the product candidates we currently are developing, we believe that diagnoses based on symptoms, in conjunction with existing genetic tests developed and administered by laboratories certified under the Clinical Laboratory Improvement Amendments, or CLIA, are sufficient to diagnose patients and will be permitted by FDA. For future product candidates, however, it may be necessary to use FDA-cleared or FDA-approved diagnostic tests to diagnose patients or to assure the safe and effective use of product candidates in trial subjects. FDA refers to such tests as *in vitro* companion diagnostic devices. On July 31, 2014, FDA announced the publication of a final guidance document describing the agency's current thinking about the development and regulation of *in vitro* companion diagnostic devices. The final guidance articulates a policy position that, when safe and effective use of a therapeutic product depends on a diagnostic device, FDA generally will require approval or clearance of the diagnostic device at the same time that FDA approves the therapeutic product. The final guidance allows for two exceptions to the general rule of concurrent drug/device approval, namely, when the therapeutic product is intended to treat serious and life-threatening conditions for which no alternative exists, and when a serious safety issue arises for an approved therapeutic agent, and no FDA-cleared or FDA-approved companion diagnostic test is yet available. At this point, it is unclear how FDA will apply this policy to our current or future gene therapy product candidates. Should FDA deem genetic tests used for diagnosing patients for our therapies to be *in vitro* companion diagnostics requiring FDA clearance or approval, we may face significant delays or obstacles in obtaining approval of a BLA for our product candidates. In the EU, the European Commission has proposed substantial revisions to the current regulations governing *in vitro* diagnostic medical devices. If adopted in their current form, these revisions may impose additional obligations on us that may impact the development and authorization of our product candidates in the EU.

***Even if we obtain regulatory approval for a product candidate, our products will remain subject to regulatory oversight.***

Even if we obtain any regulatory approval for our product candidates, they will be subject to ongoing regulatory requirements for manufacturing, labeling, packaging, storage, advertising, promotion, sampling, record-keeping and submission of safety and other post-market information. Any regulatory approvals that we receive for our product candidates also may be subject to a REMS, limitations on the approved indicated uses for which the product may be marketed or to the conditions of approval, or contain requirements for potentially costly post-marketing testing, including Phase 4 clinical trials, and surveillance to monitor the quality, safety and efficacy of the product. For example, the holder of an approved BLA is obligated to monitor and report adverse events and any failure of a product to meet the specifications in the BLA. FDA guidance advises that patients treated with some types of gene therapy undergo follow-up observations for potential adverse events for as long as 15 years, and each of our clinical trials for SPK-RPE65 includes a 15 year long-term follow-up phase. The holder of an approved BLA also must submit new or supplemental applications and obtain FDA approval for certain changes to the approved product, product labeling or manufacturing process. Advertising and promotional materials must comply with FDA rules and are subject to FDA review, in addition to other potentially applicable federal and state laws.

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In addition, product manufacturers and their facilities are subject to payment of user fees and continual review and periodic inspections by FDA and other regulatory authorities for compliance with current good manufacturing practices, or cGMP, requirements and adherence to commitments made in the BLA or foreign marketing application. If we, or a regulatory authority, discover previously unknown problems with a product, such as adverse events of unanticipated severity or frequency, or problems with the facility where the product is manufactured or disagrees with the promotion, marketing or labeling of that product, a regulatory authority may impose restrictions relative to that product, the manufacturing facility or us, including requiring recall or withdrawal of the product from the market or suspension of manufacturing.

If we fail to comply with applicable regulatory requirements following approval of any of our product candidates, a regulatory authority may:

issue a warning letter asserting that we are in violation of the law;

seek an injunction or impose administrative, civil or criminal penalties or monetary fines;

suspend or withdraw regulatory approval;

suspend any ongoing clinical trials;

refuse to approve a pending BLA or comparable foreign marketing application (or any supplements thereto) submitted by us or our strategic partners;

restrict the marketing or manufacturing of the product;

seize or detain the product or otherwise require the withdrawal of the product from the market;

refuse to permit the import or export of products; or

refuse to allow us to enter into supply contracts, including government contracts.

Any government investigation of alleged violations of law could require us to expend significant time and resources in response and could generate negative publicity. The occurrence of any event or penalty described above may inhibit our ability to commercialize our product candidates and adversely affect our business, financial condition, results of operations and prospects.

In addition, FDA's policies, and those of equivalent foreign regulatory agencies, may change and additional government regulations may be enacted that could prevent, limit or delay regulatory approval of our product candidates. We cannot predict the likelihood, nature or extent of government regulation that may arise from future legislation or administrative action, either in the United States or abroad. If we are slow or unable to adapt to changes in existing requirements or the adoption of new requirements or policies, or if we are not able to maintain regulatory compliance, we may lose any marketing approval that we may have obtained and we may not achieve or sustain profitability, which would materially and adversely affect our business, financial condition, results of operations and prospects.

***We face significant competition in an environment of rapid technological change and the possibility that our competitors may achieve regulatory approval before us or develop therapies that are more advanced or effective than ours, which may adversely affect our financial condition and our ability to successfully market or commercialize our product candidates.***

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The biotechnology and pharmaceutical industries, including the gene therapy field, are characterized by rapidly changing technologies, significant competition and a strong emphasis on intellectual property. We face substantial competition from many different sources, including large and specialty pharmaceutical and biotechnology companies, academic research institutions, government agencies and public and private research institutions.

We are aware of several companies focused on developing gene therapies in various indications, including bluebird bio, Inc., Applied Genetic Technologies Corporation, Asklepios BioPharmaceutical, Inc., Audentes

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Therapeutics, Inc., Avalanche Biotechnologies, Inc., Dimension Therapeutics, Inc., GenSight Biologics SA, NightstaRx Ltd, ReGenX Biosciences, LLC, or ReGenX, and uniQure N.V., as well as several companies addressing other methods for modifying genes and regulating gene expression. Any advances in gene therapy technology made by a competitor may be used to develop therapies that could compete against any of our product candidates.

For our particular product candidates, the main competitors include:

**RPE65.** While no approved pharmacologic agents exist for patients with RPE65-mediated IRDs, Second Sight Medical Products, Inc. has received approval from FDA and other foreign regulatory authorities for a retinal prosthesis medical device, which is being marketed to RP patients with limited or no light perception. Another retinal prosthesis medical device from Retina Implant AG has obtained a CE Certificate of Conformity from its notified body, and is similarly indicated for blinded RP patients. QLT Inc. is in Phase 1b clinical development with a vitamin A derivative to treat RP and LCA. In the gene therapy space, AGTC and several academic institutions have conducted clinical trials involving RPE65-based product candidates, but none of these organizations has completed a trial involving injection of a subject's second eye or has initiated a Phase 3 trial.

**Choroideremia.** We are aware that NightstaRx is developing an AAV-based gene therapy for the treatment of choroideremia. NightstaRx has been granted orphan product designation by the European Commission for this product candidate for the treatment of choroideremia and a Phase 1/2 trial of this product candidate is being conducted in Europe.

**Hemophilia B.** Hemophilia B patients typically are treated by a variety of plasma-derived, recombinant or long-acting products that are produced by a number of companies, including Pfizer. Many other companies are developing gene therapies to treat hemophilia B, including Baxter International Inc., uniQure and Dimension.

Many of our potential competitors, alone or with their strategic partners, have substantially greater financial, technical and other resources, such as larger research and development, clinical, marketing and manufacturing organizations. Mergers and acquisitions in the biotechnology and pharmaceutical industries may result in even more resources being concentrated among a smaller number of competitors. Our commercial opportunity could be reduced or eliminated if 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. Competitors also may obtain FDA or other regulatory approval for their products more rapidly or earlier 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. Additionally, technologies developed by our competitors may render our potential product candidates uneconomical or obsolete, and we may not be successful in marketing our product candidates against competitors.

In addition, as a result of the expiration or successful challenge of our patent rights, we could face more litigation with respect to the validity and/or scope of patents relating to our competitors' products. The availability of our competitors' products could limit the demand, and the price we are able to charge, for any products that we may develop and commercialize.

*Even if we obtain and maintain approval for our product candidates from FDA, we may never obtain approval for our product candidates outside of the United States, which would limit our market opportunities and adversely affect our business.*

Approval of a product candidate in the United States by FDA does not ensure approval of such product candidate by regulatory authorities in other countries or jurisdictions, and approval by one foreign regulatory authority does not ensure approval by regulatory authorities in other foreign countries or by FDA. Sales of our

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product candidates outside of the United States will be subject to foreign regulatory requirements governing clinical trials and marketing approval. Even if FDA grants marketing approval for a product candidate, comparable regulatory authorities of foreign countries also must approve the manufacturing and marketing of the product candidates in those countries. Approval procedures vary among jurisdictions and can involve requirements and administrative review periods different from, and more onerous than, those in the United States, including additional preclinical studies or clinical trials. In many countries outside the United States, a product candidate must be approved for reimbursement before it can be approved for sale in that country. In some cases, the price that we intend to charge for our products, if approved, is also subject to approval. We intend to submit a marketing authorization application to EMA for approval of our product candidates in the European Union, but obtaining such approval from the European Commission following the opinion of EMA is a lengthy and expensive process. Even if a product candidate is approved, FDA or the European Commission, as the case may be, may limit the indications for which the product may be marketed, require extensive warnings on the product labeling or require expensive and time-consuming additional clinical trials or reporting as conditions of approval. Regulatory authorities in countries outside of the United States and the European Union also have requirements for approval of product candidates with which we must comply prior to marketing in those countries. Obtaining foreign regulatory approvals and compliance with foreign regulatory requirements could result in significant delays, difficulties and costs for us and could delay or prevent the introduction of our product candidates in certain countries.

Further, clinical trials conducted in one country may not be accepted by regulatory authorities in other countries. Also, regulatory approval for any of our product candidates may be withdrawn. If we fail to comply with the regulatory requirements, our target market will be reduced and our ability to realize the full market potential of our product candidates will be harmed and our business, financial condition, results of operations and prospects will be adversely affected.

### **Risks related to third parties**

*We have in the past, and in the future may, enter into collaborations with third parties to develop product candidates. If these collaborations are not successful, our business could be adversely affected.*

We have entered into collaborations with Pfizer and Genable for the development and commercialization of certain product candidates and may enter into additional collaborations in the future. We 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 and our collaborators' abilities to successfully perform the functions assigned to each of us in these arrangements. In addition, our collaborators have the ability to abandon research or development projects and terminate applicable agreements. Moreover, an unsuccessful outcome in any clinical trial for which our collaborator is responsible could be harmful to the public perception and prospects of our gene therapy platform.

Our global collaboration agreement with Pfizer, which we entered into in December 2014, relates to the development and commercialization of product candidates for the treatment of hemophilia B. Under this collaboration, we maintain responsibility for clinical development through the completion of Phase 1/2 trials. Thereafter, Pfizer has responsibility for further clinical development, seeking regulatory approvals and commercialization.

Under our collaboration with Genable relating to RhoNova, which we entered into in March 2014, Genable has exclusively licensed certain of our AAV manufacturing patent rights and technology for the development of RhoNova, and we will provide certain services to Genable in connection with the development of RhoNova,

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including providing non-clinical and clinical development advice, and serving as the exclusive manufacturer to Genable. Genable will be responsible for all future clinical and commercial development of RhoNova.

We may potentially enter into collaborations with third parties in the future. Our relationships with Pfizer and Genable, and any future collaborations we enter into in the future, may pose several risks, including the following:

collaborators have significant discretion in determining the efforts and resources that they will apply to these collaborations;

collaborators may not perform their obligations as expected;

the clinical trials conducted as part of these collaborations may not be successful;

collaborators may not pursue development and commercialization of any product candidates that achieve regulatory approval or may elect not to continue or renew development or commercialization programs based on clinical trial results, 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 delay clinical trials, provide insufficient funding for clinical trials, 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;

collaborators could independently develop, or develop with third parties, products that compete directly or indirectly with our product candidates if the collaborators believe that competitive products are more likely to be successfully developed or can be commercialized under terms that are more economically attractive than ours;

product candidates developed 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 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 any such product candidate;

disagreements with collaborators, including disagreements over proprietary rights, contract interpretation or the preferred course of development of any product candidates, may cause delays or termination of the research, development or commercialization of such product candidates, may lead to additional responsibilities for us with respect to such product candidates or may result in litigation or arbitration, any of which would be time-consuming and expensive;

collaborators may not properly maintain or defend our intellectual property rights or may use our proprietary information in such a way as to invite litigation that could jeopardize or invalidate our intellectual property or proprietary information or expose us to potential litigation;



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disputes may arise with respect to the ownership of intellectual property developed pursuant to our collaborations;

collaborators may infringe the intellectual property rights of third parties, which may expose us to litigation and potential liability; and

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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.

If our collaborations 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 product candidates could be delayed and we may need additional resources to develop our product candidates. In addition, if one of our collaborators terminates its agreement with us, we may find it more difficult to attract new collaborators and the perception of us in the business and financial communities could be adversely affected. All of the risks relating to product development, regulatory approval and commercialization described in this prospectus apply to the activities of our collaborators.

We may in the future decide to collaborate with pharmaceutical and biotechnology companies for the development and potential commercialization of our product candidates. These relationships, or those like them, may require us to incur non-recurring and other charges, increase our near- and long-term expenditures, issue securities that dilute our existing stockholders or disrupt our management and business. In addition, we could face significant competition in seeking appropriate collaborators and the negotiation process is time-consuming and complex. Our ability to reach a definitive collaboration agreement 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 several factors. If we license rights to product candidates, we may not be able to realize the benefit of such transactions if we are unable to successfully integrate them with our existing operations and company culture.

***We may not be successful in finding strategic collaborators for continuing development of certain of our product candidates or successfully commercializing or competing in the market for certain indications.***

We may seek to develop strategic partnerships for developing certain of our product candidates, due to capital costs required to develop the product candidates or manufacturing constraints. We may not be successful in our efforts to establish such a strategic partnership or other alternative arrangements for our product candidates because our research and development pipeline may be insufficient, our product candidates may be deemed to be at too early of a stage of development for collaborative effort or third parties may not view our product candidates as having the requisite potential to demonstrate safety and efficacy. In addition, we may be restricted under existing collaboration agreements from entering into future agreements with potential collaborators. For example, under our collaboration with Pfizer, we are subject to certain restrictions on our ability to directly or indirectly engage in certain activities relating to competing Factor IX gene therapy products. We cannot be certain that, following a strategic transaction or license, we will achieve an economic benefit that justifies such transaction.

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, delay its potential commercialization, 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 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 and our business, financial condition, results of operations and prospects may be materially and adversely affected.

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### **Risks related to manufacturing**

*Gene therapies are novel, complex and difficult to manufacture. We could experience production problems that result in delays in our development or commercialization programs or otherwise adversely affect our business.*

We currently have a contract with CHOP to manufacture clinical supplies of our product candidates. We recently completed construction of our own manufacturing facility, and we may encounter difficulties in validating and operating this new facility. The manufacturing process we use to produce our product candidates is complex, novel and has not been validated for commercial use. Several factors could cause production interruptions, including equipment malfunctions, facility contamination, raw material shortages or contamination, natural disasters, disruption in utility services, human error or disruptions in the operations of our suppliers.

Our product candidates require processing steps that are more complex than those required for most chemical pharmaceuticals. Moreover, unlike chemical pharmaceuticals, the physical and chemical properties of a biologic such as ours generally cannot be fully characterized. As a result, assays of the finished product may not be sufficient to ensure that the product will perform in the intended manner. Accordingly, we employ multiple steps to control our manufacturing process to assure that the process works and the product candidate is made strictly and consistently in compliance with the process. Problems with the manufacturing process, even minor deviations from the normal process, could result in product defects or manufacturing failures that result in lot failures, product recalls, product liability claims or insufficient inventory. We may encounter problems achieving adequate quantities and quality of clinical-grade materials that meet FDA, EMA or other applicable standards or specifications with consistent and acceptable production yields and costs.

In addition, FDA, EMA and other foreign regulatory authorities may require us to submit samples of any lot of any approved product together with the protocols showing the results of applicable tests at any time. Under some circumstances, FDA, EMA or other foreign regulatory authorities may require that we not distribute a lot until the agency authorizes its release. Slight deviations in the manufacturing process, including those affecting quality attributes and stability, may result in unacceptable changes in the product that could result in lot failures or product recalls. We have experienced lot failures in the past and there is no assurance we will not experience such failures in the future. Lot failures or product recalls could cause us to delay product launches or clinical trials, which could be costly to us and otherwise harm our business, financial condition, results of operations and prospects.

We also may encounter problems hiring and retaining the experienced specialist scientific, quality control and manufacturing personnel needed to operate our manufacturing process, which could result in delays in our production or difficulties in maintaining compliance with applicable regulatory requirements.

Any problems in our manufacturing process or facilities could make us a less attractive collaborator for potential partners, including larger pharmaceutical companies and academic research institutions, which could limit our access to additional attractive development programs. Problems in our manufacturing process or facilities also could restrict our ability to meet market demand for our products.

*Delays in obtaining regulatory approval of our manufacturing process and facility or disruptions in our manufacturing process may delay or disrupt our commercialization efforts. To date, no cGMP gene therapy manufacturing facility in the United States has received approval from FDA for the manufacture of an approved gene therapy product.*

Before we can begin to commercially manufacture our product candidates in our own facility, we must obtain regulatory approval from FDA for our manufacturing process and facility. A manufacturing authorization must also be obtained from the appropriate European Union regulatory authorities. To date, no cGMP gene therapy manufacturing facility in the United States has received approval from FDA for the manufacture of an approved

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gene therapy product and, therefore, the timeframe required for us to obtain such approval is uncertain. In addition, we must pass a pre-approval inspection of our manufacturing facility by FDA before any of our product candidates can obtain marketing approval. In order to obtain approval, we will need to ensure that all of our processes, methods and equipment are compliant with cGMP, and perform extensive audits of vendors, contract laboratories and suppliers. If any of our vendors, contract laboratories or suppliers is found to be out of compliance with cGMP, we may experience delays or disruptions in manufacturing while we work with these third parties to remedy the violation or while we work to identify suitable replacement vendors. The cGMP requirements govern quality control of the manufacturing process and documentation policies and procedures. In complying with cGMP, we will be obligated to expend time, money and effort in production, record keeping and quality control to assure that the product meets applicable specifications and other requirements. If we fail to comply with these requirements, we would be subject to possible regulatory action and may not be permitted to sell any products that we may develop.

***Until our manufacturing facility is operating, we expect to rely on CHOP and other third parties to conduct aspects of our product manufacturing, and these third parties may not perform satisfactorily.***

Until our manufacturing facility has been properly validated to comply with FDA cGMP requirements, we will not be able to independently manufacture material for our planned preclinical and clinical programs. We currently rely, and expect to continue to rely to a significant degree, on CHOP for the production of our clinical trial materials and, therefore, we can control only certain aspects of their activities.

Under certain circumstances, CHOP is entitled to terminate their engagement with us. If we need to enter into alternative arrangements, it could delay our product development activities. Our reliance on CHOP for certain manufacturing activities will reduce our control over these activities but will not relieve us of our responsibility to ensure compliance with all required regulations. If CHOP does not successfully carry out its contractual duties, meet expected deadlines or manufacture our product candidates in accordance with regulatory requirements, or if there are disagreements between us and CHOP, we will not be able to complete, or may be delayed in completing, the preclinical studies required to support future IND submissions and the clinical trials required for approval of our product candidates. In such instances, we may need to locate an appropriate replacement third-party relationship, which may not be readily available or on acceptable terms, which would cause additional delay or increased expense prior to the approval of our product candidates and would thereby have a material adverse effect on our business, financial condition, results of operations and prospects.

In addition to CHOP, we rely on additional third parties to manufacture ingredients of our product candidates and to perform quality testing, and reliance on these third parties entails risks to which we would not be subject if we manufactured the product candidates ourselves, including:

reduced control for certain aspects of manufacturing activities;

termination or nonrenewal of manufacturing and service agreements with third parties in a manner or at a time that is costly or damaging to us; and

disruptions to the operations of our third-party manufacturers and service providers caused by conditions unrelated to our business or operations, including the bankruptcy of the manufacturer or service provider.

Any of these events could lead to clinical trial delays or failure to obtain regulatory approval, or impact our ability to successfully commercialize future product candidates. Some of these events could be the basis for FDA action, including injunction, recall, seizure or total or partial suspension of product manufacture.

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***To the extent we rely on CHOP's manufacturing facility for commercial supply, CHOP will be subject to significant regulatory oversight with respect to manufacturing our products. CHOP's manufacturing facilities may not meet regulatory requirements.***

The preparation of therapeutics for clinical trials or commercial sale is subject to extensive regulation. Components of a finished therapeutic product approved for commercial sale or used in late-stage clinical trials must be manufactured in accordance with cGMP requirements. These regulations govern manufacturing processes and procedures, including record keeping, and the implementation and operation of quality systems to control and assure the quality of investigational products and products approved for sale. Poor control of production processes can lead to the introduction of outside agents or other contaminants, or to inadvertent changes in the properties or stability of product candidates that may not be detectable in final product testing. We must supply all necessary documentation in support of a BLA or other marketing authorization application on a timely basis and must adhere to FDA's and the European Union's cGMP requirements which are enforced, in the case of FDA, through its facilities inspection program. To the extent that we utilize CHOP's facilities for commercial supply, CHOP's facilities and quality systems must pass an inspection for compliance with the applicable regulations as a condition of regulatory approval. In addition, the regulatory authorities may, at any time, audit or inspect CHOP's manufacturing facility or the associated quality systems for compliance with the regulations applicable to the activities being conducted. If these facilities do not pass a plant inspection, EMA will not issue a positive opinion concerning the marketing authorization application and FDA approval of the products will not be granted. To date, neither FDA nor other foreign authorities has inspected CHOP's facilities and quality systems with respect to the manufacturing of our product candidates. In addition, CHOP is an academic-oriented research institution with no experience in undergoing FDA inspection and validation for a commercial manufacturing facility and there can be no assurance that CHOP's facility will pass regulatory inspection.

***Failure to comply with ongoing regulatory requirements could cause us to suspend production or put in place costly or time-consuming remedial measures.***

The regulatory authorities may, at any time following approval of a product for sale, audit the manufacturing facilities for such product. If any such inspection or audit identifies a failure to comply with applicable regulations, or if a violation of product specifications or applicable regulations occurs independent of such an inspection or audit, the relevant regulatory authority may require remedial measures that may be costly or time-consuming to implement and that may include the temporary or permanent suspension of a clinical trial or commercial sales or the temporary or permanent closure of a manufacturing facility. Any such remedial measures imposed upon CHOP or us could materially harm our business, financial condition, results of operations and prospects.

If CHOP or we fails to comply with applicable cGMP regulations, FDA and foreign regulatory authorities can impose regulatory sanctions including, among other things, refusal to approve a pending application for a new product candidate or suspension or revocation of a pre-existing approval. Such an occurrence may cause our business, financial condition, results of operations and prospects to be materially harmed.

Additionally, if supply from CHOP or from our facility is interrupted, there could be a significant disruption in commercial supply of our products. We do not currently have a backup manufacturer of our product candidate supply for clinical trials or commercial sale. An alternative manufacturer would need to be qualified, through a supplement to its regulatory filing, which could result in further delay. The regulatory authorities also may require additional trials if a new manufacturer is relied upon for commercial production. Switching manufacturers may involve substantial costs and could result in a delay in our desired clinical and commercial timelines.

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

Because we currently rely on CHOP and other third parties to manufacture all or part of our product candidates and to perform quality testing, and because we collaborate with various organizations and academic institutions for the advancement of our gene therapy platform, we must, at times, share our proprietary technology and confidential information, including trade secrets, with them. We seek to protect our proprietary technology, in part, by entering into confidentiality agreements and, if applicable, material transfer agreements, collaborative research agreements, consulting agreements or other similar agreements with our collaborators, advisors, employees and consultants prior to beginning research or disclosing proprietary information. These agreements typically limit the rights of the third parties to use or disclose our confidential information. Despite the contractual provisions employed when working with third parties, the need to share trade secrets and other confidential information increases the risk that such trade secrets become known by our competitors, are inadvertently incorporated into the technology of others or are disclosed or used in violation of these agreements. Given that our proprietary position is based, in part, on our know-how and trade secrets, a competitor's discovery of our proprietary technology and confidential information or other unauthorized use or disclosure would impair our competitive position and may have a material adverse effect on our business, financial condition, results of operations and prospects.

Despite our efforts to protect our trade secrets, our competitors may discover our trade secrets, either through breach of these agreements, independent development or publication of information including our trade secrets by third parties. A competitor's discovery of our trade secrets would impair our competitive position and have an adverse impact on our business, financial condition, results of operations and prospects.

***Any contamination in our manufacturing process, shortages of raw materials or failure of any of our key suppliers to deliver necessary components could result in delays in our clinical development or marketing schedules.***

Given the nature of biologics manufacturing, there is a risk of contamination. Any contamination could materially adversely affect our ability to produce product candidates on schedule and could, therefore, harm our results of operations and cause reputational damage.

Some of the raw materials required in our manufacturing process are derived from biologic sources. Such raw materials are difficult to procure and may be subject to contamination or recall. A material shortage, contamination, recall or restriction on the use of biologically derived substances in the manufacture of our product candidates could adversely impact or disrupt the commercial manufacturing or the production of clinical material, which could materially and adversely affect our development timelines and our business, financial condition, results of operations and prospects.

***Interruptions in the supply of product or inventory loss may adversely affect our operating results and financial condition.***

Our product candidates are manufactured using technically complex processes requiring specialized facilities, highly specific raw materials and other production constraints. The complexity of these processes, as well as strict government standards for the manufacture and storage of our products, subjects us to production risks. While product batches released for use in clinical trials or for commercialization undergo sample testing, some defects may only be identified following product release. In addition, process deviations or unanticipated effects of approved process changes may result in these intermediate products not complying with stability requirements or specifications. Our product candidates must be stored and transported at temperatures within a certain range. If these environmental conditions deviate, our product candidates remaining shelf-lives could be impaired or their efficacy and safety could be adversely affected, making them no longer suitable for use.

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The occurrence, or suspected occurrence, of production and distribution difficulties can lead to lost inventories and, in some cases, product recalls, with consequential reputational damage and the risk of product liability. The investigation and remediation of any identified problems can cause production delays, substantial expense, lost sales and delays of new product launches. Any interruption in the supply of finished products or the loss thereof could hinder our ability to timely distribute our products and satisfy customer demand. Any unforeseen failure in the storage of the product or loss in supply could delay our clinical trials and, if our product candidates are approved, result in a loss of our market share and negatively affect our business, financial condition, results of operations and prospects.

## **Risks related to the commercialization of our product candidates**

*If we are unable to establish sales, medical affairs and marketing capabilities or enter into agreements with third parties to market and sell our product candidates, we may be unable to generate any product revenue.*

We currently have no sales and marketing organization. To successfully commercialize any products that may result from our development programs, we will need to develop these capabilities, either on our own or with others. The establishment and development of our own commercial team or the establishment of a contract sales force to market any products we may develop will be expensive and time-consuming and could delay any product launch. Moreover, we cannot be certain that we will be able to successfully develop this capability. We have entered into a collaboration with Pfizer for the development and commercialization of SPK-FIX product candidates for the treatment of hemophilia B pursuant to which Pfizer would commercialize such product candidates, and we would be eligible to receive specified milestone payments and royalties, for any product developed under the agreement. We may enter into collaborations regarding other of our product candidates with other entities to utilize their established marketing and distribution capabilities, but we may be unable to enter into such agreements on favorable terms, if at all. If any current or future collaborators do not commit sufficient resources to commercialize our products, or we are unable to develop the necessary capabilities on our own, we will be unable to generate sufficient product revenue to sustain our business. We compete with many companies that currently have extensive, experienced and well-funded medical affairs, marketing and sales operations to recruit, hire, train and retain marketing and sales personnel. We also face competition in our search for third parties to assist us with the sales and marketing efforts of our product candidates. Without an internal team or the support of a third party to perform marketing and sales functions, we may be unable to compete successfully against these more established companies.

As part of our plan to market SPK-RPE65 through a limited number of centers-of-excellence, we will need to train additional vitreoretinal surgeons to perform the procedure necessary to administer SPK-RPE65 to patients safely and effectively via sub-retinal injection. This procedure requires significant skill and training. If we are unable to recruit or train sufficient retinal surgeons to perform the procedure properly, the availability of SPK-RPE65 could be substantially diminished, which would adversely affect our business, financial condition, results of operations and prospects.

Our efforts to educate the medical community and third-party payors on the benefits of our product candidates may require significant resources and may never be successful. Such efforts may require more resources than are typically required due to the complexity and uniqueness of our potential products. If any of our product candidates is approved but fails to achieve market acceptance among physicians, patients or third-party payors, we will not be able to generate significant revenues from such product, which could have a material adverse effect on our business, financial condition, results of operations and prospects.

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***If the market opportunities for our product candidates are smaller than we believe they are, our product revenues may be adversely affected and our business may suffer.***

We focus our research and product development on treatments for severe genetic and orphan diseases. Our understanding of both the number of people who have these diseases, as well as the subset of people with these diseases who have the potential to benefit from treatment with our product candidates, are based on estimates. These estimates may prove to be incorrect and new studies may reduce the estimated incidence or prevalence of these diseases. The number of patients in the United States, the European Union and elsewhere may turn out to be lower than expected, may not be otherwise amenable to treatment with our products or patients may become increasingly difficult to identify and access, all of which would adversely affect our business, financial condition, results of operations and prospects.

Further, there are several factors that could contribute to making the actual number of patients who receive our potential products less than the potentially addressable market. These include the lack of widespread availability of, and limited reimbursement for, new therapies in many underdeveloped markets. Further, the severity of the progression of a disease up to the time of treatment, especially in certain degenerative conditions such as IRDs caused by mutations in the RPE65 gene, will likely diminish the therapeutic benefit conferred by a gene therapy due to irreversible cell death. Lastly, certain patients' immune systems might prohibit the successful delivery of certain gene therapy products to the target tissue, thereby limiting the treatment outcomes.

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

We expect the cost of a single administration of gene therapy products, such as those we are developing, to be substantial, when and if they achieve regulatory approval. We expect that coverage and reimbursement by government and private payors will be essential for most patients to be able to afford these treatments. Accordingly, sales of our product candidates will depend substantially, both domestically and abroad, on the extent to which the costs of our product candidates will be paid by health maintenance, managed care, pharmacy benefit and similar healthcare management organizations, or will be reimbursed by government authorities, private health coverage insurers and other third-party payors. Coverage and reimbursement by a third-party payor may depend upon several factors, including the third-party payor's determination that use of a product is:

a covered benefit under its health plan;

safe, effective and medically necessary;

appropriate for the specific patient;

cost-effective; and

neither experimental nor investigational.

Obtaining coverage and reimbursement for a product from third-party payors is a time-consuming and costly process that could require us to provide to the payor supporting scientific, clinical and cost-effectiveness data. We may not be able to provide data sufficient to gain acceptance with respect to coverage and reimbursement. If coverage and reimbursement are not available, or are available only at limited levels, we may not be able to successfully commercialize our product candidates. Even if coverage is provided, the approved reimbursement amount may not be adequate to realize a sufficient return on our investment.



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There is significant uncertainty related to third-party coverage and reimbursement of newly approved products. In the United States, third-party payors, including government payors such as the Medicare and Medicaid programs, play an important role in determining the extent to which new drugs and biologics will be covered and reimbursed. The Medicare and Medicaid programs increasingly are used as models for how private payors and government payors develop their coverage and reimbursement policies. Currently, no gene therapy product has been approved for coverage and reimbursement by the Centers for Medicare & Medicaid Services, or CMS, the agency responsible for administering the Medicare program. It is difficult to predict what CMS will decide with respect to coverage and reimbursement for fundamentally novel products such as ours, as there is no body of established practices and precedents for these types of products. Moreover, reimbursement agencies in the European Union may be more conservative than CMS. For example, several cancer drugs have been approved for reimbursement in the United States and have not been approved for reimbursement in certain European Union Member States. It is difficult to predict what third-party payors will decide with respect to the coverage and reimbursement for our product candidates.

Outside the United States, international operations generally are subject to extensive government price controls and other market regulations, and increasing emphasis on cost-containment initiatives in the European Union, Canada and other countries may put pricing pressure on us. For example, one gene therapy product was approved in the European Union in 2012 but is yet to be widely available commercially. In many countries, the prices of medical products are subject to varying price control mechanisms as part of national health systems. In general, the prices of medicines under such systems are substantially lower than in the United States. Other countries allow companies to fix their own prices for medical products, but monitor and control company profits. Additional foreign price controls or other changes in pricing regulation could restrict the amount that we are able to charge for our product candidates. Accordingly, in markets outside the United States, the reimbursement for our products may be reduced compared with the United States and may be insufficient to generate commercially reasonable product revenues.

Moreover, increasing efforts by government and third-party payors in the United States and abroad to cap or reduce healthcare costs may cause such organizations to limit both coverage and the level of reimbursement for new products approved and, as a result, they may not cover or provide adequate payment for our product candidates. Payors increasingly are considering new metrics as the basis for reimbursement rates, such as average sales price, or ASP, average manufacturer price, or AMP, and Actual Acquisition Cost. The existing data for reimbursement based on some of these metrics is relatively limited, although certain states have begun to survey acquisition cost data for the purpose of setting Medicaid reimbursement rates, and CMS has begun making pharmacy National Average Drug Acquisition Cost and National Average Retail Price data publicly available on at least a monthly basis. Therefore, it may be difficult to project the impact of these evolving reimbursement metrics on the willingness of payors to cover candidate products that we or our partners are able to commercialize. We expect to experience pricing pressures in connection with the sale of any of our product candidates due to the trend toward managed healthcare, the increasing influence of health maintenance organizations and additional legislative changes. The downward pressure on healthcare costs in general, particularly prescription drugs and surgical procedures and other treatments, has become intense. As a result, increasingly high barriers are being erected to the entry of new products such as ours.

***The commercial success of any of our product candidates will depend upon its degree of market acceptance by physicians, patients, third-party payors and others in the medical community.***

Ethical, social and legal concerns about gene therapy could result in additional regulations restricting or prohibiting our products. Even with the requisite approvals from FDA in the United States, EMA in the European Union and other regulatory authorities internationally, the commercial success of our product candidates will depend, in part, on the acceptance of physicians, patients and health care payors of gene therapy products in

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general, and our product candidates in particular, as medically necessary, cost-effective and safe. Any product that we commercialize may not gain acceptance by physicians, patients, health care payors and others in the medical community. If these products do not achieve an adequate level of acceptance, we may not generate significant product revenue and may not become profitable. The degree of market acceptance of gene therapy products and, in particular, our product candidates, if approved for commercial sale, will depend on several factors, including:

the efficacy and safety of such product candidates as demonstrated in clinical trials;

the potential and perceived advantages of product candidates over alternative treatments;

the cost of treatment relative to alternative treatments;

the clinical indications for which the product candidate is approved by FDA or the European Commission;

patient awareness of, and willingness to seek, genotyping;

the willingness of physicians to prescribe new therapies;

the willingness of the target patient population to try new therapies;

the prevalence and severity of any side effects;

product labeling or product insert requirements of FDA, EMA or other regulatory authorities, including any limitations or warnings contained in a product's approved labeling;

relative convenience and ease of administration;

the strength of marketing and distribution support;

the timing of market introduction of competitive products;

publicity concerning our products or competing products and treatments; and

sufficient third-party payor coverage and reimbursement.

Even if a potential product displays a favorable efficacy and safety profile in preclinical studies and clinical trials, market acceptance of the product will not be fully known until after it is launched.

***Our gene therapy approach utilizes vectors derived from viruses, which may be perceived as unsafe or may result in unforeseen adverse events. Negative public opinion and increased regulatory scrutiny of gene therapy may damage public perception of the safety of our product candidates and adversely affect our ability to conduct our business or obtain regulatory approvals for our product candidates.***

Gene therapy remains a novel technology, with no gene therapy product approved to date in the United States and only one gene therapy product approved to date in the European Union. Public perception may be influenced by claims that gene therapy is unsafe, and gene therapy may not gain the acceptance of the public or the medical community. In particular, our success will depend upon physicians who specialize in the treatment of genetic diseases targeted by our product candidates, prescribing treatments that involve the use of our product candidates in lieu of, or in addition to, existing treatments with which they are familiar and for which greater clinical data may be available. More restrictive government regulations or negative public opinion would have an adverse effect on our business, financial condition, results of operations and prospects and may delay or impair the development and commercialization of our product candidates or demand for any products we may develop. For example, earlier gene therapy trials led to several well-publicized adverse events, including cases of leukemia and death seen in other trials using other vectors. Serious adverse events in our

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clinical trials, or other clinical trials involving gene therapy products or our competitors' products, even if not ultimately attributable to the relevant product candidates, and the resulting publicity, could result in increased government regulation, unfavorable public perception, potential regulatory delays in the testing or approval of our product candidates, stricter labeling requirements for those product candidates that are approved and a decrease in demand for any such product candidates.

*If we obtain approval to commercialize our product candidates outside of the United States, in particular in the European Union, a variety of risks associated with international operations could materially adversely affect our business.*

We expect that we will be subject to additional risks in commercializing our product candidates outside the United States, including:

different regulatory requirements for approval of drugs and biologics in foreign countries;

reduced protection for intellectual property rights;

unexpected changes in tariffs, trade barriers and regulatory requirements;

economic weakness, including inflation, or political instability in particular foreign economies and markets;

compliance with tax, employment, immigration and labor laws for employees living or traveling abroad;

foreign currency fluctuations, which could result in increased operating expenses and reduced revenues, and other obligations incident to doing business in another country;

workforce uncertainty in countries where labor unrest is more common than in the United States;

production shortages resulting from any events affecting raw material supply or manufacturing capabilities abroad; and

business interruptions resulting from geopolitical actions, including war and terrorism or natural disasters including earthquakes, typhoons, floods and fires.

## **Risks related to our business operations**

*We may not be successful in our efforts to identify or discover additional product candidates and may fail to capitalize on programs or product candidates that may be a greater commercial opportunity or for which there is a greater likelihood of success.*

The success of our business depends upon our ability to identify, develop and commercialize product candidates based on our gene therapy platform. Research programs to identify new product candidates require substantial technical, financial and human resources. Although certain of our product candidates are currently in clinical or preclinical development, we may fail to identify other potential product candidates for clinical development for several reasons. For example, our research may be unsuccessful in identifying potential product candidates or our potential product candidates may be shown to have harmful side effects, may be commercially impracticable to manufacture or may have other characteristics that may make the products unmarketable or unlikely to receive marketing approval.

Additionally, because we have limited resources, we may forego or delay pursuit of opportunities with certain programs or product candidates or for indications that later prove to have greater commercial potential. Our spending on current and future research and development programs

may not yield any commercially viable products. If we do not accurately evaluate the commercial potential for a particular product candidate, we may

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relinquish valuable rights to that product candidate through strategic collaboration, licensing or other arrangements in cases in which it would have been more advantageous for us to retain sole development and commercialization rights to such product candidate. Alternatively, we may allocate internal resources to a product candidate in a therapeutic area in which it would have been more advantageous to enter into a partnering arrangement.

If any of these events occur, we may be forced to abandon our development efforts with respect to a particular product candidate or fail to develop a potentially successful product candidate, which could have a material adverse effect on our business, financial condition, results of operations and prospects.

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

We are highly dependent on members of our executive team, the loss of whose services may adversely impact the achievement of our objectives. While we have entered into employment agreements with each of our executive officers, any of them could leave our employment at any time, as all of our employees are at will employees. We currently do not have key person insurance on any of our employees. The loss of the services of one or more of our current employees might impede the achievement of our research, development and commercialization objectives.

Recruiting and retaining other qualified employees, consultants and advisors for our business, including scientific and technical personnel, also will be critical to our success. There currently is a shortage of skilled individuals with substantial gene therapy experience, which is likely to continue. As a result, competition for skilled personnel, including in gene therapy research and vector manufacturing, is intense and the turnover rate can be high. We may not be able to attract and retain personnel on acceptable terms given the competition among numerous pharmaceutical and biotechnology companies and academic institutions for individuals with similar skill sets. In addition, failure to succeed in preclinical or clinical trials or applications for marketing approval may make it more challenging to recruit and retain qualified personnel. The inability to recruit, or loss of services of certain executives, key employees, consultants or advisors, may impede the progress of our research, development and commercialization objectives and have a material adverse effect on our business, financial condition, results of operations and prospects.

### ***If we are unable to manage expected growth in the scale and complexity of our operations, our performance may suffer.***

If we are successful in executing our business strategy, we will need to expand our managerial, operational, financial and other systems and resources to manage our operations, continue our research and development activities and, in the longer term, build a commercial infrastructure to support commercialization of any of our product candidates that are approved for sale. Future growth would impose significant added responsibilities on members of management. It is likely that our management, finance, development personnel, systems and facilities currently in place may not be adequate to support this future growth. Our need to effectively manage our operations, growth and product candidates requires that we continue to develop more robust business processes and improve our systems and procedures in each of these areas and to attract and retain sufficient numbers of talented employees. We may be unable to successfully implement these tasks on a larger scale and, accordingly, may not achieve our research, development and growth goals.

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***Our employees, principal investigators, consultants and commercial partners may engage in misconduct or other improper activities, including non-compliance with regulatory standards and requirements and insider trading.***

We are exposed to the risk of fraud or other misconduct by our employees, principal investigators, consultants and commercial partners. Misconduct by these parties could include intentional failures to comply with FDA regulations or the regulations applicable in the European Union and other jurisdictions, provide accurate information to FDA, the European Commission and other regulatory authorities, comply with healthcare fraud and abuse laws and regulations in the United States and abroad, report financial information or data accurately or disclose unauthorized activities to us. In particular, sales, marketing and business arrangements in the healthcare industry are subject to extensive laws and regulations intended to prevent fraud, misconduct, kickbacks, self-dealing and other abusive practices. These laws and regulations restrict or prohibit a wide range of pricing, discounting, marketing and promotion, sales commission, customer incentive programs and other business arrangements. Such misconduct also could involve the improper use of information obtained in the course of clinical trials or interactions with FDA or other regulatory authorities, which could result in regulatory sanctions and cause serious harm to our reputation. We have adopted a code of conduct applicable to all of our employees, but 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 government investigations or other actions or lawsuits stemming from a failure to comply with these laws or regulations. 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, financial condition, results of operations and prospects, including the imposition of significant fines or other sanctions.

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

In the United States, there have been, and continue to be, several legislative initiatives to contain healthcare costs. For example, in March 2010, the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act, or PPACA, was passed, which substantially changes the way health care is financed by both the government and private insurers, and significantly impacts the U.S. pharmaceutical industry. The PPACA, among other things: (i) addresses 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; (ii) increases the minimum Medicaid rebates owed by manufacturers under the Medicaid Drug Rebate Program and extends the rebate program to individuals enrolled in Medicaid managed care organizations; (iii) establishes annual fees and taxes on manufacturers of certain branded prescription drugs; (iv) expands the availability of lower pricing under the 340B drug pricing program by adding new entities to the program; and (v) establishes a new Medicare Part D coverage gap discount program, in which manufacturers must agree to offer 50% point-of-sale discounts off negotiated prices of applicable brand drugs to eligible beneficiaries during their coverage gap period, as a condition for the manufacturer's outpatient drugs to be covered under Medicare Part D. Additionally, in the United States, the Biologics Price Competition and Innovation Act of 2009 created an abbreviated approval pathway for biologic products that are demonstrated to be highly similar or biosimilar or interchangeable with an FDA-approved biologic product. This new pathway could allow competitors to reference data from biologic products already approved after 12 years from the time of approval. This could expose us to potential competition by lower-cost biosimilars even if we commercialize a product candidate faster than our competitors.

Additional changes that may affect our business include those governing enrollment in federal healthcare programs, reimbursement changes, rules regarding prescription drug benefits under the health insurance

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exchanges and fraud and abuse and enforcement. Continued implementation of the PPACA and the passage of additional laws and regulations may result in the expansion of new programs such as Medicare payment for performance initiatives, and may impact existing government healthcare programs, such as by improving the physician quality reporting system and feedback program.

For each state that does not choose to expand its Medicaid program, there likely will be fewer insured patients overall, which could impact the sales, business and financial condition of manufacturers of branded prescription drugs. Where patients receive insurance coverage under any of the new options made available through the PPACA, the possibility exists that manufacturers may be required to pay Medicaid rebates on that resulting drug utilization, a decision that could impact manufacturer revenues. The U.S. federal government also has announced delays in the implementation of key provisions of the PPACA. The implications of these delays for our and our partners' business and financial condition, if any, are not yet clear.

We expect that additional state and federal healthcare reform measures will be adopted in the future, any of which could limit the amounts that federal and state governments will pay for healthcare products and services, which could result in reduced demand for our product candidates or additional pricing pressures.

***We may be subject, directly or indirectly, to federal and state healthcare fraud and abuse laws, false claims laws and health information privacy and security laws. If we are unable to comply, or have not fully complied, with such laws, we could face substantial penalties.***

If we obtain FDA approval for any of our product candidates and begin commercializing those products in the United States, our operations will be directly, or indirectly through our prescribers, customers and purchasers, subject to various federal and state fraud and abuse laws and regulations, including, without limitation, the federal Health Care Program Anti-Kickback Statute, the federal civil and criminal False Claims Act and Physician Payments Sunshine Act and regulations. These laws will impact, among other things, our proposed sales, marketing and educational programs. In addition, we may be subject to patient privacy laws by both the federal government and the states in which we conduct our business. The laws that will affect our operations include, but are not limited to:

the federal Health Care Program Anti-Kickback Statute, which prohibits, among other things, persons or entities from knowingly and willfully soliciting, receiving, offering or paying any remuneration (including any kickback, bribe or rebate), directly or indirectly, overtly or covertly, in cash or in kind, in return for the purchase, recommendation, leasing or furnishing of an item or service reimbursable under a federal healthcare program, such as the Medicare and Medicaid programs. This statute has been interpreted to apply to arrangements between pharmaceutical manufacturers on the one hand, and prescribers, purchasers and formulary managers on the other. The PPACA amends the intent requirement of the federal Anti-Kickback Statute. A person or entity no longer needs to have actual knowledge of this statute or specific intent to violate it;

federal civil and criminal false claims laws and civil monetary penalty laws which prohibit, among other things, individuals or entities from knowingly presenting, or causing to be presented, claims for payment or approval from Medicare, Medicaid or other government payors that are false or fraudulent. The PPACA provides and recent government cases against pharmaceutical and medical device manufacturers support the view that Federal Anti-Kickback Statute violations and certain marketing practices, including off-label promotion, may implicate the False Claims Act;

the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, which created new federal criminal statutes that prohibit a person from knowingly and willfully executing a scheme or from making false or fraudulent statements to defraud any healthcare benefit program, regardless of the payor (e.g., public or private);



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HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act, or HITECH, and its implementing regulations, and as amended again by the final HIPAA omnibus rule, Modifications to the HIPAA Privacy, Security, Enforcement, and Breach Notification Rules Under HITECH and the Genetic Information Nondiscrimination Act; Other Modifications to HIPAA, published in January 2013, which imposes certain requirements relating to the privacy, security and transmission of individually identifiable health information without appropriate authorization by entities subject to the rule, such as health plans, health care clearinghouses and health care providers;

federal transparency laws, including the federal Physician Payment Sunshine Act, that require disclosure of payments and other transfers of value provided to physicians and teaching hospitals, and ownership and investment interests held by physicians and other healthcare providers and their immediate family members and applicable group purchasing organizations; and

state law equivalents of each of the above federal laws, state laws that require drug manufacturers to report information related to payments and other transfers of value to physicians and other healthcare providers or marketing expenditures and state laws governing the privacy and security of health information in certain circumstances, many of which differ from each other in significant ways and may not have the same effect, thus complicating compliance efforts in certain circumstances, such as specific disease states.

Because of the breadth of these laws and the narrowness of the statutory exceptions and safe harbors available, it is possible that some of our business activities could be subject to challenge under one or more of such laws. If our operations are found to be in violation of any of the laws described above or any other government regulations that apply to us, we may be subject to penalties, including civil and criminal penalties, damages, fines, exclusion from participation in government health care programs, such as Medicare and Medicaid, imprisonment and the curtailment or restructuring of our operations, any of which could adversely affect our ability to operate our business and our results of operations.

The provision of benefits or advantages to physicians to induce or encourage the prescription, recommendation, endorsement, purchase, supply, order or use of medicinal products is prohibited in the European Union. The provision of benefits or advantages to physicians is also governed by the national anti-bribery laws of European Union Member States, such as the UK Bribery Act 2010. Infringement of these laws could result in substantial fines and imprisonment.

Payments made to physicians in certain European Union Member States must be publically disclosed. Moreover, agreements with physicians often must be the subject of prior notification and approval by the physician's employer, his or her competent professional organization and/or the regulatory authorities of the individual European Union Member States. These requirements are provided in the national laws, industry codes or professional codes of conduct, applicable in the European Union Member States. Failure to comply with these requirements could result in reputational risk, public reprimands, administrative penalties, fines or imprisonment.

The collection and use of personal health data in the European Union is governed by the provisions of the Data Protection Directive. This directive imposes several requirements relating to the consent of the individuals to whom the personal data relates, the information provided to the individuals, notification of data processing obligations to the competent national data protection authorities and the security and confidentiality of the personal data. The Data Protection Directive also imposes strict rules on the transfer of personal data out of the European Union to the United States. Failure to comply with the requirements of the Data Protection Directive and the related national data protection laws of the European Union Member States may result in fines and other administrative penalties. The draft Data Protection Regulation currently going through the adoption process is expected to introduce new data protection requirements in the European Union and substantial fines

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for breaches of the data protection rules. If the draft Data Protection Regulation is adopted in its current form it may increase our responsibility and liability in relation to personal data that we process and we may be required to put in place additional mechanisms ensuring compliance with the new data protection rules. This may be onerous and adversely affect our business, financial condition, results of operations and prospects.

***Product liability lawsuits against us could cause us to incur substantial liabilities and could limit commercialization of any product candidates that we may develop.***

We face an inherent risk of product liability exposure related to the testing of our product candidates in clinical trials and may face an even greater risk if we commercialize any products that we may develop. If we cannot successfully defend ourselves against claims that our product candidates caused injuries, we could incur substantial liabilities. Regardless of merit or eventual outcome, liability claims may result in:

decreased demand for any product candidates that we may develop;

loss of revenue;

substantial monetary awards to trial participants or patients;

significant time and costs to defend the related litigation;

withdrawal of clinical trial participants;

the inability to commercialize any product candidates that we may develop; and

injury to our reputation and significant negative media attention.

Although we maintain product liability insurance coverage in the amount of \$10 million per occurrence and \$10 million in the aggregate, this insurance may not be adequate to cover all liabilities that we may incur. We anticipate that we will need to increase our insurance coverage each time we commence a clinical trial and if we successfully commercialize any product candidate. 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 we fail to comply with environmental, health and safety laws and regulations, we could become subject to fines or penalties or incur costs that could have a material adverse effect on the success of our business.***

We are subject to numerous environmental, health and safety laws and regulations, including those governing laboratory procedures and the generation, handling, use, storage, treatment, manufacture, transportation and disposal of, and exposure to, hazardous materials and wastes, as well as laws and regulations relating to occupational health and safety. Our operations involve the use of hazardous and flammable materials, including chemicals and biologic and radioactive materials. Our operations also produce hazardous waste products. We generally contract with third parties for the disposal of these materials and wastes. We cannot eliminate the risk of contamination or injury from these materials. In the event of contamination or injury resulting from our use of hazardous materials, we could be held liable for any resulting damages, and any liability could exceed our resources. We also could incur significant costs associated with civil or criminal fines and penalties.

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



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In addition, we may incur substantial costs in order to comply with current or future environmental, health and safety laws and regulations, which have tended to become more stringent over time. These current or future laws and regulations may impair our research, development or production efforts. Failure to comply with these laws and regulations also may result in substantial fines, penalties or other sanctions or liabilities, which could materially adversely affect our business, financial condition, results of operations and prospects.

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

Our results of operations could be adversely affected by general conditions in the global economy and in the global financial markets. The most recent global financial crisis caused extreme volatility and disruptions in the capital and credit markets. A severe or prolonged economic downturn, such as the most recent global financial crisis, could result in a variety of risks to our business, including weakened demand for our product candidates and our ability to raise additional capital when needed on acceptable terms, if at all. This is particularly true in the European Union, which is undergoing a continued severe economic crisis. A weak or declining economy could strain our suppliers, possibly resulting in supply disruption, or cause delays in payments for our services by third-party payors or our collaborators. Any of the foregoing could harm our business and we cannot anticipate all of the ways in which the current economic climate and financial market conditions could adversely impact our business.

***Third parties on which we rely and we may be adversely affected by natural disasters and our business continuity and disaster recovery plans may not adequately protect us from a serious disaster.***

Natural disasters could severely disrupt our operations or the operations of CHOP's manufacturing facilities and have a material adverse effect on our business, financial condition, results of operations and prospects. If a natural disaster, power outage or other event occurred that prevented us from using all or a significant portion of our headquarters, that damaged critical infrastructure, such as CHOP's manufacturing facilities, or that otherwise disrupted operations, it may be difficult or, in certain cases, impossible for us to continue our business for a substantial period of time. The disaster recovery and business continuity plans we have in place currently are limited and may not prove adequate in the event of a serious disaster or similar event. Both CHOP's manufacturing facility and our manufacturing facility, as well as substantially all of our current supply of product candidates, are located in Philadelphia, Pennsylvania, and we do not have any existing back-up facilities in place or plans for such back-up facilities. We may incur substantial expenses as a result of the limited nature of our disaster recovery and business continuity plans, which could have a material adverse effect on our business, financial condition, results of operations and prospects.

***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 our current and any future collaborators and other contractors or consultants are vulnerable to damage from computer viruses, unauthorized access, natural disasters, terrorism, war and telecommunication and electrical failures. While we have not experienced any such material system failure, accident or security breach to date, if such an event were to occur and cause interruptions in our operations, it could result in a material disruption of our 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.

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### **Risks related to our intellectual property**

*Our rights to develop and commercialize our product candidates are subject, in part, to the terms and conditions of licenses granted to us by others.*

We do not currently own any patents or patent applications and we are heavily reliant upon licenses to certain patent rights and proprietary technology from third parties that are important or necessary to the development of our technology and products, including technology related to our manufacturing process and our gene therapy product candidates. These and other licenses may not provide exclusive rights to use such intellectual property and technology in all relevant fields of use and in all territories in which we may wish to develop or commercialize our technology and products in the future. As a result, we may not be able to prevent competitors from developing and commercializing competitive products in territories included in all of our licenses. For example, we have a co-exclusive license from the University of Pennsylvania, or Penn, to patent rights that are jointly owned by Penn, Cornell University and the University of Florida that include methods of treating patients with LCA due to RPE65 mutations. Under the terms of this co-exclusive license, Penn, on behalf of the other joint owners, has the right to grant a license of the same intellectual property to one other party. Such other party would have full rights to the patent rights that are the subject of our license, including for marketing in the territories covered by our license, which could impact our competitive position and enable such third party to commercialize products similar to ours.

Licenses to additional third-party technology that may be required for our development programs may not be available in the future or may not be available on commercially reasonable terms, or at all, which could have a material adverse effect on our business and financial condition.

In some circumstances, we may not have the right to control the preparation, filing and prosecution of patent applications, or to maintain the patents, covering technology that we license from third parties. For example, pursuant to each of our intellectual property licenses with CHOP, Penn and the University of Iowa Research Foundation, or UIRF, our licensors retain control of such activities. Therefore, we cannot be certain that these patents and applications will be prosecuted, maintained and enforced in a manner consistent with the best interests of our business. If our licensors fail to maintain such patents, or lose rights to those patents or patent applications, the rights we have licensed may be reduced or eliminated and our right to develop and commercialize any of our products that are the subject of such licensed rights could be adversely affected. In addition to the foregoing, the risks associated with patent rights that we license from third parties will also apply to patent rights we may own in the future.

Furthermore, the research resulting in certain of our licensed patent rights and technology was funded by the U.S. government. As a result, the government may have certain rights, or march-in rights, to such patent rights and technology. When new technologies are developed with government funding, the government generally obtains certain rights in any resulting patents, including a non-exclusive license authorizing the government to use the invention for non-commercial purposes. These rights may permit the government to disclose our confidential information to third parties and to exercise march-in rights to use or allow third parties to use our licensed technology. The government can exercise its march-in rights if it determines that action is necessary because we fail to achieve practical application of the government-funded technology, because action is necessary to alleviate health or safety needs, to meet requirements of federal regulations or to give preference to U.S. industry. In addition, our rights in such inventions may be subject to certain requirements to manufacture products embodying such inventions in the United States. Any exercise by the government of such rights could harm our competitive position, business, financial condition, results of operations and prospects.

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

Our success depends, in large part, on our ability to obtain and maintain patent protection in the United States and other countries with respect to our proprietary product candidates and manufacturing technology. Our licensors have sought and we intend to seek to protect our proprietary position by filing patent applications in the United States and abroad related to many of our novel technologies and product candidates that are important to our business.

The patent prosecution process is expensive, time-consuming and complex, and we may not be able to file, prosecute, maintain, enforce or license all necessary or desirable patent applications at a reasonable cost or in a timely manner. In addition, certain patents in the field of gene therapy that may have otherwise potentially provided patent protection for certain of our product candidates have expired or will soon expire. In some cases, the work of certain academic researchers in the gene therapy field has entered the public domain, which we believe precludes our ability to obtain patent protection for certain inventions relating to such work. As a result, we have not have sought, and may be unable to seek, patent protection for SPK-CHM to treat choroideremia or for SPK-RPE65 to treat RPE65-mediated IRDs other than LCA. Consequently, we will not be able to assert any such patents to prevent others from using our technology for, and developing and marketing competing products to treat, these indications. It is also possible that we will fail to identify patentable aspects of our research and development output before it is too late to obtain patent protection.

We are a party to intellectual property license agreements with CHOP, Penn and UIRF, each of which is important to our business, and we expect to enter into additional license agreements in the future. Our existing license agreements impose, and we expect that future license agreements will impose, various diligence, development and commercialization timelines, milestone payments, royalties and other obligations on us. See Business Collaboration and license agreements. If we fail to comply with our obligations under these agreements, or we are subject to a bankruptcy, the licensor may have the right to terminate the license, in which event we would not be able to market products covered by the license.

The patent position of biotechnology and pharmaceutical companies generally is highly uncertain, involves complex legal and factual questions and has, in recent years, been the subject of much litigation. As a result, the issuance, scope, validity, enforceability and commercial value of our patent rights are highly uncertain. Our pending and future patent applications may not result in patents being issued which protect our technology or product candidates or which effectively prevent others from commercializing competitive technologies and product candidates. 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 or narrow the scope of our patent protection.

We may not be aware of all third-party intellectual property rights potentially relating to our product candidates. Publications of discoveries in the scientific literature often lag the actual discoveries, and patent applications in the United States and other jurisdictions are typically not published until 18 months after filing or, in some cases, not at all. Therefore, we cannot be certain that we were the first to make the inventions claimed in any owned or any licensed patents or pending patent applications, or that we were the first to file for patent protection of such inventions.

Even if the patent applications we license or may own in the future do issue as patents, they may not issue in a form that will provide us with any meaningful protection, prevent competitors or other third parties from competing with us or otherwise provide us with any competitive advantage. Our competitors or other third parties may be able to circumvent our patents by developing similar or alternative technologies or products in a non-infringing manner.

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The issuance of a patent is not conclusive as to its inventorship, scope, validity or enforceability, and our patents may be challenged in the courts or patent offices in the United States and abroad. Such challenges may result in loss of exclusivity or in patent claims being narrowed, invalidated or held unenforceable, 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. 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 intellectual property may not provide us with sufficient rights to exclude others from commercializing products similar or identical to ours.

***Our intellectual property licenses with third parties may be subject to disagreements over contract interpretation, which could narrow the scope of our rights to the relevant intellectual property or technology or increase our financial or other obligations to our licensors.***

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.

***If we fail to comply with our obligations in the agreements under which we license intellectual property rights from third parties or otherwise experience disruptions to our business relationships with our licensors, we could lose license rights that are important to our business.***

We have entered into license agreements with third parties and may need to obtain additional licenses from others to advance our research or allow commercialization of our product candidates. It is possible that we may be unable to obtain additional licenses at a reasonable cost or on reasonable terms, if at all. In that event, we may be required to expend significant time and resources to redesign our 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 product candidates, which could harm our business significantly. We cannot provide any assurances that third-party patents do not exist which might be enforced against our current manufacturing methods, product candidates or future methods or products, resulting in either an injunction prohibiting our manufacture or sales, or, with respect to our sales, an obligation on our part to pay royalties and/or other forms of compensation to third parties.

In each of our existing license agreements, and we expect in our future agreements, patent prosecution of our licensed technology is controlled solely by the licensor, and we are required to reimburse the licensor for their costs of patent prosecution. If our licensors fail to obtain and maintain patent or other protection for the proprietary intellectual property we license from them, we could lose our rights to the intellectual property or our exclusivity with respect to those rights, and our competitors could market competing products using the intellectual property. Further, in each of our license agreements we are responsible for bringing any actions against any third party for infringing on the patents we have licensed. Certain of our license agreements also require us to meet development thresholds to maintain the license, including establishing a set timeline for developing and commercializing products and minimum yearly diligence obligations in developing and commercializing the product. 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;

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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 or ownership of inventions and know-how resulting from the joint creation or use of intellectual property by our licensors and us and our partners; and

the priority of invention of patented technology.

If disputes over intellectual property that we have licensed prevent or impair our ability to maintain our current licensing arrangements on acceptable terms, we may be unable to successfully develop and commercialize the affected product candidates.

### ***We may not be successful in obtaining necessary rights to our product candidates through acquisitions and in-licenses.***

We currently have rights to the intellectual property, through licenses from third parties, to develop our product candidates. Because our programs may require the use of proprietary rights held by third parties, the growth of our business likely will depend, in part, on our ability to acquire, in-license or use these proprietary rights. We may be unable to acquire or in-license any compositions, methods of use, processes or other intellectual property rights from third parties that we identify as necessary for our product candidates. The licensing or acquisition of third-party intellectual property rights is a competitive area, and several more established companies may pursue strategies to license or acquire third-party intellectual property rights that we may consider attractive. These established companies may have a competitive advantage over us due to their size, capital 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. We also may be unable to license or acquire third party intellectual property rights on terms that would allow us to make an appropriate return on our investment.

We sometimes collaborate with non-profit and academic institutions to accelerate our preclinical research or development under written agreements with these institutions. Typically, these institutions provide us with an option to negotiate a license to any of the institution's rights in technology resulting from the collaboration. Regardless of such option, we may be unable to negotiate a license within the specified timeframe or under terms that are acceptable to us. If we are unable to do so, the institution may offer the intellectual property rights to other parties, potentially blocking our ability to pursue our program.

If we are unable to successfully obtain rights to required third-party intellectual property rights or maintain the existing intellectual property rights we have, we may have to abandon development of the relevant program or product candidate and our business, financial condition, results of operations and prospects could suffer.

### ***Obtaining and maintaining our patent protection depends on compliance with various procedural, document submission, fee payment and other requirements imposed by government patent agencies, and our patent protection could be reduced or eliminated for non-compliance with these requirements.***

Periodic maintenance fees, renewal fees, annuity fees and various other government fees on patents and/or applications will be due to be paid to the United States Patent and Trademark Office, or USPTO, and various government patent agencies outside of the United States over the lifetime of our licensed patents and/or applications and any patent rights we may own in the future. We rely on our outside counsel or our licensing partners to pay these fees due to non-U.S. patent agencies. The USPTO and various non-U.S. government patent



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agencies require compliance with several procedural, documentary, fee payment and other similar provisions during the patent application process. We employ reputable law firms and other professionals to help us comply and we are also dependent on our licensors to take the necessary action to comply with these requirements with respect to our licensed intellectual property. In many cases, an inadvertent lapse can be cured by payment of a late fee or by other means in accordance with the applicable rules. There are situations, however, in which non-compliance can result in abandonment or lapse of the patent or patent application, resulting in partial or complete loss of patent rights in the relevant jurisdiction. In such an event, potential competitors might be able to enter the market and this circumstance could have a material adverse effect on our business.

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

Filing, prosecuting and defending patents on product candidates in all countries throughout the world would be prohibitively expensive, and our intellectual property rights in some countries outside the United States could be less extensive than those in the United States. Although our license agreements with CHOP, Penn and UIRF grant us worldwide rights, certain of our in-licensed U.S. patent rights lack corresponding foreign patents or patent applications. For example, we co-exclusively license a U.S. patent from Penn that covers methods of treating patients with LCA due to RPE65 mutations. No patents or patent applications outside the United States corresponding to this patent were ever pursued. In addition, the laws of some foreign countries do not protect intellectual property rights to the same extent as federal and state laws in the United States. Consequently, we may not be able to prevent third parties from practicing our inventions in all countries outside the United States, or from selling or importing products made using our inventions in and into the United States or other jurisdictions. Competitors may use our technologies in jurisdictions where we have not obtained patent protection to develop their own products and, further, may export otherwise infringing products to territories where we have patent protection, but enforcement is not as strong as that in the United States. These products may compete with our products and our patents or other intellectual property rights may not be effective or sufficient to prevent them from competing.

Many companies have encountered significant problems in protecting and defending intellectual property rights in foreign jurisdictions. The legal systems of certain countries, particularly certain developing countries, do not favor the enforcement of patents, trade secrets and other intellectual property protection, particularly those relating to biotechnology products, which could make it difficult for us to stop the infringement of our patents or marketing of competing products in violation of our proprietary rights generally. Proceedings to enforce our patent rights in foreign jurisdictions could result in substantial costs and divert our efforts and attention from other aspects of our business, could put our patents at risk of being invalidated or interpreted narrowly and our patent applications at risk of not issuing and could provoke third parties to assert claims against us. We may not prevail in any lawsuits that we initiate and the damages or other remedies awarded, if any, may not be commercially meaningful. Accordingly, our efforts to enforce our intellectual property rights around the world may be inadequate to obtain a significant commercial advantage from the intellectual property that we develop or license.

***Issued patents covering our product candidates could be found invalid or unenforceable if challenged in court. We may not be able to protect our trade secrets in court.***

If one of our licensing partners or we initiate legal proceedings against a third party to enforce a patent covering one of our product candidates, the defendant could counterclaim that the patent covering our product candidate is invalid 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, written description or non-enablement. Grounds for an unenforceability assertion could be an allegation that someone connected with

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prosecution of the patent withheld information material to patentability from the USPTO, or made a misleading statement, during prosecution. Third parties also may raise similar claims before administrative bodies in the United States or abroad, even outside the context of litigation. Such mechanisms include re-examination, post grant review, *inter partes* review and equivalent proceedings in foreign jurisdictions. Such proceedings could result in the revocation or cancellation of or amendment to our patents in such a way that they no longer cover our product candidates. The outcome following legal assertions of invalidity and unenforceability is unpredictable. With respect to the validity question, for example, we cannot be certain that there is no invalidating prior art, of which the patent examiner and we or our licensing partners were unaware during prosecution. If a defendant were to prevail on a legal assertion of invalidity or unenforceability, we could lose at least part, and perhaps all, of the patent protection on one or more of our product candidates. Such a loss of patent protection could have a material adverse impact on our business.

In addition to the protection afforded by patents, we rely on trade secret protection and confidentiality agreements to protect proprietary know-how that is not patentable or that we elect not to patent, processes for which patents are difficult to enforce and any other elements of our product candidate discovery and development processes that involve proprietary know-how, information or technology that is not covered by patents. However, trade secrets can be difficult to protect and some courts inside and outside the United States are less willing or unwilling to protect trade secrets. We seek to protect our proprietary technology and processes, in part, by entering into confidentiality agreements with our employees, consultants, scientific advisors and contractors. We cannot guarantee that we have entered into such agreements with each party that may have or have had access to our trade secrets or proprietary technology and processes. We also seek to preserve the integrity and confidentiality of our data and trade secrets by maintaining physical security of our premises and physical and electronic security of our information technology systems. While we have confidence in these individuals, organizations and systems, agreements or security measures may be breached, and we may not have adequate remedies for any breach. In addition, our trade secrets may otherwise become known or be independently discovered by competitors.

***Third parties may initiate legal proceedings alleging that we are infringing 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 the proprietary rights and intellectual property of third parties. The biotechnology and pharmaceutical industries are characterized by extensive and complex litigation regarding patents and other intellectual property rights. We may in the future become party to, or be threatened with, adversarial proceedings or litigation regarding intellectual property rights with respect to our product candidates and technology, including interference proceedings, post grant review and *inter partes* review before the USPTO. Third parties may assert infringement claims against us based on existing patents or patents that may be granted in the future, regardless of their merit. We are aware of certain third party patents relating to gene delivery to ocular cells and certain vector manufacturing methods that may relate to, and potentially could be asserted to encompass, SPK-RPE65, SPK-CHM and our SPK-FIX program. There is a risk that third parties may choose to engage in litigation with us to enforce or to otherwise assert their patent rights against us. Even if we believe such claims are without merit, a court of competent jurisdiction could hold that these third-party patents are valid, enforceable and infringed, which could materially and adversely affect our ability to commercialize SPK-RPE65, SPK-CHM, SPK-FIX product candidates or any other of our product candidates or technologies covered by the asserted third-party patents. In order to successfully challenge the validity of any such U.S. patent in federal court, we would need to overcome a presumption of validity. As this burden is a high one requiring us to present clear and convincing evidence as to the invalidity of any such U.S. patent claim, there is no assurance that a court of competent

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jurisdiction would invalidate the claims of any such U.S. patent. If we are found to infringe a third party's valid and enforceable intellectual property rights, we could be required to obtain a license from such third party to continue developing, manufacturing and marketing our product candidates and technology. 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 it 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 candidates. In addition, we could be found liable for monetary damages, including treble damages and attorneys' fees, if we are found to have willfully infringed a patent or other intellectual property right. A finding of infringement could prevent us from manufacturing and commercializing our product candidates or force us to cease some of our business operations, which could materially harm our business. Claims that we have misappropriated the confidential information or trade secrets of third parties could have a similar negative impact on our business, financial condition, results of operations and prospects.

### ***Intellectual property litigation could cause us to spend substantial resources and distract our personnel from their normal responsibilities.***

Competitors may infringe our patents or the patents of our licensing partners, or we may be required to defend against claims of infringement. To counter infringement or unauthorized use claims or to defend against claims of infringement can be expensive and time consuming. 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 adequately conduct such litigation or proceedings. 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 more mature and developed intellectual property portfolios. Uncertainties resulting from the initiation and continuation of patent litigation or other proceedings could have a material adverse effect on our ability to compete in the marketplace.

### ***We may be subject to claims asserting that our employees, consultants or advisors have wrongfully used or disclosed alleged trade secrets of their current or former employers or claims asserting ownership of what we regard as our own intellectual property.***

Many of our employees, consultants or advisors are currently, or were previously, employed at universities or other biotechnology or pharmaceutical companies, including our competitors or potential competitors. Although we try to ensure that our employees, consultants and advisors 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. If we fail in defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights or personnel. Even if we are successful in defending against such claims, litigation could result in substantial costs and be a distraction to management.

In addition, while it is our policy to require our employees and contractors who may be involved in the conception or 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, conceives or develops intellectual

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property that we regard as our own. The assignment of intellectual property rights may not be self-executing or the assignment agreements may be breached, and we may be forced to bring claims against third parties, or defend claims that they may bring against us, to determine the ownership of what we regard as our intellectual property.

***Changes in U.S. patent law could diminish the value of patents in general, thereby impairing our ability to protect our products.***

Recent patent reform legislation could increase the uncertainties and costs surrounding the prosecution of patent applications and the enforcement or defense of issued patents. On September 16, 2011, the Leahy-Smith America Invents Act, or the Leahy-Smith Act, was signed into law. The Leahy-Smith Act includes several significant changes to U.S. patent law. These include provisions that affect the way patent applications are prosecuted and also may affect patent litigation. These also include provisions that switched the United States from a first-to-invent system to a first-to-file system, allow third-party submission of prior art to the USPTO during patent prosecution and set forth additional procedures to attack the validity of a patent by the USPTO administered post grant proceedings. Under a first-to-file system, assuming the other requirements for patentability are met, the first inventor to file a patent application generally will be entitled to the patent on an invention regardless of whether another inventor had made the invention earlier. The USPTO recently developed new regulations and procedures to govern administration of the Leahy-Smith Act, and many of the substantive changes to patent law associated with the Leahy-Smith Act, and in particular, the first to file provisions, only became effective on March 16, 2013. Accordingly, it is not clear what, if any, impact the Leahy-Smith Act will have on the operation of our business. However, the Leahy-Smith Act and its implementation could increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our issued patents, all of which could have a material adverse effect on our business, financial condition, results of operations and prospects.

The patent positions of companies engaged in the development and commercialization of biologics and pharmaceuticals are particularly uncertain. Two cases involving diagnostic method claims and gene patents have recently been decided by the Supreme Court of the United States, or Supreme Court. On March 20, 2012, the Supreme Court issued a decision in *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, or *Prometheus*, a case involving patent claims directed to a process of measuring a metabolic product in a patient to optimize a drug dosage for the patient. According to the Supreme Court, the addition of well-understood, routine or conventional activity such as administering or determining steps was not enough to transform an otherwise patent-ineligible natural phenomenon into patent-eligible subject matter. On July 3, 2012, the USPTO issued a guidance memo to patent examiners indicating that process claims directed to a law of nature, a natural phenomenon or a naturally occurring relation or correlation that do not include additional elements or steps that integrate the natural principle into the claimed invention such that the natural principle is practically applied and the claim amounts to significantly more than the natural principle itself should be rejected as directed to not patent-eligible subject matter. On June 13, 2013, the Supreme Court issued its decision in *Association for Molecular Pathology v. Myriad Genetics, Inc.*, or *Myriad*, a case involving patent claims held by Myriad Genetics, Inc. relating to the breast cancer susceptibility genes BRCA1 and BRCA2. Myriad held that an isolated segment of naturally occurring DNA, such as the DNA constituting the BRCA1 and BRCA2 genes, is not patent eligible subject matter, but that complementary DNA, which is an artificial construct that may be created from RNA transcripts of genes, may be patent eligible.

On March 4, 2014, the USPTO issued a guidance memorandum to patent examiners entitled 2014 Procedure For Subject Matter Eligibility Analysis Of Claims Reciting Or Involving Laws Of Nature/Natural Principles, Natural Phenomena, And/Or Natural Products. These guidelines instruct USPTO examiners on the ramifications of the *Prometheus* and *Myriad* rulings and apply the *Myriad* ruling to natural products and principles including all naturally occurring nucleic acids. Patents for certain of our product candidates contain claims related to

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specific DNA sequences that are naturally occurring and, therefore, could be the subject of future challenges made by third parties. In addition, the recent USPTO guidance could make it impossible for us to pursue similar patent claims in patent applications we may prosecute in the future.

We cannot assure you that our efforts to seek patent protection for our technology and products will not be negatively impacted by the decisions described above, rulings in other cases or changes in guidance or procedures issued by the USPTO. We cannot fully predict what impact the Supreme Court's decisions in Prometheus and Myriad may have on the ability of life science companies to obtain or enforce patents relating to their products and technologies in the future. These decisions, the guidance issued by the USPTO and rulings in other cases or changes in USPTO guidance or procedures could have a material adverse effect on our existing patent portfolio and our ability to protect and enforce our intellectual property in the future.

Moreover, although the Supreme Court has held in Myriad that isolated segments of naturally occurring DNA are not patent-eligible subject matter, certain third parties could allege that activities that we may undertake infringe other gene-related patent claims, and we may deem it necessary to defend ourselves against these claims by asserting non-infringement and/or invalidity positions, or paying to obtain a license to these claims. In any of the foregoing or in other situations involving third-party intellectual property rights, if we are unsuccessful in defending against claims of patent infringement, we could be forced to pay damages or be subjected to an injunction that would prevent us from utilizing the patented subject matter. Such outcomes could harm our business, financial condition, results of operations or prospects.

***If we do not obtain patent term extension and data exclusivity for our product candidates, our business may be materially harmed.***

Depending upon the timing, duration and specifics of any FDA marketing approval of our product candidates, one or more of our U.S. patents may be eligible for limited patent term extension under the Drug Price Competition and Patent Term Restoration Act of 1984, or Hatch-Waxman Amendments. The Hatch-Waxman Amendments permit a patent extension term of up to five years as compensation for patent term lost during the FDA regulatory review process. A patent term extension cannot extend the remaining term of a patent beyond a total of 14 years from the date of product approval, only one patent 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. However, we may not be granted an extension 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 applicable time period or the scope of patent protection afforded could be less than we request. If we are unable to obtain patent term extension or the term of any such extension is less than we request, our competitors may obtain approval of competing products following our patent expiration, and our revenue could be reduced, possibly materially.

***If our trademarks and trade names are not adequately protected, then we may not be able to build name recognition in our markets of interest and our business may be adversely affected.***

We have pending trademark applications with the USPTO for the mark SPARK and the Spark logo, approval of which is not guaranteed. Once registered, our trademarks or trade names may be challenged, infringed, circumvented or declared generic or determined to be infringing on other marks. We may not be able to protect our rights to these trademarks and trade names, which we need to build name recognition among potential partners or customers in our markets of interest. At times, competitors may adopt trade names or trademarks similar to ours, thereby impeding our ability to build brand identity and possibly leading to market confusion. In addition, there could be potential trade name or trademark infringement claims brought by owners of other registered trademarks or trademarks that incorporate variations of our registered or unregistered trademarks

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or trade names. Over the long term, if we are unable to establish name recognition based on our trademarks and trade names, then we may not be able to compete effectively and our business may be adversely affected. Our efforts to enforce or protect our proprietary rights related to trademarks, trade secrets, domain names, copyrights or other intellectual property may be ineffective and could result in substantial costs and diversion of resources and could adversely impact our financial condition or results of operations.

*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:

others may be able to make gene therapy products that are similar to our product candidates but that are not covered by the claims of the patents 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 make the inventions covered by the issued patent or pending patent application 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 licensed intellectual property rights;

it is possible that our pending licensed patent applications or those that we may own 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 may not develop additional proprietary technologies that are patentable;

the patents of others may have an adverse effect on our business; and

we may choose not to file a patent for 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 significantly harm our business, financial condition, results of operations and prospects.

## **Risks related to this offering and ownership of our common stock**

*After this offering, our executive officers, directors and principal stockholders will maintain the ability to control all matters submitted to stockholders for approval.*

## Edgar Filing: Spark Therapeutics, Inc. - Form S-1/A

Assuming the sale by us of 6,500,000 shares of common stock in this offering (or 7,475,000 shares if the underwriters exercise their option to purchase additional shares in full), our executive officers, directors and stockholders who owned more than 5% of our outstanding common stock before this offering will, in the

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aggregate, beneficially own shares representing approximately 71.5% of our capital stock (or 70.7% if the underwriters exercise their option to purchase additional shares in full). As a result, if these stockholders were 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 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 voting power could delay or prevent an acquisition of our company on terms that other stockholders may desire or result in management of our company that our public stockholders disagree with.

Our principal stockholders have indicated an interest in purchasing an aggregate of up to approximately \$15 million in shares of our common stock in this offering at the initial public offering price. However, because indications of interest are not binding agreements or commitments to purchase, these stockholders may determine to purchase fewer shares than they indicate an interest in purchasing or not to purchase in this offering. It also is possible that these stockholders could indicate an interest in purchasing more shares of our common stock. In addition, the underwriters could determine to sell fewer shares to any of these stockholders than the stockholders indicate an interest in purchasing or not to sell any shares to these stockholders. Accordingly, the foregoing discussion does not reflect any purchases by these potential purchasers.

***A significant portion of our total outstanding shares are restricted from immediate resale but may 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 performing well.***

Sales of a substantial number of shares of our common stock in the public market could occur at any time, subject to certain restrictions described below. These sales, or the perception in the market that 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 outstanding 22,990,367 shares of common stock based on the number of shares outstanding as of January 15, 2015 assuming the conversion of our preferred stock, including shares of preferred stock that are issuable as accrued dividends, assuming the closing of this offering occurs on February 4, 2015 (or 23,965,367 shares if the underwriters exercise their option to purchase additional shares in full). This includes the 6,500,000 shares that we are selling in this offering (or 7,475,000 shares if the underwriters exercise their option to purchase additional shares in full), which may be resold in the public market immediately without restriction, unless purchased by our affiliates. The remaining 16,490,367 shares currently are restricted as a result of securities laws or lock-up agreements but will be able to be sold after the offering as described in the Shares eligible for future sale and Underwriting sections of this prospectus. Moreover, after this offering, holders of an aggregate of approximately 10,200,050 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. We 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 Underwriting section of this prospectus.

***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 will be substantially higher than the 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 net tangible book value per share after this offering. To the extent outstanding options are exercised, you will incur further dilution. Based on an assumed initial public offering price of \$20.00 per share, which is the midpoint of the price range set forth on the cover page of this prospectus, you will experience immediate dilution of \$12.14 per share, representing the difference between our pro forma net tangible book value per share after giving effect to this offering at the assumed initial public offering price. In addition, purchasers of common stock in this offering will have contributed approximately 48% of the aggregate price paid by all purchasers of our stock but will own only approximately



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28% of our common stock outstanding after this offering (or 52% and 31%, respectively, if the underwriters exercise their option to purchase additional shares in full), excluding any shares they may have acquired prior to this offering. See Dilution.

*If securities analysts do not publish research or reports about our business or if they publish negative evaluations of our stock, the price 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, 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 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 biopharmaceutical companies in particular, has 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 clinical trials of our product candidates or those of our competitors;

the success of competitive products or technologies;

commencement or termination of collaborations;

regulatory or legal developments in the United States and other countries;

developments or disputes concerning patent applications, issued patents or other 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 additional product candidates;

actual or anticipated changes in estimates as to financial results, development timelines or recommendations by securities analysts;

variations in our financial results or those 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.

If our quarterly operating results fall below the expectations of investors or securities analysts, the price of our common stock could decline substantially. Furthermore, any quarterly fluctuations in our operating results may, in turn, cause the price of our stock to fluctuate substantially. We believe that quarterly comparisons of our financial results are not necessarily meaningful and should not be relied upon as an indication of our future performance.

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In the past, following periods of volatility in the market price of a company's securities, securities class-action litigation often has been instituted against that company. Such litigation, if instituted against us, could cause us to incur substantial costs to defend such claims and divert management's attention and resources, which could seriously harm our business, financial condition, results of operations and prospects.

### ***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 will be determined through negotiations with the underwriters. Although we have been approved to have our common stock listed on The NASDAQ Global Select 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.

### ***We have broad discretion in the use of our cash and cash equivalents, including the net proceeds from this offering, and may not use them effectively.***

Our management will have broad discretion in the application of our cash and cash equivalents, including 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 have a material adverse effect on our business, cause the price of our common stock to decline and delay the development of our product candidates. Pending their use, we may invest our cash and cash equivalents, including the net proceeds from this offering, in a manner that does not produce income or that loses value. See "Use of proceeds."

### ***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 JOBS Act. We will remain an EGC until the earlier of: (i) the last day of the fiscal year in which we have total annual gross revenues of \$1 billion or more; (ii) the last day of the fiscal year following the fifth anniversary of the date of the completion of this offering; (iii) the date on which we have issued more than \$1 billion in nonconvertible debt during the previous three years; or (iv) the date on which we are deemed to be a large accelerated filer under the rules of the Securities and Exchange Commission or SEC, which means the first day of the year following the first year in which the market value of our common stock that is held by non-affiliates exceeds \$700 million as of June 30. 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 emerging growth companies. These exemptions include:

not being required to comply with the auditor attestation requirements of Section 404 of the Sarbanes-Oxley Act of 2002;

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 shareholder approval of any golden parachute payments not previously approved.

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We may choose to take advantage of some, but not all, of the available exemptions. We have taken advantage of reduced reporting burdens in this prospectus. In particular, we have not included all of the executive compensation 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 certain or all of 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 provides that an EGC may 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 irrevocably elected not to avail ourselves of this exemption from new or revised accounting standards and, therefore, we will be subject to the same new or revised accounting standards as other public companies that are not emerging growth companies.

***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.***

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. In addition, the Sarbanes-Oxley Act of 2002 and rules subsequently implemented by the SEC and NASDAQ have imposed 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 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. Overall, we estimate that our incremental costs resulting from operating as a public company may be between \$1.0 million and \$3.0 million per year.

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, including an attestation report on internal control over financial reporting issued by our independent registered public accounting firm. 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, 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 neither we nor our independent registered public accounting firm will be able to conclude within the prescribed timeframe that our internal control over financial reporting is effective as required by Section 404. This could result in an adverse reaction in the financial markets due to a loss of confidence in the reliability of our financial statements.

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

Provisions in our corporate charter 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 us that stockholders may

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consider favorable, including transactions in which you might otherwise receive a premium for your shares. These provisions also could 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 not all members of the board are elected at one time;

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 the board;

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 shareholder rights plan, or so-called 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 certain provisions of our charter or bylaws.

Moreover, because we are incorporated in Delaware, we are governed by the provisions of Section 203 of the Delaware General Corporation Law, 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.

***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. In addition, the terms of any future debt agreements may preclude us from paying dividends. As a result, capital appreciation, if any, of our common stock will be your sole source of gain for the foreseeable future.

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## **Special note regarding forward-looking statements**

This prospectus contains forward-looking statements. All statements other than statements of historical facts contained in this prospectus, including statements regarding our future results of operations and financial position, business strategy and plans and objectives of management for future operations, are forward-looking statements. These statements involve known and unknown risks, uncertainties and other important factors that may cause our actual results, performance or achievements to be materially different from any future results, performance or achievements expressed or implied by the forward-looking statements.

The words may, will, should, expects, plans, anticipates, could, intends, target, projects, contemplates, believes, estim or the negative of these terms or other 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:

the timing, progress and results of clinical trials for SPK-RPE65, SPK-CHM, SPK-FIX product candidates and our other product candidates, including statements regarding the timing of initiation and completion of clinical trials, dosing of subjects and the period during which the results of the trials will become available;

the timing, scope or likelihood of regulatory filings and approvals, including timing of our BLA filing for, and final FDA approval of, SPK-RPE65;

our estimates regarding the potential market opportunity for SPK-RPE65, SPK-CHM and SPK-FIX product candidates;

the initiation, timing, progress and results of future preclinical studies and clinical trials, and our research and development programs for our other product candidates;

our ability to achieve milestones and receive payments under our collaborations;

our plans to develop and commercialize our product candidates;

our commercialization, marketing and manufacturing capabilities and strategy;

the implementation of our business model, strategic plans for our business, product candidates and technology;

the scalability and commercial viability of our proprietary manufacturing methods;

the rate and degree of market acceptance and clinical utility of our product candidates, in particular, and gene therapy in general;

our competitive position;

our intellectual property position;

developments and projections relating to our competitors and our industry;

our ability to maintain and establish collaborations or obtain additional funding;

our expectations related to the use of proceeds from this offering;

our estimates regarding expenses, future revenue, capital requirements and needs for additional financing;

the impact of government laws and regulations; and

our expectations regarding the time during which we will be an EGC under the JOBS Act.

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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 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, joint ventures or investments that we may make.

You should read this prospectus, the documents that we reference in this prospectus and the documents that we 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. 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 law.



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## **Use of proceeds**

We estimate that the net proceeds to us of the sale of the common stock that we are offering will be approximately \$117.9 million, assuming an initial public offering price of \$20.00 per share, which is the midpoint of the range listed on the cover page of this prospectus, and after deducting the estimated underwriting discounts and commissions and estimated offering expenses payable by us. If the underwriters exercise their option to purchase additional shares in full, we estimate that our net proceeds will be approximately \$136.0 million.

A \$1.00 increase (decrease) in the assumed initial public offering price of \$20.00 per share would increase (decrease) the net proceeds to us from this offering by approximately \$6.0 million, assuming the number of shares offered by us, as set forth on the cover page of this prospectus, remains the same and after deducting estimated underwriting discounts and commissions and estimated offering expenses payable by us.

As of September 30, 2014, we had cash and cash equivalents of \$67.3 million. We intend to use the net proceeds from this offering as follows:

approximately \$11.0 million to fund external research and development expenses for our lead product candidate SPK-RPE65 for the treatment of inherited retinal dystrophies caused by RPE65 mutations;

approximately \$8.0 million to fund external research and development expenses for our product candidate SPK-CHM for the treatment of choroideremia;

approximately \$5.0 million to fund external research and development expenses for our SPK-FIX program for the treatment of hemophilia B;

approximately \$14.0 million to fund external research and development expenses for preclinical product candidates; and

the remainder for working capital, general and administrative expenses, internal research and development expenses and other general corporate purposes, including pre-commercial activities, in-licenses and potential acquisitions.

We believe opportunities may exist from time to time to expand our current business through acquisitions or in-licenses of complementary products or technologies or acquisitions of companies with complementary products or technologies. While we have no current agreements, commitments or understandings for any specific acquisitions or in-licenses at this time, we may use a portion of the net proceeds for these purposes.

This expected use of net proceeds from this offering 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, the status of, and results from, clinical trials, the potential need to conduct additional clinical trials to obtain approval of our product candidates for all intended indications, as well as any additional 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 and our existing cash and cash equivalents, along with the \$20.0 million upfront payment received under the Pfizer collaboration, we estimate that such funds will be sufficient to enable us to complete the submission of a BLA and prepare for commercialization of SPK-RPE65, complete our Phase 1/2 trial for SPK-CHM, complete our planned Phase 1/2 trial for our lead SPK-FIX product candidate in collaboration with Pfizer, advance certain of our other pipeline product

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candidates and fund our operating expenses and capital expenditure requirements into late 2017. The foregoing estimate does not contemplate the receipt of any milestone payments under our collaboration with Pfizer. Moreover, we have based this estimate on assumptions that may prove to be wrong, and we could use our available capital resources sooner than we currently expect.

Pending use of the proceeds as described above, we intend to invest the proceeds in short-term, interest-bearing, investment-grade securities.

## **Dividend policy**

We have not declared or paid any cash dividends on our capital stock since our inception. We intend to retain future earnings, if any, to finance the operation and expansion of our business and do not anticipate paying any cash dividends in the foreseeable future.

## **Industry and other data**

We obtained the industry, market and competitive position data contained in this prospectus from our own internal estimates and research as well as from industry publications and research, surveys and studies conducted by third parties. Industry publications, studies and surveys generally state that they have been obtained from sources believed to be reliable, although they do not guarantee the accuracy or completeness of such information.

Table of Contents**Capitalization**

The following table sets forth our cash and cash equivalents and capitalization as of September 30, 2014, as follows:

on an actual basis;

on a pro forma basis to reflect (1) the issuance of 200,000 shares of restricted stock that are subject to certain milestone-based vesting conditions and were issued to Penn in connection with entry into our license agreement in December 2014; (2) the automatic conversion of all outstanding shares of our preferred stock, including shares of our preferred stock issuable as accrued stock dividends, into 10,200,050 shares of common stock upon the closing of this offering, assuming the closing occurs on February 4, 2015; and (3) the filing of our restated certificate of incorporation as of the closing date of this offering; and

on a pro forma as adjusted basis to give further effect to our issuance and sale of 6,500,000 shares of common stock in this offering (assuming no exercise by the underwriters of the option to purchase additional shares) at an assumed initial public offering price of \$20.00 per share, the midpoint of the price range listed on the cover page of this prospectus, after deducting the estimated underwriting discounts and commissions and estimated offering expenses payable by us.

Our capitalization following the closing of this offering will be adjusted based on the actual initial public offering price and other terms of the offering determined at pricing. You should read the information in this Capitalization section in conjunction with our 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 and other financial information contained in this prospectus.

	As of September 30, 2014		
	Actual	Pro forma (unaudited)	Pro forma as adjusted
	(in thousands, except share and per share data)		
Cash and cash equivalents	\$ 67,273	\$ 67,273	\$ 185,446
Series A preferred stock, par value \$0.001 per share; 5,000,000 shares authorized, issued and outstanding, actual; no shares authorized, issued or outstanding, pro forma and pro forma as adjusted	\$ 10,000	\$	\$
Series B preferred stock, par value \$0.001 per share; 45,186,334 shares authorized, issued and outstanding, actual; no shares authorized, issued or outstanding, pro forma and pro forma as adjusted	72,437		
Preferred Stock, \$0.001 par value per share; 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, par value \$0.001 per share; 95,700,000 shares authorized, 6,090,317 shares issued and outstanding, actual; 150,000,000 shares authorized, pro forma and pro forma as adjusted; 16,490,367 shares issued and outstanding, pro forma; 22,990,367 shares issued and outstanding pro forma as adjusted	6	16	23
Additional paid-in capital	52,869	135,296	253,189
Accumulated deficit	(72,587)	(72,587)	(72,587)
Total stockholders' equity	62,725	62,725	180,625
Total capitalization	\$ 62,725	\$ 62,725	\$ 180,625



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A \$1.00 increase (decrease) in the assumed initial public offering price of \$20.00 per share, which is the midpoint of the range listed on the cover page of this prospectus, would increase (decrease) the pro forma as adjusted amount of each of cash and cash equivalents, additional paid-in capital, total stockholders' equity and total capitalization by approximately \$6.0 million, assuming that the number of shares offered by us, as set forth on the cover page of this prospectus, remains the same and after deducting estimated underwriting discounts and commissions and estimated offering expenses payable by us.

The table above does not include:

1,732,995 shares of common stock issuable upon exercise of stock options outstanding as of September 30, 2014 at an exercise price of \$3.45 per share;

741,003 shares of common stock reserved as of September 30, 2014 for future issuance under our 2014 company equity incentive plan;

1,830,000 additional shares of common stock that will be available for future issuance, as of the effectiveness of the registration statement for this offering, under our 2015 stock incentive plan, of which we expect to grant options to purchase an aggregate of 146,000 shares to our recently appointed director and certain recently hired employees upon the commencement of trading of our common stock on the NASDAQ Global Select Market;

220,000 additional shares of common stock that will be available for future issuance as of the closing of this offering under our 2015 employee stock purchase plan; and

changes to our cash and cash equivalents after September 30, 2014, including receipt of the \$20.0 million upfront payment under the Pfizer collaboration.

The number of shares of common stock issuable upon the automatic conversion of the outstanding shares of our preferred stock will increase as a result of the issuance of additional shares of preferred stock accrued as stock dividends at a rate of 8% per annum during the period from November 23, 2014 through the date of the closing of this offering. For each day occurring between February 4, 2015 and the date of the closing of this offering, the number of shares of common stock issuable upon the automatic conversion of the outstanding shares of our preferred stock will increase by approximately 2,200 shares.

**Table of Contents****Dilution**

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

Our net tangible book value as of September 30, 2014 was approximately \$62.7 million, or \$10.30 per share of common stock. Our net tangible book value is the amount of our total tangible assets less our total liabilities. Net historical tangible book value per share is our net tangible book value divided by the number of shares of common stock outstanding as of September 30, 2014.

Our pro forma net tangible book value as of September 30, 2014 was \$62.7 million, or \$3.80 per share of our common stock. Pro forma net tangible book value per share represents our total tangible assets reduced by the amount of our total liabilities, divided by the total number of shares of our common stock outstanding after giving effect to the automatic conversion of all outstanding shares of our preferred stock, including shares of our preferred stock issuable as accrued stock dividends, upon the closing of this offering, assuming the closing occurs on February 4, 2015, as well as our issuance of 200,000 shares of restricted stock in December 2014.

After giving effect to the sale of 6,500,000 shares of common stock that we are offering at an assumed initial public offering price of \$20.00 per share, which is the midpoint of the range listed on the cover page of this prospectus, and after deducting the estimated underwriting discounts and commissions and estimated offering expenses payable by us, our pro forma as adjusted net tangible book value as of September 30, 2014 would have been approximately \$180.6 million, or approximately \$7.86 per share. This amount represents an immediate increase in pro forma net tangible book value of \$4.06 per share to our existing stockholders and an immediate dilution in pro forma net tangible book value of approximately \$12.14 per share to new investors purchasing shares of common stock in this offering. We determine dilution by subtracting the pro forma, as adjusted net tangible book value per share after this offering from the amount of cash that a new investor paid for a share of common stock. The following table illustrates this dilution:

Assumed initial public offering price per share		\$ 20.00
Net tangible book value per share as of September 30, 2014		\$ 10.30
Pro forma decrease in net tangible book value per share as of September 30, 2014 attributable to the conversion of outstanding preferred stock, including shares issued as accrued dividends, as well as shares issued in December 2014	6.50	
Pro forma net tangible book value per share as of September 30, 2014 before giving effect to this offering		3.80
Increase per share attributable to new investors		4.06
Pro forma as adjusted net tangible book value per share after this offering		7.86
Dilution per share to new investors		\$ 12.14

A \$1.00 increase (decrease) in the assumed initial public offering price of \$20.00 per share, which is the midpoint of the range listed on the cover page of this prospectus, would increase (decrease) the pro forma as adjusted net tangible book value per share after this offering by approximately \$0.26, and dilution in pro forma net tangible book value per share to new investors by approximately \$0.74, assuming that the number of shares offered by us, as set forth on the cover page of this prospectus, remains the same and after deducting estimated 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 in this offering, the pro forma as adjusted net tangible book value after the offering would be \$8.29 per share, the increase in pro forma net tangible book value per share to existing stockholders would be \$4.49 and the

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dilution to new investors would be \$11.71 per share, in each case assuming an initial public offering price of \$20.00 per share, which is the midpoint of the range listed on the cover page of this prospectus.

The following table summarizes, on a pro forma basis as of September 30, 2014, the differences between the number of shares purchased from us, the value of the total consideration paid to us in cash or other consideration and the average price per share that existing stockholders and new investors paid. The calculation below is based on an assumed initial public offering price of \$20.00 per share, which is the midpoint of the range listed on the cover page of this prospectus, before deducting the estimated underwriting discounts and commissions and estimated offering expenses payable by us.

	Shares purchased		Total consideration		Average price per share
	Number	Percent	Amount	Percent	
Existing stockholders	16,490,367	71.7%	\$ 138,530,251	51.6%	\$ 8.40
New investors	6,500,000	28.3	130,000,000	48.4	\$ 20.00
<b>Total</b>	<b>22,990,367</b>	<b>100%</b>	<b>268,530,251</b>	<b>100%</b>	

A \$1.00 increase (decrease) in the assumed initial public offering price of \$20.00 per share, which is the midpoint of the range listed on the cover page of this prospectus, would increase (decrease) the total consideration paid by new investors by \$6.5 million, and increase (decrease) the percentage of total consideration paid by new investors by approximately 1.2%, assuming that the number of shares offered by us, as set forth on the cover page of this prospectus, remains the same and before deducting estimated underwriting discounts and commissions and estimated offering expenses payable by us.

The foregoing tables and calculations are based on the number of shares of our common stock outstanding as of September 30, 2014 after giving effect to the automatic conversion of all outstanding shares of our preferred stock upon the closing of this offering, assuming the closing of this offering occurred on September 30, 2014, as well as our issuance of 200,000 shares of restricted stock in December 2014, and excludes:

1,732,995 shares of common stock issuable upon exercise of stock options outstanding as of September 30, 2014 at an average exercise price of \$3.45 per share;

741,003 shares of common stock reserved as of September 30, 2014 for future issuance under our 2014 equity incentive plan; and

changes to our cash and cash equivalents after September 30, 2014, including receipt of the \$20.0 million upfront payment under the Pfizer collaboration.

To the extent any of these outstanding options are exercised, there will be further dilution to new investors. To the extent all of such outstanding options had been exercised as of September 30, 2014, the pro forma as adjusted net tangible book value per share after this offering would be \$7.55, and total dilution per share to new investors would be \$12.45.

For purposes of the foregoing tables and calculations, the number of shares of common stock issuable upon the automatic conversion of the outstanding shares of our preferred stock is based on an assumed closing date for this offering of February 4, 2015. The number of shares of common stock issuable upon the automatic conversion of the outstanding shares of our preferred stock will continue to increase if the closing occurs after February 4, 2015 as a result of the issuance of additional shares of preferred stock accruing as preferred stock dividends at a rate of 8% per annum. For each day occurring between February 4, 2015 and the closing of this offering, if any, the number of shares of common stock issuable upon the automatic conversion of the outstanding shares of our preferred stock will increase by approximately 2,200 shares. To the extent the





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number of shares of preferred stock that are issued as a result of the accrual of stock dividends increases as a result of the passage of time between February 4, 2015 and the date of the closing of this offering, and the number of shares of common stock issuable upon the automatic conversion of the outstanding shares of our preferred stock similarly increases, there will be further dilution to new investors.

If the underwriters exercise their option to purchase additional shares in full:

the percentage of shares of common stock held by existing stockholders will decrease to approximately 68.8% of the total number of shares of our common stock outstanding after this offering; and

the number of shares held by new investors will increase to 7,475,000, or approximately 31.2% of the total number of shares of our common stock outstanding after this offering.

Effective immediately upon closing of this offering, an aggregate of 2,039,500 shares of our common stock will be reserved for issuance under our 2015 stock incentive plan and 220,000 shares of our common stock will be reserved for issuance under our 2015 employee stock purchase plan, and these share reserves will also be subject to automatic annual increases in accordance with the terms of the plans. Furthermore, we may choose to raise additional capital through the sale of equity or equity-linked securities due to market conditions or strategic considerations even if we believe we have sufficient funds for our current or future operating plans. To the extent that new equity awards are issued under our equity incentive plans or we issue additional shares of common stock or other equity or equity-linked securities in the future, there will be further dilution to investors participating in this offering.

Our principal stockholders have indicated an interest in purchasing an aggregate of up to approximately \$15 million in shares of our common stock in this offering at the initial public offering price. However, because indications of interest are not binding agreements or commitments to purchase, these stockholders may determine to purchase fewer shares than they indicate an interest in purchasing or not to purchase any shares in this offering. It also is possible that these stockholders could indicate an interest in purchasing more shares of our common stock. In addition, the underwriters could determine to sell fewer shares to any of these stockholders than the stockholders indicate an interest in purchasing or not to sell any shares to these stockholders. Accordingly, the foregoing discussion and tables do not reflect any potential purchases by these stockholders or their affiliated entities.

Table of Contents**Selected financial data**

You should read the following selected financial data in conjunction with Management's discussion and analysis of financial condition and results of operations and our financial statements and the related notes appearing elsewhere in this prospectus.

The statements of operations data for the period from March 13, 2013 (inception) to December 31, 2013 and the balance sheet data at December 31, 2013, are derived from our audited financial statements appearing elsewhere in this prospectus. The statements of operations data for the period from March 13, 2013 (inception) to September 30, 2013 and the nine months ended September 30, 2014 and the balance sheet data at September 30, 2014 are derived from our unaudited financial statements included in this prospectus. The unaudited financial statements include, in the opinion of management, all adjustments that management considers necessary for the fair presentation of the financial information set forth in those statements. Our historical results are not necessarily indicative of the results to be expected in any future period.

	Period from March 13, 2013 (inception) to December 31, 2013	Period from March 13, 2013 (inception) to September 30, 2013	Nine months ended September 30, 2014  (unaudited)
	(in thousands, except unit/share and per unit/share amounts)		
<b>Statements of Operations Data:</b>			
Revenues	\$	\$	\$ 20
Operating expenses:			
Research and development	4,897	2,968	10,169
Acquired in-process research and development	50,000		
General and administrative	2,381	661	5,162
Total operating expenses	57,278	3,629	15,331
Loss from operations	(57,278)	(3,629)	(15,311)
Interest income			2
Net loss	\$ (57,278)	\$ (3,629)	\$ (15,309)
Basic and diluted net loss per common unit/share(1)	\$ (8.44)(2)		\$ (2.87)
Weighted average basic and diluted common units/shares outstanding(1)	6,788,396 (2)		5,334,610
Unaudited pro forma net loss	\$ (57,278)		\$ (15,309)
Unaudited pro forma basic and diluted net loss per common share(1)	\$ (35.27)		\$ (1.44)
Unaudited pro forma weighted average basic and diluted common shares outstanding(1)	1,623,891		10,638,070

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- (1) See Note 3(f) to our audited financial statements and Note 3(i) to our unaudited financial statements included elsewhere in this prospectus for an explanation of the method used to calculate (a) basic and diluted net loss per common unit/share and weighted average basic and diluted common units/shares outstanding used to calculate the per common unit/share amounts and (b) unaudited pro forma net loss per common share and the unaudited pro forma weighted average basic and diluted common shares outstanding used to calculate the pro forma per common share amounts. The unaudited pro forma information for the nine-month period ended September 30, 2014 does not give effect to the issuance of any shares after such date.
  
- (2) Basic and diluted net loss per common unit and weighted average basic and diluted common units outstanding for the period from March 13, 2013 (inception) to December 31, 2013 do not give effect to the one-for-five reverse stock split that became effective on January 16, 2015 as only units of Spark LLC were outstanding during 2013 and the reverse split was not applicable to the units.

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	As of December 31, 2013	As of September 30, 2014 (unaudited) (in thousands)
<b>Balance Sheet Data:</b>		
Cash and cash equivalents	\$	\$ 67,273
Working capital	\$ 3,369	\$ 62,281
Total assets	\$ 4,861	\$ 80,914
Total preferred stock(1)	\$ 10,000	\$ 82,437
Total stockholders' equity	\$ 3,369	\$ 62,725

(1) The balance of total preferred stock is included in total stockholders' equity.

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## **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 our financial statements and related notes appearing in 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. See Special note regarding forward-looking statements.*

### **Overview**

We are a leader in the field of gene therapy, seeking to transform the lives of patients suffering from debilitating genetic diseases by developing one-time, life-altering treatments. The goal of gene therapy is to overcome the effects of a malfunctioning, disease-causing gene by delivering a normal, functional copy of the same gene. Our product candidates have the potential to provide long-lasting effects, dramatically and positively changing the lives of patients with conditions where no, or only palliative, therapies exist. Our initial focus is on treating orphan diseases, and we have demonstrated promising clinical outcomes with our first product candidate targeting rare blinding conditions, which has received both breakthrough therapy and orphan product designation. We also have built a pipeline of product candidates targeting rare blinding conditions, hematological disorders and neurodegenerative diseases, including a second product candidate targeting another rare blinding condition, for which we have initiated enrollment in a clinical trial, and a collaboration with Pfizer Inc., or Pfizer, for the development and commercialization of a gene therapy for the treatment of hemophilia B. Our platform technology is based on more than two decades of gene therapy research, development, manufacturing and clinical trials conducted at The Children's Hospital of Philadelphia, or CHOP.

Our most advanced product candidate, SPK-RPE65, which is in a pivotal Phase 3 clinical trial, targets a group of rare blinding conditions known as inherited retinal dystrophies, or IRDs, caused by non sex-linked, or autosomal recessive, mutations in the RPE65 gene. Patients suffering from RPE65-mediated IRDs are affected by a range of severe visual impairments, which ultimately lead to blindness, that make independent activities of daily living challenging. For example, affected children often depend on visual aids to carry out classroom activities while adults with these diseases may face diminished employment opportunities and may be stripped of some of the rewards of parenting, such as watching a child play his or her favorite sport. We estimate that there are approximately 3,500 individuals with RPE65-mediated IRDs in the United States and the five major European markets.

To date, results from our two Phase 1 clinical trials, along with reports from our clinical study team and other feedback regarding the subjects in the trial, suggest that SPK-RPE65 enables subjects to perform activities of daily living with greater independence than prior to treatment and has long-lasting effects in restoring functional vision, with subjects having been followed for a period of at least five years. Notably, as reported by our clinical study team, following a single injection of SPK-RPE65 in one eye, the children from our initial Phase 1 trial no longer depended on visual aids to carry out classroom activities and were able to walk and play like normally-sighted kids. Furthermore, inclusive of the subjects in our ongoing Phase 3 clinical trial, we have not observed any drug-related serious adverse events to date.

We are conducting a fully enrolled, pivotal Phase 3 clinical trial of SPK-RPE65 in which we have dosed all subjects in the treatment group and currently are collecting data. We anticipate reporting final results during

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the second half of 2015. If successful, we plan to submit a biologics license application, or BLA, to the U.S. Food and Drug Administration, or FDA, in 2016. SPK-RPE65 has the potential to be the first gene therapy approved in the United States for the treatment of a genetic disease and the first approved pharmacologic treatment for any IRD.

We believe that we have a significant competitive advantage in the field of gene therapy as a result of the collective experience of our scientific and management team and the advanced stage of development of our product candidates. Our scientists and scientific advisors have accumulated over 150 years of collective experience in the field of gene therapy, contributing key insights and significant developments that have coincided with a resurgence of interest in gene-based medicines. Our proprietary manufacturing processes produce consistent yields of highly pure and stable gene therapies, including both adeno-associated virus, or AAV, and lentiviral vectors. Our vectors are disabled viruses that carry genetic material into target cells, where they deliver a functional gene that allows production of a normal protein.

We are building a fully integrated gene therapy platform to accelerate the development of product candidates across multiple therapeutic areas. We engineered our initial product candidates using AAV vectors to efficiently enter target cells in different tissue types and deliver their gene payload.

We are pursuing other follow-on product candidates targeting other IRDs, including SPK-CHM for the treatment of choroideremia. We have initiated enrollment in a dose-escalating Phase 1/2 trial for SPK-CHM. We expect to begin dosing subjects in this trial in the first quarter of 2015.

We have established human proof-of-concept in using gene therapy to deliver and express a therapeutic gene in the liver as part of our SPK-FIX program for the treatment of hemophilia B, and we expect to initiate a Phase 1/2 clinical trial for our lead SPK-FIX product candidate in the first half of 2015. In December 2014, we entered into a global collaboration agreement with Pfizer for the development and commercialization of SPK-FIX product candidates for the treatment of hemophilia B. Under the terms of the agreement, we are entitled to a \$20.0 million upfront payment, and are eligible to receive up to \$260.0 million in aggregate milestone payments, as well as royalties calculated as a low-teen percentage of net product sales.

We have in-licensed extensive preclinical data and are developing several gene therapy programs targeting other hematologic disorders and neurodegenerative diseases.

We were formed as AAVenue Therapeutics, LLC, a Delaware limited liability company, on March 13, 2013. On October 14, 2013, we acquired or exclusively in-licensed the commercial and development rights to certain clinical and preclinical programs and intellectual property from CHOP and the University of Iowa Research Foundation, or UIRF, and in-licensed additional intellectual property from the University of Pennsylvania or Penn. On October 15, 2013, we changed our name to Spark Therapeutics, LLC. On May 2, 2014, we converted from a Delaware limited liability company into a Delaware corporation, pursuant to which we changed our name to Spark Therapeutics, Inc. Our operations to date have been focused on developing our product candidates, organizing and staffing our company, business planning and raising capital.

We have never been profitable and have incurred net losses since inception. Our net losses were \$72.6 million from inception through September 30, 2014, \$57.3 million from inception through December 31, 2013, \$3.6 million for the period from inception through September 30, 2013 and \$15.3 million for the nine months ended September 30, 2014. Substantially all of our net losses resulted from costs incurred in connection with our research and development programs and from general and administrative expenses associated with our operations. From inception through September 30, 2013, we incurred approximately \$3.0 million of research and development expenses and approximately \$0.7 million of general and administrative expenses. From inception through September 30, 2014, we incurred approximately \$15.1 million of research and development expenses, \$50.0 million of acquired in-process research and development expense and approximately \$7.5 million of general and administrative expenses.

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We expect to incur losses for the foreseeable future, and we expect these losses to increase as we continue our development of, and seek regulatory approvals for, our product candidates, hire additional personnel and initiate commercialization of any approved products. Because of the numerous risks and uncertainties associated with product development, we are unable to predict the timing or amount of increased expenses or when, or if, we will be able to achieve or maintain profitability. Even if we are able to generate revenues from the sale of any commercial products, we may not become profitable. If we fail to become profitable, or are unable to sustain profitability on a continuing basis, then we may be unable to continue our operations at planned levels and be forced to reduce our operations.

Through September 30, 2014, we have received aggregate net proceeds of \$82.4 million from sales of our equity securities.

## **Financial operations overview**

### ***Revenue***

To date, we have not generated any revenues from product sales.

In March 2014, we entered into a development and manufacturing collaboration with Genable Technologies Limited, or Genable, in which we will be the exclusive manufacturer and provide development advice and expertise in the ongoing development of Genable's lead therapeutic product candidate, RhoNova, to treat rhodopsin-linked autosomal dominant retinitis pigmentosa, or RHO-adRP. RHO-adRP is an IRD that is a genetic subtype of retinitis pigmentosa, or RP, that results in severe vision loss and often blindness. Under the collaboration, we granted Genable a license to certain AAV vector manufacturing patents and as consideration for the license grant and certain development consulting services we have agreed to provide Genable, we are eligible to earn development milestone payments and mid-single-digit royalties on any future product sales of RhoNova. We also entered into a manufacturing agreement with Genable under which we will receive payment for the manufacture and supply of RhoNova. During the nine months ended September 30, 2014, we recognized \$20,000 of revenue and \$0.4 million of current deferred revenue included on our balance sheet related to our collaboration with Genable.

In April 2014, we entered into discussions with a pharmaceutical company concerning a potential manufacturing technology collaboration. We received a one-time, nonrefundable payment of \$1.0 million for engaging in due diligence. The payment is creditable against any early milestone payment that may be negotiated as part of a definitive agreement for such collaboration. As of September 30, 2014, there is \$1.0 million of current deferred revenue included on our balance sheet related to this payment.

In December 2014, we entered into a global collaboration agreement with Pfizer for the development and commercialization of product candidates in our SPK-FIX program for the treatment of hemophilia B. Under this collaboration, we maintain responsibility for the clinical development of SPK-FIX product candidates through the completion of Phase 1/2 trials. Thereafter, Pfizer has responsibility for further clinical development, regulatory approvals and commercialization. In connection with entering into this agreement, we received a \$20.0 million upfront payment.

Our ability to generate product revenue and become profitable depends upon our ability to successfully commercialize products.

### ***Research and development expenses***

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

employee-related expenses, including salaries, benefits, travel and other compensation expenses;

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expenses incurred under our agreements with contract research organizations, or CROs, and clinical sites that will conduct our preclinical studies and clinical trials and the cost of clinical consultants;

costs associated with regulatory filings;

costs of laboratory supplies and the acquiring, developing and manufacturing of preclinical and clinical study materials; and

costs of facilities, depreciation and other expenses, which include direct and allocated expenses for rent and maintenance of facilities, insurance and other operating costs.

Research and development costs are expensed as incurred. Expenses for certain development activities are recognized based on an evaluation of the progress to completion of specific tasks using information and data provided by our vendors and our clinical sites.

From inception through September 30, 2014, we incurred \$15.1 million in research and development expenses. We plan to increase our research and development expenses for the foreseeable future as we continue development of our product candidates. Our current and planned research and development activities include the following:

completion of a pivotal Phase 3 clinical trial in the United States to evaluate the efficacy and safety of SPK-RPE65;

proposed regulatory submissions for SPK-RPE65;

a Phase 1/2 clinical trial for SPK-CHM;

clinical trials to evaluate the safety and efficacy of SPK-FIX product candidates, which are in development in collaboration with Pfizer;

research and development for additional product candidates addressing other IRDs;

research and development for our preclinical programs for hemophilia A and neurodegenerative diseases; and

continued acquisition and manufacture of clinical trial materials in support of our clinical trials.



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We do not allocate personnel-related costs, including stock-based compensation, costs associated with broad technology platform improvements or other indirect costs, to specific programs, as they are deployed across multiple projects under development and, as such, are separately classified as personnel and other related costs and other expenses in the table below. The following table summarizes our research and development expenses by product candidate or program for the period from inception to December 31, 2013 and for the nine months ended September 30, 2014:

	<b>Period from March 13, 2013 (inception) to December 31, 2013</b>	<b>Nine months ended September 30, 2014 (unaudited)</b>
	(in thousands)	
<b>External research and development expenses:</b>		
SPK-RPE65	\$ 4,038	\$ 3,693
SPK-CHM	230	155
SPK-FIX	255	1,597
Other product candidates	115	831
Total external research and development expenses	4,638	6,276
Total internal research and development expenses	259	3,893
Total research and development expenses	\$4,897	\$10,169

The successful development of our product candidates is highly uncertain and subject to numerous risks including, but not limited to:

the scope, rate of progress and expense of our research and development activities;

clinical trial results;

the scope, terms and timing of regulatory approvals;

the expense of filing, prosecuting, defending and enforcing patent claims and other intellectual property rights;

the cost, timing and our ability to manufacture sufficient clinical and commercial supplies for any product candidates and products that we may develop; and

the risks disclosed in the section entitled "Risk factors" beginning on page 12 of this prospectus.

A change in the outcome of any of these variables could mean a significant change in the expenses and timing associated with the development of any product candidate.

*General and administrative expenses*

General and administrative expenses consist primarily of salaries and related costs for personnel, including stock-based compensation and travel expenses for our employees in executive, operational, finance, legal and human resource functions. Other general and administrative expenses include facility-related costs, professional fees for directors, accounting and legal services, consultants and expenses associated with obtaining and maintaining patents.

We anticipate that our general and administrative expenses will increase in the future as we increase our headcount to support our continued research and development and the potential commercialization of our

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product candidates. We also anticipate increased expenses related to costs associated with being a public company, including audit, legal, regulatory and tax-related services associated with maintaining compliance as a public company, director and officer insurance premiums and investor relations costs. Additionally, prior to the potential regulatory approval of our first product candidate, we anticipate an increase in payroll and related expenses as a result of our preparation for commercial operations, especially as it relates to sales and marketing.

### ***Income taxes***

From inception through May 1, 2014, we were a limited liability company for federal and state tax purposes and, therefore, all items of income or loss through May 1, 2014 flowed through to the members of the limited liability company. Effective May 2, 2014, we converted from a limited liability company to a C corporation for federal and state income tax purposes. Accordingly, prior to the conversion to the C corporation, we did not record deferred tax assets or liabilities or have any net operating loss carryforwards. At September 30, 2014, we concluded that a full valuation allowance is necessary for our deferred tax assets.

## **Critical accounting policies and significant judgments and estimates**

Management's discussion and analysis of our financial condition and results of operations is based on our financial statements, which have been prepared in accordance with U.S. generally accepted accounting principles. The preparation of these financial statements requires us to make estimates and judgments that affect the reporting amounts of assets, liabilities and expenses and the disclosure of contingent assets and liabilities in our financial statements. On an ongoing basis, we evaluate our estimates and judgments, including those related to accrued expenses and stock-based compensation. We base our estimates on historical experience, known trends and events and various other factors that we believe to be reasonable under the circumstances, the results of which form the basis for making judgments about the carrying value of assets and liabilities that are not readily apparent from other sources. Actual results may differ from these estimates under different assumptions or conditions.

While our significant accounting policies are described in more detail in the notes to our financial statements appearing elsewhere in this prospectus, we believe the following accounting policies to be the most critical to the judgments and estimates used in the preparation of our financial statements.

### ***Revenue recognition***

Our recognized revenues to date are from our Genable collaboration. We account for revenue arrangements that contain multiple deliverables in accordance with Financial Accounting Standards Board, or FASB, Accounting Standards Codification, or ASC, Topic 605-25, Revenue Recognition for Arrangements with Multiple Elements, which addresses the determination of whether an arrangement involving multiple deliverables contains more than one unit of accounting. A delivered item within an arrangement is considered a separate unit of accounting only if both of the following criteria are met:

the delivered item has value to the customer on a stand-alone basis; and

if the arrangement includes a general right of return relative to the delivered item, delivery or performance of the undelivered item is considered probable and substantially in control of the vendor.

Under FASB ASC Topic 605-25, if both of the criteria above are not met, then separate accounting for the individual deliverables is not appropriate. Revenue recognition for arrangements with multiple deliverables constituting a single unit of accounting is recognized generally over the greater of the term of the arrangement

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or the expected period of performance, either on a straight-line basis or on a modified proportional performance method.

Non-refundable license fees are recognized as revenue when we have a contractual right to receive such payment, the contract price is fixed or determinable, the collection of the receivable is reasonably assured and we have no future performance obligations under the license agreement.

We will account for milestones related to research and development activities in accordance with FASB ASC Topic 605-28, milestone method of revenue recognition. FASB ASC Topic 605-28 allows for the recognition of consideration which is contingent on the achievement of a substantive milestone, in its entirety, in the period the milestone is achieved. A milestone is considered to be substantive if all of the following criteria are met: the milestone is commensurate with either (1) the performance required to achieve the milestone or (2) the enhancement of the value of the delivered items resulting from the performance required to achieve the milestone, the milestone relates solely to past performance, and the milestone payment is reasonable relative to all of the deliverables and payment terms within the agreement.

Amounts received prior to satisfying the revenue recognition criteria are recorded as deferred revenue on our balance sheet. Amounts expected to be recognized as revenue in the next twelve months following the balance sheet date are classified as current liabilities.

### ***Research and development costs and expenses***

Research and development costs are expensed as incurred. We recognize costs for certain development activities based on an evaluation of the progress to completion of specific tasks using information and data provided to us by our vendors and our clinical sites. We determine accrual estimates through financial models that take into account discussion with applicable personnel and service providers as to the progress or state of completion of trials. Our clinical trial accrued and prepaid assets are dependent, in part, upon the receipt of timely and accurate reporting from CROs and other third-party vendors. Although we do not expect our estimates to differ materially from amounts we actually incur, our understanding of the status and timing of services performed relative to the actual status and timing of services performed may vary and may result in us reporting amounts that are too high or too low for any particular period. When contracts for outside research products or testing require advance payment, they are recorded on the balance sheet as prepaid items and expensed when the service is provided or reaches a specific milestone outlined in the contract.

### ***Stock-based compensation and fair value of stock***

We issue stock-based awards to employees and non-employees, generally in the form of stock options and restricted stock. We are a privately held company with no active public market of our common stock. Therefore, our board of directors has estimated the fair value of our common stock at various dates, with input from management, considering our most recently available third-party valuations of common stock and the board's assessment of additional objective and highly subjective factors that it believed were relevant. Once a public trading market for our common stock has been established in connection with the closing 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 restricted stock. In the absence of a public trading market for our common stock, we apply the fair value recognition provisions of FASB ASC Topic 718, Compensation - Stock Compensation, or ASC 718. ASC 718 requires all stock-based payments to employees and directors, including stock option grants and modifications to existing stock options, to be recognized in the statements of operations based on their fair values. We recognize compensation expense for the portion of the award that is ultimately expected to vest over the period during which the recipient renders the required services using the straight-line, single option method. Non-employee awards are revalued until the awards vest.

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We use the Black-Scholes option-pricing model to value our stock options. Use of this valuation methodology requires management to apply judgment and make estimates, including:

the volatility of our common stock;

the expected term of our stock options;

the risk-free rate for a period that approximates the expected term of our stock options;

the expected dividend yield; and

the fair value of our common stock on date of grant.

As a privately held company with a limited operating history, we use comparable public companies to estimate our expected stock price volatility. We selected companies from the biopharmaceutical industry with similar characteristics to ours including technology, enterprise value, risk profile, position within the industry and with historical price information sufficient to meet the expected life of our stock-based awards. We intend to continue to consistently apply this process using comparable companies until a sufficient amount of historical information regarding the volatility of our own share price becomes available. The expected term is based on the simplified method provided by Securities and Exchange Commission, or SEC, guidance. We use the simplified method as prescribed by the SEC Staff Accounting Bulletin, or SAB, No. 107, Stock-based Payment, to calculate the expected term of stock option grants to employees, as we do not have sufficient history to provide a reasonable basis upon which to make an estimate. The risk-free interest rate is based on U.S. Treasury yield curve with a remaining term equal to the expected life assumed at grant. We utilize a dividend yield of zero, based on the fact that we have never paid cash dividends and have no current intention to pay cash dividends. If factors change and different assumptions are used, our stock-based compensation expense could be materially different in the future.

We historically have granted restricted stock and stock options at exercise prices not less than the fair value of our common stock. As there has been no public market for our common stock to date, the estimated fair value of our common stock has been determined contemporaneously by our board of directors utilizing independent third-party valuations prepared in accordance with the guidance outlined in the American Institute of Certified Public Accountants Practice Aid, *Valuation of Privately-Held Company Equity Securities Issued as Compensation*, also known as the Practice Aid for financial reporting purposes.

We performed contemporaneous valuations of our common stock concurrently with the achievement of significant milestones or with major financing events as of October 14, 2013, April 15, 2014, May 23, 2014, October 30, 2014 and December 1, 2014. In conducting these valuation analyses, we considered all objective and subjective factors that we believed to be relevant for each valuation conducted, including external market conditions affecting the biotechnology industry sector and the prices at which we sold shares of preferred stock, the superior rights and preferences of securities senior to our common stock at the time of each grant and the likelihood of achieving a liquidity event.

### ***JOBS Act***

As an emerging growth company, or EGC, under the Jumpstart Our Business Startups Act of 2012, or the JOBS Act, we 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 irrevocably elected not to avail ourselves of this extended transition period and, as a result, we will adopt new or revised accounting standards on the relevant dates on which adoption of such standards is required for other public companies.

We are in the process of evaluating the benefits of relying on other exemptions and reduced reporting requirements under the JOBS Act. Subject to certain conditions, as an EGC, we intend to rely on certain of these



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exemptions, including without limitation (i) providing an auditor's attestation report on our system of internal controls over financial reporting pursuant to Section 404(b) of the Sarbanes-Oxley Act of 2002 and (ii) complying with any requirement that may be adopted by the Public Company Accounting Oversight Board, or PCAOB, regarding mandatory audit firm rotation or a supplement to the auditor's report providing additional information about the audit and the financial statements, known as the auditor discussion and analysis. We will remain an EGC until the earliest of: (i) the last day of the fiscal year in which we have total annual gross revenues of \$1 billion or more; (ii) the last day of the fiscal year following the fifth anniversary of the date of the completion of this offering; (iii) the date on which we have issued more than \$1 billion in nonconvertible debt during the previous three years; and (iv) the date on which we are deemed to be a large accelerated filer under the rules of the SEC.

**Results of operations**

*March 13, 2013 (inception) to December 31, 2013 and nine months ended September 30, 2014 (unaudited)*

	Period from March 13, 2013 (inception) to December 31, 2013	Nine months ended September 30, 2014
	(in thousands)	
Revenues	\$	\$ 20
Operating expenses:		
Research and development	4,897	10,169
Acquired in-process research and development	50,000	
General and administrative	2,381	5,162
Total operating expenses	57,278	15,331
Loss from operations	(57,278)	(15,311)
Interest income		2
Net loss	\$ (57,278)	\$ (15,309)

**Revenues**

We did not recognize any revenue in 2013. In the nine months ended September 30, 2014, we recognized \$20,000 of revenue associated with our Genable collaboration.

**Research and development expenses**

Our research and development expenses for the period March 13, 2013 (inception) to December 31, 2013 were \$4.9 million and for the nine months ended September 30, 2014 were \$10.2 million. Research and development expenses primarily were for clinical trials for SPK-RPE65 and a predecessor product candidate under our SPK-FIX program, as well as preclinical studies for our SPK-CHM and SPK-FIX programs, development of other product candidates and salaries and related costs, including stock-based compensation.

**Acquired in-process research and development expense**

Our acquired in-process research and development expense for the period March 13, 2013 (inception) to December 31, 2013 was \$50.0 million. This amount represents the fair value of the Spark LLC Series 1 common units, which have since converted into 5.0 million shares of our common stock, issued to CHOP and UIRF in





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consideration for our acquisition and in-license of certain rights and property. We recognized this amount as acquired-in-process research and development because additional research and development efforts and marketing approval are required in order to commercialize the licensed technology.

***General and administrative expenses***

Our general and administrative expenses for the period March 13, 2013 (inception) to December 31, 2013 were \$2.4 million and for the nine months ended September 30, 2014 were \$5.2 million. General and administrative expenses consisted primarily of salaries and related costs, including stock-based compensation, for new hires, legal and patent costs and other professional fees.

**Liquidity and capital resources**

The following table sets forth the primary sources and uses of cash and cash equivalents for each period set forth below:

	<b>Period from March 13, 2013 (inception) to December 31, 2013</b>	<b>Nine months ended September 30, 2014 (unaudited)</b>
	<b>(in thousands)</b>	
Net cash provided by (used in):		
Operating activities	\$(5,139)	\$ (4,788)
Investing activities		(4,964)
Financing activities	5,139	77,025
<b>Net increase in cash and cash equivalents</b>	<b>\$</b>	<b>\$67,273</b>

***Operating activities***

The net cash used by operating activities was \$5.1 million from inception through December 31, 2013, and consisted primarily of a net loss of \$57.3 million, adjusted for non-cash items including the acquired-in-process research and development of \$50.0 million, stock-based compensation expense of \$0.6 million and an increase of \$1.5 million in accrued expenses.

The net cash used by operating activities was \$4.8 million for the nine months ended September 30, 2014, and consisted primarily of a net loss of \$15.3 million adjusted for non-cash items, including stock-based compensation expense of \$2.2 million, non-cash rent expense of \$0.4 million and a net increase in operating assets and liabilities of \$7.9 million. The significant items in the change in operating assets and liabilities include an increase in deferred rent of \$4.7 million related to our tenant improvement allowance, an increase in current deferred revenue of \$1.4 million, of which \$0.4 million is related to our Genable collaboration and \$1.0 million is the non-refundable payment received for engaging in due diligence with a potential manufacturing technology partner, and an increase of \$2.3 million in accounts payable and accrued expenses, offset by a \$0.6 million increase in prepaid expenses and other assets.

***Investing activities***

Net cash used in investing activities for the nine months ended September 30, 2014 was \$5.0 million, consisting of costs related to the purchase of property and equipment.



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Net cash provided by financing activities from inception through December 31, 2013 was \$5.1 million, consisting of the sale to CHOP of Series A preferred units for \$10.0 million, less the \$4.9 million receivable due from CHOP at December 31, 2013.

Net cash provided by financing activities for the nine months ended September 30, 2014 was \$77.0 million, consisting of the collection of the \$4.9 million receivable from CHOP and the \$72.4 million of proceeds from the issuance of Series B preferred stock, offset by transaction costs of \$0.3 million.

**Funding requirements**

We expect our expenses to increase compared to prior periods in connection with our ongoing activities, particularly as we continue research and development, continue and initiate clinical trials and seek regulatory approvals for our product candidates. In anticipation of regulatory approval for any of our product candidates, we expect to incur significant pre-commercialization expenses related to product sales, marketing, distribution and manufacturing. Furthermore, upon the closing of this offering, we expect to incur additional costs associated with operating as a public company.

The expected use of our cash and cash equivalents, including the net proceeds from this offering, along with the \$20.0 million upfront payment under the Pfizer collaboration, 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, the status of, and results from, clinical trials, the potential need to conduct additional clinical trials to obtain approval of our product candidates for all intended indications, as well as any additional 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 our existing cash and cash equivalents and the net proceeds from this offering.

Based on our planned use of the net proceeds from this offering and our existing cash and cash equivalents, along with the \$20.0 million upfront payment under the Pfizer collaboration, we estimate that such funds will be sufficient to enable us to complete the submission of a BLA and prepare for commercialization of SPK-RPE65, complete our Phase 1/2 trial for SPK-CHM, complete our planned Phase 1/2 trial for our lead SPK-FIX product candidate in collaboration with Pfizer, advance certain of our other pipeline product candidates and fund our operating expenses and capital expenditure requirements into late 2017. The foregoing estimate does not contemplate the receipt of any milestone payments under our collaboration with Pfizer. Moreover, we have based this estimate on assumptions that may prove to be wrong, and we could use our available capital resources sooner than we currently expect.

**Contractual obligations and commitments**

The following table summarizes our contractual obligations as of September 30, 2014:

	Total	Payments due by period (in thousands)			
		Less than 1 year	1-3 years	3-5 years	More than 5 years
Operating leases(1)	\$ 17,633	\$	\$ 2,985	\$ 3,294	\$ 11,354
Total(2)	\$ 17,633	\$	\$ 2,985	\$ 3,294	\$ 11,354

(1) Operating lease obligations reflect our obligation to make payments in connection with leases for our corporate headquarters.

(2) This table does not include: (a) any milestone payments which may become payable to third parties under license agreements as the timing and likelihood of such payments are not known with certainty; (b) any royalty payments to third parties as the amounts, timing and likelihood of such payments are not known

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with certainty; and (c) contracts that are entered into in the ordinary course of business which are not material in the aggregate in any period presented above.

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**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 under the SEC rules.

**Quantitative and qualitative disclosures about market risk**

We are exposed to market risk and changes in interest rates. As of September 30, 2014, we had cash and cash equivalents of \$67.3 million, consisting of investments in cash and money market accounts. Due to the short-term duration of our investment portfolio, an immediate 100 basis point change in interest rates would not have a material effect on the fair market value of our portfolio.

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**Business**

**Overview**

We are a leader in the field of gene therapy, seeking to transform the lives of patients suffering from debilitating genetic diseases by developing one-time, life-altering treatments. The goal of gene therapy is to overcome the effects of a malfunctioning, disease-causing gene by delivering a normal, functional copy of the same gene. Our product candidates have the potential to provide long-lasting effects, dramatically and positively changing the lives of patients with conditions where no, or only palliative, therapies exist. Our initial focus is on treating orphan diseases, and we have demonstrated promising clinical outcomes with our first ophthalmic product candidate targeting rare blinding conditions, which has received both breakthrough therapy and orphan product designation. We also have built a pipeline of product candidates targeting additional blinding conditions, hematologic disorders and neurodegenerative diseases, including a second product candidate targeting another rare blinding condition, for which we have initiated enrollment in a clinical trial, and a collaboration with Pfizer Inc., or Pfizer, for the development and commercialization of a gene therapy for the treatment of hemophilia B. Our platform technology is based on more than two decades of gene therapy research, development, manufacturing and clinical trials conducted at The Children's Hospital of Philadelphia, or CHOP.

Our most advanced product candidate, SPK-RPE65, which is in a pivotal Phase 3 clinical trial, targets a group of rare blinding conditions known as inherited retinal dystrophies, or IRDs, caused by non-sex linked, or autosomal recessive, mutations in the RPE65 gene. Patients suffering from RPE65-mediated IRDs are affected by a range of severe visual impairments, which ultimately lead to blindness, that make independent activities of daily living challenging. For example, affected children often depend on visual aids to carry out classroom activities while adults with these diseases may face diminished employment opportunities and may be stripped of the rewards of parenting, such as watching a child play his or her favorite sport. We estimate that there are approximately 3,500 individuals with RPE-mediated IRDs in the United States and the five major European markets.

To date, results from our two Phase 1 clinical trials, along with reports from our clinical study team and other feedback regarding the subjects in the trials, suggest that SPK-RPE65 enables subjects to perform activities of daily living with greater independence than prior to treatment and has long-lasting effects in restoring functional vision, with subjects having been followed for a period of at least five years. Notably, as reported by our clinical study team, following a single injection of SPK-RPE65 in one eye, the children from our initial Phase 1 trial no longer depended on visual aids to carry out classroom activities and were able to walk and play more like normally-sighted kids. Furthermore, inclusive of the subjects in our ongoing Phase 3 clinical trial, we have not observed any drug-related serious adverse events to date.

We are conducting a fully enrolled, pivotal Phase 3 clinical trial of SPK-RPE65 in which we have dosed all subjects in the treatment group and currently are collecting data. We anticipate reporting final results during the second half of 2015. If successful, we plan to submit a biologics license application, or BLA, to the U.S. Food and Drug Administration, or FDA, in 2016. SPK-RPE65 has the potential to be the first gene therapy approved in the United States for the treatment of a genetic disease and the first approved pharmacologic treatment for any IRD.

We believe that we have a significant competitive advantage in the field of gene therapy as a result of the collective experience of our scientific and management team and the advanced stage of development of our product candidates. Our scientists and scientific advisors have accumulated over 150 years of collective experience in the field of gene therapy, contributing key insights and significant developments that have coincided with a resurgence of interest in gene-based medicines. Our proprietary manufacturing processes produce consistent yields of highly pure and stable gene therapies, including both adeno-associated virus, or AAV, and lentiviral vectors. Our vectors are disarmed viruses that carry genetic material into target cells, where

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they deliver a functional gene that allows production of a normal protein. We are building a fully integrated gene therapy platform to accelerate the development of product candidates across multiple therapeutic areas. We engineered our initial product candidates using AAV vectors to efficiently enter target cells in different tissue types and deliver their gene payload.

We are pursuing multiple follow-on product candidates targeting other IRDs, including SPK-CHM for the treatment of choroideremia, or CHM. CHM is an IRD linked to the X-chromosome, which manifests in affected males in childhood as night blindness and a reduction of visual field, followed by progressive constriction of visual fields. For CHM patients, it is often in middle age, when people typically are at or near their greatest income-earning potential, that visual impairment begins to limit independent activities of daily living, leading to a severe decrease in vision and, eventually, blindness. We have initiated enrollment in a Phase 1/2 trial for SPK-CHM. We expect to begin dosing subjects in this trial in the first quarter of 2015.

We have established human proof-of-concept in using gene therapy to deliver and express a therapeutic gene in the liver as part of a program for the treatment of hemophilia B. In December 2014, we entered into a global collaboration agreement with Pfizer for the development and commercialization of product candidates in our SPK-FIX program for the treatment of hemophilia B. Under the terms of the agreement, we received a \$20.0 million upfront payment and are eligible to receive up to \$260.0 million in aggregate milestone payments as well as royalties calculated as a low-teen percentage of net product sales. We intend to initiate a Phase 1/2 clinical trial for our current lead SPK-FIX product candidate in the first half of 2015.

We have in-licensed extensive preclinical data and are developing several gene therapy programs targeting hemophilia A and neurodegenerative diseases.

Gene therapies made using our platform technology have been, or are being, used by several biopharmaceutical companies in clinical trials of their own gene therapy product candidates, as well as in multiple clinical trials from other sponsors through a program funded by the U.S. National Institutes of Health, or NIH. Since 2007, our manufacturing platform in use at CHOP has been selected as the sole source of clinical grade AAV for NIH investigators. We have a supply agreement with CHOP to make clinical and commercial material. We recently completed the build-out of our own state-of-the-art current Good Manufacturing Practices, or cGMP, facility to manufacture clinical and commercial grade AAV vectors.

*SPK-RPE65 for the treatment of IRDs caused by autosomal recessive RPE65 mutations*

Our most advanced product candidate, SPK-RPE65, is in a fully enrolled, pivotal Phase 3 clinical trial. Patients with RPE65 mutations suffer from a variety of symptoms ranging from night blindness to a total inability to perceive light, with the onset of symptoms occurring at varying ages from infancy through young adulthood. Depending on the severity and age of onset, patients may be more or less limited in their ability to conduct activities of daily living independently. For example, many school-age children with IRDs caused by RPE65 mutations require full-time aides and are not able to carry out normal classroom activities without the use of visual aids, such as braille. As the disease progresses, affected individuals may be unable to drive, watch television, care for children or grandchildren or participate in everyday activities, including sports. Regardless of the age of onset, RPE65 mutations invariably lead to a decline in functional vision and eventual blindness. There are no approved pharmacologic treatments for IRDs, including IRDs caused by RPE65 mutations.

Our pivotal Phase 3 clinical trial is fully enrolled with 28 subjects with a clinical diagnosis of LCA due to RPE65 mutations, as confirmed by genetic testing. The primary efficacy endpoint for the Phase 3 trial is designed to measure functional vision based on a mobility test that we developed. We have dosed all subjects in the treatment group and currently are collecting data. We expect to report the results of the Phase 3 trial during the second half of 2015.

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We demonstrated initial safety and proof-of-concept for SPK-RPE65 in a Phase 1 dose-escalating trial in which we administered SPK-RPE65 to one eye of 12 subjects with a clinical diagnosis of LCA due to RPE65 mutations, as confirmed by genetic testing. We further demonstrated initial safety and efficacy of SPK-RPE65 in a second Phase 1 clinical trial in which we administered the highest dose used in our first Phase 1 clinical trial to the contralateral eye of all eligible (11 of the 12) subjects from the first Phase 1 trial.

Our second Phase 1 trial used the same dose of SPK-RPE65 that is being used in the Phase 3 trial. Three of the 11 subjects in our second Phase 1 trial would have been excluded from the Phase 3 trial, as discussed more fully below. All of the other eight subjects improved on the mobility test and five of the eight improved to the maximum attainable level of performance measured in the test. The chart below shows the mobility test change scores for each of these subjects comparing performance one year following administration of SPK-RPE65 to performance at baseline.

Over the past decade, scientific advancements have made genetic testing more accessible and cost effective and, according to key opinion leaders, the diagnosis of IRDs has begun to shift from clinical classifications to a diagnosis of disease based on the specific underlying causal gene. We believe this approach to diagnosis will allow more efficient and effective treatment of IRDs, as new gene therapies such as SPK-RPE65 that target a defective gene by delivering a normally functioning gene are developed.

We have received orphan product designation in both the United States and the European Union for SPK-RPE65 for the treatment of patients with LCA due to RPE65 mutations. This mutation is referred to as LCA Type 2, or LCA2. We intend to request an expansion of the orphan product designation for SPK-RPE65 to other IRDs caused by autosomal recessive RPE65 mutations, including RP Type 20, or RP20. We also have received breakthrough therapy designation for SPK-RPE65 from FDA for LCA2 patients with nyctalopia, or night blindness.

We estimate that there are approximately 3,500 individuals with RPE65-related IRDs in the United States, as well as France, Germany, Italy, Spain and the United Kingdom, which are referred to as the five major European markets. We believe SPK-RPE65 could benefit patients who retain enough viable retinal cells to experience improved functional vision.

### *SPK-CHM for Choroideremia; other IRD programs*

The RPE65 gene is one of more than 220 genes that have been identified to cause IRDs. We are expanding our portfolio of product candidates to target additional IRDs caused by gene mutations for which we will be able to leverage our experience with SPK-RPE65. Our first such follow-on product candidate is SPK-CHM.

CHM, is an IRD linked to the X-chromosome, which manifests in affected males in childhood as night blindness and a reduction of visual field, followed by progressive constriction of visual fields. For CHM patients, it is often



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in middle age, when people typically are at or near their greatest income-earning potential, that visual impairment begins to limit independent activities of daily living leading to a severe decrease in vision and, eventually, blindness. We estimate that CHM affects approximately 12,500 males in the United States and the five major European markets.

SPK-CHM uses the same vector design, administration method and manufacturing process that we use for SPK-RPE65. We have initiated enrollment in a dose-escalating, Phase 1/2 clinical trial of SPK-CHM, in which we currently expect to enroll up to 10 subjects. We expect to begin dosing subjects in this trial in the first quarter of 2015. We have received orphan product designation for SPK-CHM for the treatment of CHM in both the United States and the European Union.

In 2014, we entered into a collaboration with Genable Technologies Limited, or Genable, for the development of a gene therapy candidate addressing rhodopsin-linked autosomal dominant RP, or RHO-adRP, an IRD that we believe affects approximately one in 30,000 people, or approximately 30,000 people in North America and the European Union, combined. In exchange for upfront, milestone and royalty payments, the collaboration utilizes our data, our manufacturing expertise and capacity and our experience with clinical trial design and execution and regulatory affairs. This collaboration demonstrates our ability to leverage our experience in the development of gene therapy product candidates, not only through internal development, but also with third parties. We expect to benefit from this collaboration by obtaining insight into a novel therapeutic approach of simultaneously knocking down a dysfunctional gene and supplying a normal copy of the mutant gene, a technique that could be applicable to a wide range of genetic diseases, including other IRDs.

### *SPK-FIX program for the treatment of hemophilia B*

Our gene therapy platform also enables us to develop gene therapies that target tissues other than the eye. Our pipeline portfolio includes product candidates targeting expression of genes in the liver, with an initial focus on hemophilia B. Hemophilia B is a serious and rare inherited disease characterized by a mutation in the Factor IX, or FIX, gene, which leads to deficient blood coagulation and an increased risk of bleeding or hemorrhaging, primarily affecting males. People with hemophilia B typically are reliant on frequent and expensive intravenous infusions of recombinant FIX to facilitate blood clotting. The cost of providing prophylactic FIX treatment to an average adult has been estimated to reach up to \$300,000 or more each year. According to the 2012 World Federation of Hemophilia Annual Global Survey, approximately 28,000 people worldwide suffer from hemophilia B.

In December 2014, we entered into a global collaboration agreement with Pfizer for the development and commercialization of product candidates in our SPK-FIX program for the treatment of hemophilia B. Pfizer and we are developing proprietary, bio-engineered AAV vectors utilizing a high-activity transgene and a treatment protocol designed to mitigate immune responses seen in other hemophilia B gene therapy trials, including our own, that have limited the duration of efficacy. Under the collaboration, we maintain responsibility for the clinical development of SPK-FIX product candidates through the completion of Phase 1/2 trials. Thereafter, Pfizer has responsibility for further clinical development, regulatory approvals and commercialization. We intend to initiate a Phase 1/2 trial of our current lead SPK-FIX product candidate in the first half of 2015. Under the terms of the agreement, we are entitled to a \$20.0 million upfront payment, and are eligible to receive up to \$260.0 million in aggregate milestone payments, as well as royalties calculated as a low-teen percentage of net product sales.

### *Other preclinical gene therapy programs*

We also have preclinical programs in development for the treatment of hemophilia A and neurodegenerative diseases. We have exclusively in-licensed a broad range of rights for these preclinical programs.

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### *Corporate history / milestones*

We were formed in March 2013 to complete the development of, and to commercialize, gene therapy programs advanced over the past two decades at CHOP. We began operations in October 2013, at which time we acquired or exclusively in-licensed the development and commercial rights to certain clinical and preclinical programs and intellectual property from CHOP and the University of Iowa Research Foundation, or UIRF, and in-licensed additional intellectual property from the University of Pennsylvania, or Penn. We continue to collaborate with CHOP on gene therapy programs that are in the preclinical stage of development.

Since October 2013, several highly experienced members of the CHOP gene therapy team, including Dr. Katherine A. High, the former director of the Center for Cellular and Molecular Therapeutics, or CCMT, at CHOP, the former head of clinical and regulatory at CCMT and the head of manufacturing at CCMT, have joined, or are expected to join, our team. The most senior members of our scientific team have worked together for at least the last 10 years and have been responsible for a number of important milestones in clinical gene therapy development, including:

conducting the first clinical trial worldwide of AAV introduced into skeletal muscle tissue;

conducting the first clinical trial worldwide of AAV infused into the liver;

conducting the first clinical trial in the United States of AAV injected into the sub-retinal space; and

conducting the first gene therapy trial for a non-lethal disorder in pediatric subjects.

In May 2014, we completed a \$72.7 million private placement of shares of Series B convertible preferred stock, or our Series B financing. Investors in our Series B financing include investment funds managed by, or affiliated with, Sofinnova Ventures, Brookside Capital, Deerfield Management Company, Rock Springs Capital, T. Rowe Price Associates, Wellington Management Company and two other healthcare investment funds. CHOP also participated in the Series B financing.

In October 2014, we moved into a 28,000 square foot facility that we designed to meet the needs of our fully integrated gene therapy platform. The facility houses cGMP manufacturing suites, research laboratories as well as office space.

In December 2014, we entered into our global collaboration agreement with Pfizer for the development and commercialization of product candidates in our SPK-FIX program for the treatment of hemophilia B.

## **Our strengths**

We believe the combination of our technology, expertise and know-how will allow us to maintain our leadership position in the gene therapy field. Our strengths include:

A product candidate, SPK-RPE65, in late-stage clinical development targeting RPE65-mediated IRDs, for which there are no approved pharmacologic treatments, and that is designed to have dramatic, long-lasting effects;

An additional IRD product candidate, SPK-CHM, for which we have initiated enrollment in a Phase 1/2 clinical trial;

An additional program, SPK-FIX, for which we expect to begin a Phase 1/2 clinical trial during the first half of 2015 and that we are developing in collaboration with Pfizer;

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A first-mover advantage in gene therapy with what we believe is the most advanced gene therapy product candidate addressing an IRD;

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Two corporate collaborations, one with Pfizer, for the development and global commercialization of SPK-FIX product candidates, and the other with Genable, for the development of RhoNova;

Worldwide commercial rights to all of our product candidates and development programs except SPK-FIX product candidates, to which we granted Pfizer global commercial rights, and RhoNova, to which we licensed technology to Genable;

An integrated gene therapy development platform, amassing substantial know-how across disciplines, including early research and development, product design, manufacturing, clinical trial design and execution, regulatory affairs, process development and assay development and validation;

The ability to develop gene therapies across multiple indications and targeting multiple tissues;

Product candidates which, to date, use recombinant AAV vector technology, which is a well-studied, versatile and efficient gene therapy approach;

Manufacturing capabilities that provide a secure and reliable supply to enable efficient and rapid clinical development and that have been scaled to meet the anticipated commercial needs of SPK-RPE65 and likely other IRD product candidates;

A high quality production process that provides consistency during clinical investigation, a foundation for commercial-scale manufacturing and an asset for potential partnering; and

Scientists and clinicians who have a track record of identifying appropriate disease targets as well as overcoming obstacles to safe and efficient gene transfer into particular target tissues.

## **Our strategy**

Our goal is to transform the lives of patients by being the leading, fully integrated gene therapy company. We are seeking to develop, manufacture and commercialize multiple product candidates targeting rare genetic diseases across multiple tissue types and therapeutic areas. To achieve our goal, we are pursuing the following strategies:

**Successfully complete clinical development and obtain marketing approval for SPK-RPE65.** We expect to report results from our pivotal Phase 3 clinical trial of SPK-RPE65 during the second half of 2015. Upon completion of the Phase 3 trial, if successful, we intend to file a BLA with FDA in 2016 and, subsequently, an MAA with EMA. We believe that given its advanced stage of clinical development, SPK-RPE65 has the potential to be the first FDA-approved gene therapy in the United States for the treatment of a genetic disease and the first approved pharmacologic treatment for any IRD.

**Establish a global commercial infrastructure.** We currently possess all commercial rights to our product candidates and development programs except for SPK-FIX product candidates, to which we granted Pfizer global commercial rights, and RhoNova, to which we licensed technology to Genable. If approved, we intend to commercialize SPK-RPE65, initially in the United States and the European Union. We believe the value proposition for patients, families and payors would be significant, given the potentially long-lasting benefits anticipated from such therapies, delivered through a single administration. We plan to employ a small, targeted commercial and medical affairs infrastructure to build and promote access to the product through centers-of-excellence that treat IRDs in the United States and the European Union and potentially other major markets, including in Latin America and Asia. We believe that this patient-centered approach will provide the foundation for future commercial and medical affairs operations, particularly for additional gene therapy product candidates for IRDs.



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**Establish a franchise of gene therapies for IRDs.** The RPE65 gene is one of more than 220 genes that have been identified to cause IRDs. We believe our capabilities and know-how will allow us to develop treatments for a number of these genetic conditions. In connection with our development of SPK-CHM for choroideremia and other potential product candidates for additional IRDs, we anticipate utilizing technology similar to that developed in our SPK-RPE65 program while leveraging our clinical experience to optimize the clinical trials to best evaluate the safety and efficacy of the particular product candidate.

**Continue to build a liver-directed gene therapy platform, with an initial focus on the treatment of hemophilia B.** We believe that our technology, coupled with our know-how, will enable the development of liver-directed gene therapies. In December 2014, we entered into a global collaboration agreement with Pfizer for the development and commercialization of product candidates in our SPK-FIX program for the treatment of hemophilia B. In addition to our planned Phase 1/2 clinical trial of our lead SPK-FIX product candidate for the treatment of hemophilia B, we have a program in preclinical development for hemophilia A, for which we retain all development and commercial rights. We believe that successful development of our hemophilia gene therapy product candidates could potentially enable further development in a series of other diseases where gene delivery to the liver may have therapeutic benefit.

**Advance preclinical neurodegenerative programs into clinical development.** We have programs targeting neurodegenerative diseases in preclinical development and intend to commence an IND-enabling preclinical study in 2015 and advance one or more of these programs into clinical development.

**Leverage our proprietary manufacturing platform to partner selectively with other pharmaceutical and biotechnology companies.** From time to time we evaluate potential collaboration opportunities that arise from our recognized manufacturing and clinical development capabilities. We expect to work opportunistically with pharmaceutical and biotechnology companies seeking to utilize our technology and know-how for developing additional gene therapy product candidates.

## **Our product candidates**

The following table summarizes information regarding our product candidates and development programs.

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### ***SPK-RPE65 for IRDs caused by autosomal recessive RPE65 gene mutations***

#### *Overview*

Mutations in the RPE65 gene lead to IRDs characterized by a range of visual impairments. As reflected in the diagram below, the RPE65 gene is expressed in the retinal pigment epithelium, or RPE, layer of the retina. RPE cells serve as nurse cells for the photoreceptors and carry out some of the key metabolic functions in the visual cycle. The RPE65 gene encodes a protein that helps convert the light entering the eye into electrical signals that are transmitted to the brain, enabling sight. Without the properly functioning protein encoded by the RPE65 gene, the visual cycle is disrupted, resulting in debilitating visual impairments, progressing to blindness.

Loss of vision makes many independent activities of daily living challenging for affected individuals. Children affected by RPE65 mutations often are placed into sight-assisted classrooms and use a white cane, as compared to other children who are able to engage in normal childhood activities such as playing sports. For young adults, an IRD caused by RPE65 mutations can limit the ability to travel independently and to socialize with friends, especially at night when navigation becomes extremely difficult. For adults with RPE65 mutations, employment opportunities may be significantly diminished and they may miss many of the rewards of parenthood, such as seeing their child on the field playing their favorite sport.

#### *RPE65-mediated IRDs*

In the clinical setting, RPE65 mutations manifest in various ways, including:

nyctalopia, or night blindness, which affects patients' ability to conduct normal activities in low light;

diminished light sensitivity, characterized by sluggish, or no, pupillary light reflex;

reduced visual fields, which affect patients' peripheral vision and ability to orient to their surroundings;

nystagmus, a condition characterized by involuntary eye movements; and

severely reduced vision, characterized by the ability to detect hand motion only, light perception only or no light perception at all. RPE65-mediated IRDs historically have been distinguished from one another based on clinical presentation and findings and have been characterized most frequently as Leber's congenital amaurosis, or LCA, or retinitis pigmentosa, or RP. One of the inclusion criteria in our clinical trials is a clinical diagnosis of LCA due to RPE65

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mutations, as confirmed by genetic testing. This type of LCA is referred to as LCA Type 2 or LCA2. Similar to LCA2, RP20 is a subtype of RP caused by mutations in the RPE65 gene. The key differences in the clinical diagnosis of LCA2 as compared to RP20 are that onset of LCA2 typically occurs at birth, or in the first few months of life, while the onset of RP20 typically occurs later in life, and that the rate of degeneration associated with LCA2 is typically more severe than that associated with RP20.

Through genetic testing, clinicians now generally understand that many IRDs once classified as distinct from each other have the same pathophysiology caused by mutations of different severity in the same gene. According to key opinion leaders, over the past decade, as a result of the availability of genetic testing for IRDs, the diagnosis of IRDs has begun to shift from clinical classification to a diagnosis based on the specific underlying causal gene. We believe that SPK-RPE65 will have broad application to all IRDs caused by autosomal recessive RPE65 mutations. As a result, while our clinical trials include only patients diagnosed with LCA2, we may seek FDA approval of SPK-RPE65 for the treatment of patients with any IRD mediated by an RPE65 mutation. If FDA does not agree with us, we may need to conduct additional clinical trials in order to receive an expanded label for SPK-RPE65 that includes RP20 and other IRDs caused by RPE65 mutations.

We estimate that there are approximately 3,500 individuals with RPE65-related IRDs in the United States and the five major European markets. We estimate that RP affects approximately one in every 4,500 individuals and LCA affects approximately one in every 81,000 individuals. We believe the prevalence of RPE65 mutations in the RP population is approximately 2%, implying a total population of approximately 2,800 individuals with RP20 in the United States and the five major European markets. Estimates of the prevalence of RPE65 mutations within the RP population range from approximately 1% to 3%. We believe that the prevalence of RPE65 mutations in the LCA population is approximately 8.5%, implying a total population of approximately 700 individuals with LCA2 within the United States and the five major European markets. Estimates of the prevalence of RPE65 mutations within the LCA population range from approximately 6% to 11%.

As a result of a funded research effort referred to as Project 3000, a large percentage of patients with IRDs diagnosed as LCA have undergone genetic screening. We believe that approximately 90% of patients with LCA2 in the United States and approximately 85% of patients with LCA2 in the five major European markets have been identified.

There has been no funded effort to identify patients with RP20 like Project 3000. We believe the availability of an approved genetic therapy for an IRD will raise awareness among physicians and patients, leading to a significant increase in the rate of genetic testing and diagnosis.

IRDs lead to progressive degeneration of the retina throughout a patient's lifetime, until the photoreceptor and RPE cells are so severely damaged that restoration of proper RPE65 protein production may not have an appreciable benefit on functional vision outcomes. We believe SPK-RPE65 should have a profound benefit by improving functional vision in patients who retain sufficient viable retinal cells.

### *SPK-RPE65*

SPK-RPE65 is our product candidate for the treatment of IRDs caused by autosomal recessive RPE65 mutations. By re-enabling proper protein production through the delivery of a normally functioning RPE65 gene, we believe that SPK-RPE65 has the potential to restore the function to RPE cells and, thus, to restore the visual cycle, resulting in the rapid restoration of functional vision for patients affected by these mutations.

SPK-RPE65 is administered through an injection into the sub-retinal space. Pre-operatively, the surgeon conducts an evaluation of the anatomy and function of the diseased retina to determine the optimal location for the injection. The surgeon performs a standard vitrectomy procedure, which creates a pathway for the



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subretinal injection, followed by the injection of SPK-RPE65. The initial safety and accuracy of the injection are observed in the operating room, which provides confirmation that the intended dose has been delivered to the target area. In our Phase 1 clinical trials, the procedure was performed for all subjects by the same surgeon at our clinical trial site at CHOP. For the Phase 3 trial, to date, four vitreoretinal surgeons have performed the injection at two sites.

### *Clinical development of SPK-RPE65*

Our first clinical trial for SPK-RPE65, which we refer to as our 101 trial, was an open-label, dose-escalating, Phase 1 clinical trial in which subjects received a single dose in one eye, which was the worse of the subject's eyes as determined upon enrollment in the trial. The second trial, also an open-label, Phase 1 clinical trial, which we refer to as our 102 trial, evaluated treatment of the contralateral eye of all eligible subjects (11 of the 12) from the 101 trial using the highest dose used in the 101 trial. This is the dose that we are evaluating in our pivotal Phase 3 clinical trial. The IND for SPK-RPE65 originally was submitted to FDA by CHOP in June 2007 and subsequently was transferred to Spark in January 2014.

### *Evaluating treatment outcomes*

Currently, there is no approved pharmacologic treatment for any IRD and, consequently, there are no precedent endpoints that have been used in a successful pivotal trial to assess the therapeutic benefits of a pharmaceutical product under development for an IRD. The baseline level of visual and retinal function in individuals with RPE65-mediated IRDs can be poor, with the limited vision deteriorating over time so that, eventually, no useful visual function remains for many patients. The characteristics of LCA2 patients, in particular their youth and the involuntary roving eye movements associated with nystagmus, make collecting and analyzing meaningful data from traditional ophthalmic tests challenging.

### *The mobility test – a measure of functional vision*

The overarching goal of developing a therapeutic addressing IRDs is to be able to improve a patient's quality of life. Traditional vision tests measure a discrete aspect of visual function such as visual fields, which is referred to as peripheral vision, or visual acuity, which is referred to as central vision. These individual tests may not reflect accurately a patient's ability to function in a visual environment and carry out typical activities of daily living. Accordingly, with initial input from FDA, we developed a novel test that assesses light sensitivity, visual fields, visual acuity and functional mobility. This mobility test is designed to evaluate the functional vision of subjects with IRDs by measuring the ability of subjects to successfully navigate a course designed to replicate challenges they face in the activities of daily living under defined lighting conditions.

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While taking the test, each subject follows arrows on the floor, makes numerous turns following those arrows, steps over objects that are in their path, goes up and down steps, avoids ordinary household items like waste baskets, finds a door and exits the course through that door. Below is a diagram of a sample mobility course design:

In order to reduce the impact of a potential learning effect, the mobility course is re-configured between each attempt by a subject, using 12 different standardized templates in a randomized sequence with each course containing the same number of turns, objects and hazards. Subjects are tested under several different standardized light levels to determine the lowest light level at which the subject can navigate the course with each eye individually and using both eyes together.

The lighting conditions, which range from darkness to bright light, are measured by lux level, and are designed to approximate different lighting conditions encountered in daily life. The seven lux levels used in our pivotal Phase 3 clinical trial are as follows:

1 lux: approximately equivalent to a moonless summer night or indoor nightlight;

4 lux: approximately equivalent to an outdoor parking lot at night or Christmas tree lights;

10 lux: approximately equivalent to an hour following sunset in a city setting or a bus stop at night;

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50 lux: approximately equivalent to an outdoor train station at night or the inside of a stairwell;

125 lux: approximately equivalent to half-an-hour before sunrise or the interior of a shopping mall or train or bus at night;

250 lux: approximately equivalent to the interior of an elevator or office hallway; and

400 lux: approximately equivalent to an office setting.

Each attempt at the mobility course is videotaped and graded on a pass or fail basis. A grade of fail is given to an attempt if the subject either (i) needs to be re-guided, steps off the course, skips tiles or collides with obstacles on four or more occasions in total or (ii) takes longer than three minutes to complete the course. Trained reviewers grade each attempt without access to information that would identify the timing of the attempt (baseline vs. follow-up evaluation) or in which study (either Phase 1 trial, our mobility test validation study, or MTVS, (discussed below) or the Phase 3 trial) or in which group (treatment vs. control) the subject was assigned. Each video is graded as either pass or fail by two reviewers working independently, and an adjudicator reviews the video if the two initial grades do not agree. Analysis of reproducibility of grades based on a sample of over 2,500 videos to date has shown approximately 97.5% agreement for successive grading of the same video demonstrating both inter- and intra-grader reproducibility.

To quantify the results of the mobility test and to assess effects of SPK-RPE65 over time, a change score is used. The change score compares the lowest lux level at which a subject can successfully pass the test to the lux level at which they were able to pass at baseline. For example, if the lowest lux level at which a subject can pass is three levels lower (i.e., dimmer) than the baseline lux level, the subject would have a change score of positive three. The positive score reflects the subject's improved ability to pass the course at lower or dimmer lux levels. Conversely, if the lowest lux level at which a subject can pass is two lux levels higher (i.e., brighter) than the baseline lux level, the subject would have a change score of negative two.

### Mobility test validation study

As the mobility test is a new test of functional vision, we conducted a separate, non-IND study to validate the hypothesis that, absent medical intervention, performance on the mobility test does not improve over time. For the MTVS, we collected data on 26 normal-sighted and 28 visually impaired subjects with an IRD over a one-year period with no intervening medical treatment. Subjects were tested twice upon study entry to establish a baseline lux level at which they were able to successfully navigate the mobility course and at the one-year time point to measure a change score.

In the MTVS and under the binocular testing condition:

all normal-sighted subjects showed no change in performance between the baseline and one-year assessments; all were able to complete the test at the lowest lux level at both time points;

no visually impaired subjects improved from baseline to the one-year assessment; and

five visually impaired subjects declined in performance from baseline to the one-year assessment.  
Through the MTVS, we reached several key findings, including:

the mobility test is able to distinguish between visually impaired and normally sighted subjects in terms of time and accuracy;

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high reproducibility of the scoring system, as graders have shown approximately a 97.5% agreement for successive grading of the same video, both inter- and intra- grader; and

the 12 different courses of the mobility test are of comparable difficulty based on performance by both normal-sighted and visually impaired subjects.

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### *Other measurements of vision*

We also collect data with respect to a variety of traditional and non-traditional visual and retinal function tests, including, but not limited to, the following:

FST: The full-field light sensitivity threshold, or FST, test measures the light sensitivity of the entire visual field by administering a series of light flashes of various luminance and recording the luminance at which a subject reports seeing the dimmest flash of light.

Visual acuity: Visual acuity testing measures changes in central vision by assessing the ability of the subject to read a standard eye chart.

PLR: The pupillary light reflex, or PLR, test measures the amplitude and velocity of involuntary or reflexive constriction of the pupil one eye at a time as a function of exposure to light of different intensities.

Of these secondary endpoints, we believe that light sensitivity testing, as measured by FST, may be the best correlate to improvement in the visual cycle following injection of SPK-RPE65.

### *Phase 1 proof-of-concept trials*

#### *Trial design*

In October 2007, we initiated the 101 trial of SPK-RPE65 in subjects with a diagnosis of LCA due to RPE65 mutations, as confirmed by genetic testing. The primary objective was to evaluate the safety and tolerability of SPK-RPE65. A secondary goal was to assess both objective and subjective clinical measures of efficacy as well as the relevance of these measurements as a clinical endpoint. The 101 trial was limited to subjects at least eight years of age and consisted of 12 subjects ranging in age from eight to 44 years, with an average age of 20.8 and a median age of 19.5, at the time of the injection. Subjects received a single dose of SPK-RPE65 in their eye with worse function, or their non-preferred eye if visual and retinal function testing did not differentiate between the two eyes. There were three doses evaluated in this trial, with three subjects receiving a dose of  $1.5 \times 10^{10}$  vector genomes, or vg, six subjects receiving  $4.8 \times 10^{10}$  vg and three subjects receiving  $1.5 \times 10^{11}$  vg.

In November 2010, we initiated the 102 trial to evaluate the safety of administration of SPK-RPE65 to the uninjected eye of the 11 eligible subjects from the 101 trial. One subject from our 101 trial had glaucoma in the contralateral eye and was, therefore, ineligible for the 102 trial. All 11 eligible subjects in the follow-on trial received a dose equal to the highest dose level used in the 101 trial,  $1.5 \times 10^{11}$  vg.

#### *Phase 1 safety outcome measure results*

SPK-RPE65 was well tolerated, with no drug-related serious adverse events. Clinical examinations and immunology studies following injection demonstrated the initial safety of SPK-RPE65. We did not reach a dose limiting toxicity. Adverse events related to participation in the trials primarily were ocular adverse events in the study eye related to the surgical injection procedure and generally resolved within weeks after surgery. We did not observe any meaningful clinical immunologic reactions to SPK-RPE65.

In the 102 trial, there was one serious adverse event due to complications from the vitrectomy procedure performed prior to the administration of SPK-RPE65. This was not considered to be related to SPK-RPE65 or the sub-retinal injection procedure. Instead, it was determined to be associated with treatment given for a known but rare infectious complication resulting from the vitrectomy. We subsequently modified the medical regimen to be used in the event of this complication, to reduce the risk of any recurrence of this serious adverse event. To date we have had no recurrences of this complication.

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### **Phase 1 efficacy outcome measure results**

In contrast to other classes of therapeutics, Phase 1 trials of gene therapies are conducted in subjects presenting with the disease, rather than in healthy volunteers. Subjects from these trials have been followed over a period of at least five years. The results of our Phase 1 trials to date, and reports from our clinical study team and other feedback regarding the subjects in the trials, suggest that SPK-RPE65 enables subjects to perform activities of daily living with greater independence than prior to treatment and has long-lasting effects in restoring visual function. Notably, as reported by our clinical study team, following a single dose of SPK-RPE65 in one eye, the children from the 101 trial no longer depended on visual aids to carry out classroom activities and were able to walk and play like normally sighted kids.

The endpoints we evaluated during the Phase 1 trials evolved throughout the time we were conducting the 101 trial and the 102 trial. As a result, some data are only available for a subset of the subjects. The mobility test being used in the Phase 3 trial is modeled on the mobility test from the 102 trial and includes the same course layouts, grading protocol, independent reviewers and a majority of the same lux levels.

### **Mobility test results**

Three of the 11 subjects in the 102 trial would be excluded from the Phase 3 trial. The chart below shows the mobility test change scores from the 102 trial for the other eight subjects. These eight subjects all improved at least one lux level and five of these eight improved to the minimum lux level, which is the same level at which all normal-sighted subjects navigated the mobility test in the MTVS. The chart below shows the mobility test change scores for each of these subjects comparing performance one year following administration of SPK-RPE65 to performance at baseline.

Three subjects in the 102 trial are not included in the results presented above:

NP-04: Subject NP-04 was able to pass the mobility test at the lowest lux level at baseline and thereby would not have qualified for inclusion in our Phase 3 trial. This subject suffered the vitrectomy-related serious adverse event discussed above. Treatment for this event resulted in a steroid-induced cataract which negatively impacted vision. At the one-year time point, NP-04 was unable to complete the mobility test using the eye with the cataract at any lux level but was able to pass the mobility test at the lowest lux level using the non-cataract eye.

CH-06: In addition to having an IRD caused by an RPE65 mutation, this subject has a mutation in another retina-specific gene. It is hypothesized that this complicating factor accounted for the fact that the results of the test were inconsistent and difficult to interpret. Due to the complicating additional IRD, this subject would not be qualified for inclusion in the Phase 3 trial.

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**CH-12:** This subject was unable to pass the mobility test at any lux level and, therefore, was unable to establish a baseline from which a change score could be calculated. Due to the inability to establish a baseline, this subject would not qualify for inclusion in the Phase 3 trial.

*Other measures of efficacy*

**FST:** In the 101 trial, there were eight subjects evaluable for FST testing. FST of the injected eye at one year following injection was compared to baseline. Of the evaluable subjects, all eight subjects had a better score.

In the 102 trial, there were 11 subjects evaluable for FST testing. FST of the second injected eye one year following injection was compared to baseline of the second eye established prior to administration in the second eye, but after administration in the first eye. Of the evaluable subjects, nine had a better score and two had a worse score.

**Visual acuity:** In the 101 trial, there were 12 subjects evaluable for visual acuity testing. Visual acuity of the injected eye at one year following injection was compared to baseline. Of the evaluable subjects, nine had a better score, one had no change and two had a worse score.

In the 102 trial, there were 11 subjects evaluable for visual acuity testing. Visual acuity of the second injected eye one year following injection was compared to a baseline of the second eye established prior to administration in the second eye, but after administration in the first eye. Of the evaluable subjects, eight had a better score and three had a worse score.

**PLR:** In the 101 trial, there were 10 subjects evaluable for PLR testing. A majority of these subjects demonstrated a trend toward improvement as evidenced by a higher proportion of tests in which the pupil of the injected eye responded more vigorously to light stimulus than that of the uninjected eye after injection of SPK-RPE65.

We are in the process of completing the analysis of the PLR testing data from the 102 trial. Without the uninjected contralateral eye as a control, however, this endpoint may be of less utility than in the 101 trial of SPK-RPE65.

### *Pivotal Phase 3 clinical trial*

#### Regulatory interaction

Beginning in December 2008, we had several interactions with FDA regarding the design of the pivotal Phase 3 clinical trial. FDA agreed to the following changes from the Phase 1 trials: (1) a reduction in the lower age limit for subjects from eight years to three years; (2) a reduction in the interval between administration in successive subjects; and (3) the use of a bilateral, non-simultaneous administration. FDA also indicated that data should be measured at one year following injection, with the safety database to include data through two years, and that any BLA should address surgical standardization and surgical training plans.

In September 2010, we initiated discussions with FDA regarding the use of the mobility test as the primary endpoint for the Phase 3 trial. At an FDA advisory committee meeting on gene therapy products for the treatment of retinal disorders convened by CBER in June 2011, we presented a summary of our clinical data to date, as well as our then-proposed Phase 3 trial design. In May 2012, reviewers from FDA, CBER and several ophthalmologists from multiple divisions of FDA provided feedback. They stated that improvement in the ability to navigate the mobility test at a lower light level may represent an improvement in functional vision, but also stated that we had not demonstrated that the magnitude of performance improvement on the mobility test that we consider a success correlates to improvement in a patient's activities of daily living. Consequently, FDA recommended that

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we provide evidence that the amount of improvement that we deem a success, the magnitude of difference between each designated light level, corresponds to a meaningful change in functional vision. FDA recommended further that to obtain such evidence, we conduct real world performance assessments of each subject before and after treatment, where the assessments are conducted and evaluated under the direct supervision of individuals with orientation and mobility training, who are masked to the treatment assignment.

We also received scientific advice and feedback from EMA with regard to the design of the Phase 3 trial. In June 2013, EMA indicated that a primary efficacy analysis one year following injection was reasonable. EMA was supportive of the use of mobility testing to address multiple aspects of vision, but recommended a change wherein only binocular testing be used in primary efficacy endpoint analysis, to better represent a patient's functional vision.

In September 2014, SPK-RPE65 received breakthrough therapy designation from FDA for the treatment of nyctalopia, or night blindness, in patients with a diagnosis of LCA2.

### **Trial design**

The trial is open-label for the investigating physicians and subjects. There is no sham injection, since the trial includes pediatric subjects. Subjects in our pivotal Phase 3 clinical trial receive administration of  $1.5 \times 10^{11}$  vg of SPK-RPE65, which is the dose level used in the 102 trial, in each eye. A single eye is injected at each surgery, with both eyes to be injected within a period of 18 days.

After comprehensive baseline testing, subjects were randomized, in a 2:1 ratio, to either the intervention or control group. The two arms of the trial were balanced for age and the baseline lux level at which subjects were able to pass the mobility test. Control group subjects participate in trial visits that include visual and retinal function testing on the same schedule as the subjects in the intervention group. After completion of the one-year testing, control subjects are eligible to crossover to the treatment group. Additional annual visits or telephone contacts will be conducted to evaluate the subjects for measures of efficacy for five years post-injection and to evaluate safety for 15 years following injection. We have included this monitoring to assess the long-term safety and therapeutic effect of SPK-RPE65.

The following graphic illustrates the overall design of our pivotal Phase 3 clinical trial:

The primary objective of the Phase 3 trial is to determine whether SPK-RPE65 improves subjects' functional vision, as demonstrated by their ability to navigate the mobility test at different lux levels. Mobility test performance one year following the administration of SPK-RPE65 will be compared to subjects' pre-administration baseline. The trial was sized to be adequately powered based on the mobility test change scores observed in the 102 trial.

Subjects will be evaluated at baseline and 30 days, 90 days, 180 days and one year following administration of SPK-RPE65. The final score for statistical analysis will be calculated based on the lowest lux level at which a subject receives a grade of "pass" one-year following injection as compared to baseline. We consider a positive change score of one or more on the mobility test to be a clinically meaningful improvement in functional vision.



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The secondary efficacy endpoints for our pivotal Phase 3 clinical trial include FST, visual acuity and PLR testing. As a tertiary endpoint, there will be in-home evaluations of subjects, at both baseline and the one-year time point, by independent orientation and mobility experts, masked as to the treatment condition of the subjects, to support use of mobility testing as a surrogate for patients' daily activities of living in the real world.

### **Status**

In November 2012, we initiated our pivotal Phase 3 clinical trial to assess the efficacy, safety and tolerability of a sequential, bilateral, sub-retinal administration of SPK-RPE65 in subjects with a clinical diagnosis of LCA due to RPE65 mutations, as confirmed through genetic testing. The Phase 3 trial is fully enrolled with 28 eligible subjects, ranging in age from four to 44, with an average age of 14.6 years and a median age of 10.0 years, enrolled at clinical sites at either CHOP or the University of Iowa. All 19 intervention subjects and all eight of the control subjects that have completed one-year testing have received injections of SPK-RPE65 with no serious adverse events. One additional subject received treatment but was later determined to be ineligible based on trial exclusion criteria. We expect to report the results of the Phase 3 trial in the second half of 2015.

### **Commercialization**

We possess global rights to SPK-RPE65. If approved, we intend to commercialize SPK-RPE65 initially in the United States and the European Union. We plan to employ a small, targeted commercial and medical affairs infrastructure to build and promote access to the product through centers-of-excellence that treat IRDs in the United States and the European Union and potentially other major markets, including in Latin America and Asia. We believe that this patient-centered approach will provide the foundation for future commercial and medical affairs operations, particularly for additional gene therapy product candidates for IRDs.

### **SPK-CHM for the treatment of choroideremia**

#### **Overview**

Choroideremia, or CHM, is an IRD linked to the X-chromosome. Clinically, CHM manifests in affected males in childhood as night blindness and a reduction of visual field, followed by progressive constriction of visual fields. For CHM patients, it is often in middle age, when people typically are at or near their greatest income-earning potential, that visual impairment begins to limit independent activities of daily living leading to a severe decrease in vision and, eventually, blindness. We estimate prevalence of CHM is between approximately 1 in 50,000 and 1 in 100,000 people, implying a total population of up to approximately 12,500 males in the United States and the five major European markets.

CHM is characterized by deletions or mutations in the CHM gene, resulting in defective or absent Rab escort protein-1, or REP-1, which is the encoded protein of the CHM gene. Rab proteins are escorted by REP-1 as part of an essential process in normal vision. Absence, or deficiency, of REP-1 due to mutations in the CHM gene leads to cellular death and degeneration of the retinal pigment epithelium, the choroid, which is the vascular layer of the eye, and the retinal photoreceptors, which convert light into visual signals. Although in normal retinas the CHM gene is expressed in multiple cell types, including RPE cells, photoreceptors and choroidal cells, there is evidence that the RPE cell is the primary disease-causing cell type for CHM. A corrective gene delivered to the RPE may restore proper CHM gene function and may halt degeneration and restore the RPE, retinal vasculature and photoreceptors.

#### **SPK-CHM**

SPK-CHM is our product candidate for the treatment of IRDs caused by CHM gene mutations. Our SPK-CHM program is technically similar to our SPK-RPE65 program, including use of the same vector, targeting the same

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types of RPE cells and utilizing the same route of administration through sub-retinal injection. The manufacturing process for SPK-CHM is similar to that of SPK-RPE65, which could lead to shorter development timelines. We intend to leverage our experience with SPK-RPE65, especially in the areas of clinical operations and regulatory affairs, in order to reduce development timelines and efficiently establish the efficacy and safety of our product candidate for the treatment of CHM. Further, if SPK-CHM is approved, we intend to utilize any commercial infrastructure we put in place for SPK-RPE65. We have received orphan product designation for SPK-CHM in both the United States and the European Union.

### *Preclinical studies of SPK-CHM*

In preclinical models, we demonstrated the ability of SPK-CHM to restore REP-1 protein production, intracellular trafficking and retinal structure. We completed preliminary safety studies in normal-sighted preclinical models at two dose levels. The results of these studies support the safety of SPK-CHM at the doses we intend to use in our clinical trials and demonstrate robust reversal of the biochemical and protein trafficking deficits in the cell models with an encouraging safety profile. We submitted an IND for SPK-CHM to FDA in August 2014.

### *Initial Phase 1/2 clinical trial*

We have initiated enrollment in a Phase 1/2 dose-escalating clinical trial of SPK-CHM. We currently anticipate enrolling up to 10 subjects with a CHM gene mutation in this Phase 1/2 trial. We expect to begin dosing subjects in this trial in the first quarter of 2015. The primary objective is to evaluate the safety and tolerability of subretinal administration of SPK-CHM. Toxicity related to the administration of SPK-CHM will be monitored in the eye and systemically, and the trial will advance to the higher dosage level upon approval by the data safety monitoring board. The secondary objectives of the trial are to define the dose of SPK-CHM required to achieve stable, or improved, visual function and functional vision in subjects with CHM, characterize the immune response and identify appropriate endpoints for subsequent clinical trials.

We will evaluate efficacy primarily by assessing functional vision, as measured by standard ophthalmic tests. Subjects who are administered SPK-CHM will be followed clinically for safety outcomes for 15 years after injection.

### *RhoNova collaboration with Genable*

We are collaborating with Genable on the development of a gene therapy product candidate, RhoNova, which is currently in preclinical development, to treat RHO-adRP. RHO-adRP is an IRD that results in severe vision loss and often blindness and is a subset of RP that results from a diverse array of mutations in the RHO gene. We believe that RHO-adRP affects approximately 1 in 30,000 people, or approximately 30,000 people in North America and the European Union, combined.

Unlike our existing product candidates, which add the functional gene to the target cells, RhoNova is evaluating a novel therapeutic strategy for treating RHO-adRP by delivering both a suppressor to knock down the mutant and normal endogenous RHO genes, and then add back a suppressor-resistant replacement functional gene to improve vision. Delivery of the suppressor and the replacement gene is by separate AAV vectors delivered at the same time. Under our collaboration agreement, we will produce both the suppressor and replacement vectors for clinical and commercial use. Under this collaboration, we are providing know-how and manufacturing capabilities, have licensed certain data and patent rights to Genable and have the right to receive near term revenue from the manufacture and supply of the AAV vectors, certain milestone payments, as well as mid-single-digit royalties based on net sales of RhoNova, assuming successful development and commercialization. See Collaboration and license agreements Genable. Additionally, this collaboration will allow us to obtain insight into the novel therapeutic approach of knocking down dysfunctional genes, which could be applicable to a wide range of autosomal dominant diseases.

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### *Hematologic disorders*

Our product development portfolio includes product candidates targeting expression of genes in the liver, with an initial focus on hematologic disorders.

#### *Hemophilia B*

##### Background

Hemophilia B is a serious and rare inherited disease characterized by insufficient blood clotting that results from the lack of functional FIX, a blood clotting factor normally produced by cells located in the liver. Hemophilia B is caused by mutations in the gene that encodes the coagulation FIX protein. The condition can lead to repeated and sometimes life-threatening episodes of spontaneous bleeding. According to the 2012 World Federation of Hemophilia Annual Global Survey, approximately 28,000 people worldwide suffer from hemophilia B.

The severity of hemophilia B is determined by the circulating levels of FIX. Mild hemophilia B is classified as a level of FIX in the blood equal to greater than 5% of normal but less than 50% of normal. People with mild hemophilia B typically experience bleeding only after serious injury, trauma or surgery. Moderate hemophilia B is classified as a level of FIX in the blood equal to or greater than 1% of normal but less than 5% of normal. People with moderate hemophilia B may have bleeds following trauma, or may have spontaneous bleeding episodes, but these will occur less frequently than in those with severe hemophilia B. Severe hemophilia B is classified as a level of FIX in the blood of less than 1% of normal. People with severe hemophilia B experience frequent spontaneous bleeding episodes, often into their joints and muscles.

The current standard of care for hemophilia B is either prophylactic or on-demand FIX protein replacement therapy, in which frequent intravenous administrations of recombinant or plasma-derived FIX are required to stop or prevent bleeding. Prophylactic therapy for hemophilia B, which has been shown to lead to the best outcomes, is practiced only by some adult patients in the United States due to the significant expense, patient inconvenience, concern about lifetime insurance caps and concern about the risk of blood-borne disease transmission from plasma-derived products. We believe that an average adult patient with severe hemophilia B who treats only in response to bleeds uses, on average, \$100,000 of FIX concentrate each year. The cost to treat an average adult patient with severe hemophilia B prophylactically has been estimated to reach up to \$300,000 or more each year. A gene therapy treatment could offer patients the benefits of prophylaxis without the need for frequent factor infusion.

##### Hemophilia B historical clinical trials

Our SPK-FIX hemophilia B gene therapy program leverages the long track record of hemophilia gene therapy research conducted at CHOP. Our scientific team has substantial experience in clinical trials for hemophilia B gene therapies and, through our agreements with CHOP, we have obtained significant proprietary preclinical and clinical data developed over multiple trials spanning more than a decade. The results of these trials have formed the basis for our further investigation of gene therapies aimed at the expression of FIX for the treatment of hemophilia B.

*Clinical trial successfully administering FIX to skeletal muscle.* Beginning in 1999, a clinical trial was conducted administering the FIX gene utilizing an AAV2 vector to subjects with severe hemophilia B via intramuscular injection. This was the first trial of an AAV vector introduced into skeletal muscle in humans, and the first trial of parenteral administration of AAV. Vector injection was shown to be safe and produced expression of FIX, however, the data did not show levels of expression sufficient to correct disease symptoms at the doses tested.

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*Clinical trial successfully administering FIX to the liver.* Beginning in 2001, a clinical trial was conducted administering the FIX gene utilizing an AAV2 vector to subjects with severe hemophilia B via hepatic artery infusion. This was the first trial of AAV infused into the liver in humans. Although FIX expression lasting for six years was observed following administration of vector in preclinical models, this trial resulted in therapeutic levels of FIX expression in one subject at the highest dose persisting for only 10 weeks. We believe the limited duration of expression was a result of a capsid-specific T-cell immune response seen in humans but not in preclinical models.

*Clinical trial successfully administering FIX to the liver and confirming capsid T-cell response.* In 2011, St. Jude Children's Research Hospital-University College London, or SJCRH-UCL, announced preliminary results in the *New England Journal of Medicine* from a clinical trial administering the FIX gene utilizing an AAV8 vector to six subjects with severe hemophilia B via a single, peripheral, intravenous injection. This trial was modified to include a provision for a short course of steroids to suppress the immune response if subjects began to demonstrate an immune response. CHOP collaborated on this study to investigate the immune response to the AAV vector capsid. This trial resulted in increased levels of FIX sufficient to improve severe hemophilia B to a mild or moderate disease state. In addition to establishing increased FIX production, the SJCRH-UCL clinical trial helped to confirm that activation of capsid-specific T-cell mediated immunity appears to be dose dependent. Moreover, it provided evidence that short-term immunosuppression could ameliorate the effects of the T-cell response to capsid.

*Clinical trial successfully producing sustained FIX expression in one patient.* In 2012, we initiated a dose-escalating Phase 1 clinical trial administering the FIX gene utilizing an AAV8 vector to three subjects with severe hemophilia B via a single, peripheral, intravenous injection. In one subject that was infused in July 2013 at the low dose, we observed sustained FIX levels, after an initial maximum FIX level of 8% of normal, which persisted for over one year following administration. This level of FIX was sufficient to reduce this subject's need for intravenous clotting factor to a single infusion over the year, as compared to approximately 50 times annually prior to treatment. Following the initial year, we observed a decrease in this subject's FIX levels and he recently received additional intravenous clotting factor. A second subject, infused at the low dose, initially showed therapeutic FIX levels consistent with moderate disease, but then failed to continue to express substantial FIX after approximately two months, with loss of expression accompanied by evidence of a T-cell response. The third subject, infused at a higher dose level, initially showed a FIX level of 16% of normal, but expression was limited in duration, with loss of expression accompanied by a T-cell response to the vector capsid.

While certain tissues in the human body, such as the eye, are immune privileged, systemic administration of recombinant vectors, must overcome at least two hurdles presented by the human immune response, in order to effect successful gene transfer. First, administration of recombinant vectors must successfully avoid pre-existing neutralizing antibodies, prevalent in the adult population. Second, after the vector is within the target cell, it must avoid the cellular immune response that can result in the removal of transduced cells by activated T-cells thereby diminishing the therapeutic effect of the gene therapy. We have in-licensed a patent relating to an adjunct therapy to reduce inhibitory antibodies against FIX administered via gene therapy and a patent application relating to specific modifications of the FIX gene that enhances secretion of FIX.

**Lead SPK-FIX product candidate for the treatment of hemophilia B**

Based on our clinical experience, we have refined our research around the immune response to systemic AAV gene therapy administration and developed a proprietary, bio-engineered AAV vector for use in our SPK-FIX program. We selected this vector from among several that we have bio-engineered and evaluated, based on three characteristics: (i) low prevalence of pre-existing neutralizing antibodies to this capsid within the human population; (ii) high levels of liver transduction in preclinical models; and (iii) a favorable bio-distribution

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profile, which refers to the specific tissues throughout the body to which the vector migrates following infusion. In addition to the bio-engineered vector, we have: (i) developed a more versatile immunosuppression regimen to suppress the T-cell response; (ii) introduced a different transgene, known as FIX-Padua, encoding a naturally occurring high-activity FIX variant that confers a six- to eight-fold increase in the specific activity of FIX; and (iii) developed a proprietary approach to manufacturing product candidates in our SPK-FIX program.

In December 2014, we entered into a global collaboration agreement with Pfizer for the development and commercialization of product candidates in our SPK-FIX program for the treatment of hemophilia B. Under the terms of the agreement, we received a \$20.0 million upfront payment and are eligible to receive up to \$260.0 million in aggregate milestone payments, as well as royalties calculated as a low-teen percentage of net product sales. We are conducting IND-enabling safety studies of our lead SPK-FIX product candidate in preclinical models and intend to initiate a Phase 1/2, open label dose-escalation clinical trial of this next-generation hemophilia B product candidate in the first half of 2015. We intend to enroll two to five subjects in each of three dose cohorts, injecting the SPK-FIX product candidate incorporating the modified FIX-Padua gene via a single, peripheral, intravenous injection. Under this collaboration, we maintain responsibility for the clinical development of SPK-FIX product candidates through the completion of Phase 1/2 trials. Thereafter, Pfizer has responsibility for further clinical development, regulatory approvals and commercialization.

### *Hemophilia A*

Hemophilia A is a serious and rare inherited disease characterized by insufficient blood clotting that results from the lack of functional Factor VIII, a blood clotting factor normally produced by cells located in the liver. Hemophilia A is caused by mutations in the gene that encodes the coagulation Factor VIII protein. The condition can lead to repeated and sometimes life-threatening episodes of spontaneous bleeding. According to the 2012 World Federation of Hemophilia Annual Global Survey, approximately 140,000 people worldwide suffer from hemophilia A. We currently have a preclinical gene therapy program in development for the treatment of hemophilia A.

### *Neurodegenerative diseases*

We have preclinical programs in development for the treatment of certain neurodegenerative diseases. We intend to commence an IND-enabling preclinical study in 2015 and advance one or more of these programs into clinical development.

## **Our manufacturing platform**

Our manufacturing platform was developed by our scientists over the past decade. This industry-leading platform can produce AAV and lentiviral based vectors, not only for our own product development, but also to provide a basis for co-development and collaboration with other pharmaceutical companies seeking to leverage our capabilities to facilitate the development of new gene therapy based medicines. Vectors produced using our manufacturing platform have been, or are being, used in 12 different clinical trials, including trials conducted in the United States and the European Union by other biopharmaceutical companies and academic and government institutions, and have been safely administered to over 150 human subjects through five different routes of administration: sub-retinal injection, intracranial injection, peripheral intravenous infusion, hepatic artery infusion and intramuscular injection.

Using a chemical method we refer to as transfection, we insert many copies of DNA plasmids encoding the specific therapeutic gene sequence, or transgene, into human embryonic kidney cells that have already been grown to high density. During an incubation period following transfection, each cell produces vectors through

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biosynthesis using the natural machinery available within the cell. At the end of the incubation period the newly generated vectors are collected from the cells that have been broken apart or, alternatively, from the cell culture medium.

We have made significant investments in developing optimized manufacturing processes and believe that our processes and methods provide the most comprehensive manufacturing process developed to date for AAV-based vector product candidates, including:

sufficient scale to support commercial manufacturing requirements for some of our product candidates, including those for IRDs;

stable manufactured AAV vectors with sufficient longevity that a small number of initial batches will likely provide adequate commercial supply for multiple years;

a proprietary AAV vector manufacturing processes and techniques that produce a highly purified product candidate, as evidenced by the approximately 25- to 30-fold reduction in non-infectious vector related impurities as compared to vectors used in many previous clinical trials;

approximately 30 assays to accurately characterize our process and the AAV vectors we produce; and

a series of high-efficiency purification processes, adapted and customized for multiple different AAV capsids, which allows us to produce higher purity AAV vector solutions, with higher concentrations of active vectors and that are essentially free of empty capsids.

We believe these improvements and our continued investment in our manufacturing platform will enable us to develop best-in-class, next generation gene therapy products.

We are working with FDA to ensure our facility and procedures are cGMP compliant in all aspects and we are also receiving Protocol Assistance and Scientific Advice from EMA. Upon completion of our own manufacturing facility, we intend to seek cGMP validation of our facility to produce commercial supplies of our product candidates. We are engaged in efforts to expand capacity to meet future manufacturing needs through investment in process development.

While our lead programs utilize AAV vectors, we also have experience in developing and manufacturing lentiviral vectors. Lentiviral vectors may have significant benefits for certain genetic diseases that we are not currently pursuing. Lentiviral vectors provide the ability to integrate the functional gene into a chromosome located in the DNA of the target cell, as well as having an expanded carrying capacity of up to 8,000 DNA base pairs, as compared to the approximately 5,000 DNA base pair capacity of AAV vectors. While we are not currently pursuing the development of any proprietary lentiviral gene therapies, we opportunistically may make our manufacturing capabilities available to strategic partners who may be pursuing the development of lentiviral treatments.

## **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 relating to our proprietary technology platform and on know-how, continuing technological innovation and in-licensing opportunities to develop, strengthen and maintain our proprietary position in the field of gene therapy. Additionally, we intend to rely on regulatory protection afforded through orphan drug designations, data exclusivity and market exclusivity as well as patent term extensions, where available.

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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 our patents; preserve the confidentiality of our trade secrets; and operate without infringing the valid enforceable patents and proprietary rights of third parties. Our ability to stop third parties from making, using, selling, offering to sell or importing our products may depend on the extent to which we have rights under valid and enforceable patents or trade secrets that cover these activities. With respect to both our owned and licensed intellectual property, we cannot be sure that patents will issue with respect to any of the pending patent applications to which we license rights or with respect to any patent applications that we or our licensors may file in the future, nor can we be sure that any of our licensed patents or any patents that may be issued in the future to us or our licensors will be commercially useful in protecting our product candidates and methods of manufacturing the same. Moreover, we have not sought, and may be unable to obtain, patent protection for certain of our product candidates generally, including SPK-CHM, as well as with respect to certain indications. See **Risk factors** **Risks related to our intellectual property** for a more comprehensive description of risks related to our intellectual property.

We have licensed numerous patents and patent applications and possess substantial know-how and trade secrets relating to our product candidates. Our proprietary intellectual property, including patent and non-patent intellectual property, generally is directed to AAV vectors, methods of treatment of clinical indications important for our development programs, transferring genetic material into cells, inhibiting antibody responses to gene therapies, processes to manufacture and purify our AAV- and lentiviral-based product candidates and other proprietary technologies and processes related to our lead product candidates. We are heavily dependent on the patented or proprietary technologies that we license from third parties. We anticipate that we will require additional licenses to third party intellectual property rights relating to our development programs in the future, which may not be available on commercially reasonable terms, if at all.

*Licensed patents and patent applications*

As of January 15, 2015, our patent portfolio included approximately 159 U.S. and foreign patents and patent applications licensed from CHOP, UIRF, Penn and NIH. These patents and patent applications cover technology used in our own development programs, as well as technology used in our collaborations with Pfizer and Genable. We have granted Pfizer an exclusive worldwide license for the development and commercialization of product candidates for the treatment of hemophilia B under the patents and other rights listed below that relate to our SPK-FIX program.

*Manufacturing platform*

We exclusively in-license three patent application families from CHOP relating to scalable manufacturing for producing high-purity gene therapy vectors. The first relates to manufacture of our own product candidates as well as the product candidates and development programs that are the subject of our collaborations with Pfizer and Genable, and is pending in the United States, Australia, Brazil, Canada, China, Europe, Israel, India, Japan and Mexico. We expect that patents issuing from these applications, if any, would expire in 2031, excluding any potential patent term extension or adjustment. The second and third application families relate to scalable manufacturing and purification of lentiviral vectors. The second application family is pending in the United States, Australia, Canada, Europe and Japan. We expect that patents issuing from these applications, if any, would expire in 2032, excluding any potential patent term extension or adjustment. The third application family is comprised of a pending United States application and a corresponding Patent Cooperation Treaty, or PCT, application. We expect that patents issuing from these applications, if any, would expire in 2034, excluding any potential patent term extension or adjustment.

We refer to these three patent application families as our manufacturing patent applications.

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### *Modified AAV vectors and gene delivery*

We are developing additional technology in a number of different areas to improve or expand upon our current product candidates. This technology is exclusively licensed from CHOP and generally relates to modifying gene therapy vectors, adding a companion therapy or diagnostic or developing other therapeutic genes. The licensed patent rights underlying this technology include:

Six U.S. patent applications that relate to alternate, or modified, AAV vectors for gene delivery that we believe have certain technical advantages that are broadly applicable to all of our current, and potentially to our future, clinical programs, including transducing certain target cells, modifications to AAV vectors, modifying AAV vectors to reduce antibody binding, and producing reduced amounts of contaminating AAV particles. We expect that patents issuing from these applications, if any, would expire from 2028 up until 2034, excluding any potential patent term extension or adjustment.

Two pending U.S. patent applications that generally relate to inhibiting immune responses to AAV vector and measuring antibodies that bind to AAV. We expect that patents issuing from these applications, if any, would expire between 2032 and 2034, excluding any potential patent term extension or adjustment.

We believe our manufacturing patent applications and related know-how and trade secrets may provide us with additional intellectual property protection relating to our planned use of this technology.

### *Ophthalmic indications*

We have a co-exclusive in-license from Penn of a U.S. patent co-owned by Penn, Cornell University and the University of Florida that relates to methods of treating patients with LCA due to RPE65 mutations. This patent is expected to expire in 2022, excluding any potential patent term extension or adjustment. A related continuing application currently is pending with the USPTO. There are no issued patents or pending patent applications outside of the United States that correspond to this patent.

We also in-licensed from CHOP U.S. and PCT patent applications co-owned by CHOP and Penn relating to testing functional vision with a mobility course, which can be used as an assessment tool to assess improvements in vision following treatment of an IRD. We expect that any patents issuing from these applications would expire in 2034, excluding any potential patent term extension or adjustment.

We have exclusively in-licensed a U.S. patent application from Penn that relates to a certain plasmid used in the manufacture of SPK-CHM. We believe any patent issuing from this application would expire in 2032.

We believe our manufacturing patent applications and related know-how and trade secrets may provide us with additional intellectual property protection relating to SPK-RPE65 and SPK-CHM.

### *Hematologic disorders*

We exclusively in-licensed certain patents and patent applications from CHOP related to our SPK-FIX program and hemophilia A program. In general, these patents and patent applications relate to AAV-mediated FIX gene therapy treatment of hemophilia B, adjunct therapy to use with gene therapy treatment of hemophilia B, modified AAV vectors and modified forms of FIX. These licensed patent rights include:

A U.S. patent that we believe provides us with exclusivity in the United States for treating hemophilia B with a Factor IX gene containing AAV vector. A related patent provides coverage on an AAV vector with a mutated FIX. Both U.S. patents are expected to expire in 2018, excluding any potential patent term extension or adjustment. Corresponding patents issued in Australia, Europe and Japan are expected to expire in 2018.



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A PCT patent application relating to modified AAV vector for delivery of FIX. We expect that a patent issuing from this application, if any, would expire in 2034, excluding any potential patent term extension or adjustment.

A U.S. patent relating to an adjunct therapy to reduce inhibitory antibodies against FIX administered via gene therapy. This patent is expected to expire in 2020, excluding any potential patent term extension or adjustment.

A U.S. patent application relating to certain modifications to a FIX gene that enhances secretion of FIX. We expect that a patent issuing from this application, if any, would expire in 2021, excluding any potential patent term extension or adjustment.

We believe our manufacturing patent applications and related know-how and trade secrets may provide us with additional intellectual property protection relating to our SPK-FIX program and hemophilia A program.

We also have exclusively in-licensed from CHOP a U.S. patent that relates to a Factor VIII heavy chain with enhanced secretion, which will expire in 2023, excluding any potential patent term extension or adjustment. There are no issued patents or pending patent applications outside of the United States that correspond to this U.S. patent.

### *Neurodegenerative disorders*

We exclusively in-licensed a portfolio of approximately 65 U.S. and foreign patents and patent applications from UIRF that relate to treatment of a broad array of CNS and neurodegenerative diseases.

### *Trade secrets*

In addition to patents and licenses, we rely on trade secrets and know-how to develop and maintain our competitive position. For example, significant aspects of our AAV and lentiviral vector and manufacturing processes and gene therapies are based upon trade secrets and know-how. However, trade secrets can be difficult to protect. We seek to protect our proprietary technology and processes, and obtain and maintain ownership of certain technologies, in part, through confidentiality agreements and invention assignment agreements with our employees, consultants, scientific advisors, contractors and commercial partners. We also seek to preserve the integrity and confidentiality of our data, trade secrets and know-how including by implementing measures intended to maintain the physical security of our premises and the physical and electronic security of our information technology systems.

## **Collaboration and license agreements**

### *Pfizer*

In December 2014, we entered into a global collaboration agreement with Pfizer for the development and commercialization of SPK-FIX product candidates in our gene therapy program for the treatment of hemophilia B. Under the agreement, we have granted Pfizer an exclusive worldwide license under specified patent rights and know-how relating to any FIX gene therapy that we develop, manufacture or commercialize prior to December 31, 2024, to develop, manufacture and commercialize such licensed FIX gene therapy products for the diagnosis, prevention, treatment and cure of hemophilia B.

Under the terms of the agreement, we are primarily responsible for conducting research and development activities through completion of Phase 1/2 clinical trials of hemophilia B product candidates. Pfizer and we will share development costs incurred under an agreed product development plan for each product candidate, with

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our share of development costs under the agreement limited to \$10.6 million. Following the completion of Phase 1/2 clinical trials, Pfizer will be primarily responsible for development, manufacture, regulatory approval and commercialization, including all costs associated therewith.

During the period through completion of Phase 1/2 clinical trials, which we refer to as the collaboration period, the hemophilia B program will be governed by a joint steering committee, or JSC, consisting of representatives of Pfizer and us. The JSC will, among other responsibilities, provide operational and strategic oversight to the activities to be performed under the product development plan, will monitor and assess the progress of collaboration activities and serve as a forum for the parties to communicate regarding collaboration issues and resolve disputes. During the collaboration period, if the JSC is unable to reach agreement, we generally have final decision-making authority regarding the conduct of the agreed product development plan and, following the collaboration period, Pfizer generally has final decision-making authority regarding the further development and commercialization of licensed compounds and licensed products.

Under the terms of the agreement, we received a \$20.0 million upfront payment. We also are eligible to receive up to \$260.0 million in aggregate milestone payments under the agreement, \$140.0 million of which relate to potential development, regulatory and commercial milestones for the first product candidate to achieve each milestone and \$120.0 million of which relate to potential regulatory milestones for additional product candidates. In addition, we are entitled to receive royalties, calculated as a low-teen percentage of net sales of licensed products. The royalties may be subject to certain reductions, including for a specified portion of royalty payments that Pfizer may become required to pay under any third-party license agreements, subject to a minimum royalty. Under the agreement, we remain solely responsible for the payment of license payments payable by us under specified license agreements.

The agreement will expire on a country-by-country basis upon the latest of: (i) the expiration of the last-to-expire valid claim, as defined in the agreement, in the licensed patent rights covering a licensed product, (ii) the expiration of the last-to-expire regulatory exclusivity granted with respect to a licensed product or (iii) 15 years after the first commercial sale of the last licensed product to be launched, in each case in the applicable country. The last to expire patent right licensed to Pfizer, if it issues as a patent, is currently expected to expire in 2034, excluding any applicable patent term extension or adjustment, although we could obtain rights to additional patents, including through the issuance of pending patent applications, with later expiration dates, which would be subject to Pfizer's license under the agreement. After expiration, but not termination, of the agreement as to a country, Pfizer's licenses will become fully paid-up, royalty-free, perpetual and irrevocable as to licensed products in the applicable country.

Pfizer may terminate the agreement, on a licensed product-by-licensed product and a country-by-country basis, or in its entirety, for any or no reason (i) upon 90 days' written notice prior to the commencement of commercialization of a licensed product or (ii) upon 180 days' written notice after the commencement of commercialization of a licensed product. Either party may, subject to a cure period, terminate the agreement in the event of the other party's uncured material breach. Either party also may terminate the agreement upon the occurrence of specified bankruptcy events. If the agreement is terminated, rights to licensed products that were being developed, manufactured or commercialized at that time generally revert to us.

If the agreement is terminated by Pfizer after the initiation of a pivotal clinical trial and we continue development utilizing intellectual property rights or data developed by Pfizer through its activities under the agreement, we will be required to pay Pfizer a royalty, calculated as a single-digit percentage of net sales of licensed products, with the percentage determined based on the stage of development or commercialization of the product candidate at the time of Pfizer's termination.

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### *Genable*

In March 2014, we entered into a license agreement, a 10-year manufacturing agreement and a development consultancy agreement with Genable Technologies Limited, or Genable, granting Genable a worldwide, exclusive license under certain of our patent rights and technology for AAV-based agents for the treatment of RHO-adRP. Any improvements on the licensed patent rights and technology discovered or invented by us are included automatically in the license to Genable. Under the terms of these agreements, Genable is required to use commercially reasonable efforts to develop and commercialize licensed products. Genable will pay us milestone payments upon certain regulatory achievements, up to an aggregate maximum of \$625,000. We also are entitled to receive an aggregate tiered mid-single-digit percentage royalty on net sales of the licensed product.

This license will expire on a country-by-country basis upon the later of expiration of all of the patent rights subject to the license or 10 years after first commercial sale of the licensed product in such country. If any of the pending patent applications that currently are licensed to Genable issue as patents, we expect the last to expire of any such patents would expire in 2034, excluding any applicable patent term extension or adjustment. We may terminate the license agreement upon uncured material breaches by Genable of the terms of the license and Genable may terminate the license at any time upon giving 90 days prior written notice to us. Either party may also terminate the license upon the bankruptcy of the other party and we may terminate the license if Genable challenges the grant or validity of the licensed patents. Genable and we can only terminate the manufacturing agreement upon material breach of this agreement by the other party. The manufacturing agreement terminates upon termination or expiration of the license agreement. The development consultancy agreement expires with regard to services when Genable receives regulatory approval for licensed products incorporating RhoNova in both the United States and the European Union. Either party may terminate the development consultancy agreement if the other party fails to make payments when due, in the event of an uncured material breach by the other party or upon the bankruptcy of the other party. Genable may also terminate the development consultancy agreement without cause at any time upon 90 days prior written notice or if a designated project director becomes unwilling or unable to provide the services to Genable and a reasonable substitute is not available. Upon termination by Genable under certain conditions, the development consultancy agreement specifies cessation or adjustment of royalty payments.

### *In-license agreements*

We have rights to use and exploit multiple issued and pending patents under licenses from other entities. We consider the commercial terms of these licenses, which provide for modest milestone and royalty payments, and their provisions regarding diligence, insurance, indemnification and other similar matters, to be reasonable and customary for our industry.

### The Children's Hospital of Philadelphia

In October 2013, we entered into a technology assignment agreement with CHOP. Under this agreement, CHOP assigned to us CHOP's rights to the preclinical and clinical programs and intellectual property that we are currently advancing as well as know-how, standard operating procedures, trade secrets and proprietary processes related to our manufacturing platform. Furthermore, under this agreement, we obtained commercial rights to the drug master file, batch records and related data associated with the manufacture of AAV and lentiviral vectors using our manufacturing platform.

We also entered into a license agreement with CHOP under which CHOP granted us an exclusive worldwide license in the field of gene therapy, with the right to sublicense, under a broad portfolio of gene therapy and viral vector patent rights and gene therapy know-how related to vector manufacturing technology, the treatment of hemophilia and other gene therapy indications. CHOP also granted us a non-exclusive worldwide

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license in the field of gene therapy, with the right to sublicense, to other know-how owned or controlled by CHOP, existing as of the effective date of the license agreement and not explicitly covered by the exclusive licenses, that is necessary or useful for making, using, selling or importing any products we may develop that are covered by our exclusive license. Under both license grants, we have the right to research, develop, manufacture and commercialize products covered by the licensed patent rights or the licensed know-how in the field of gene therapy. Under the terms of the license agreement, we are obligated to use commercially reasonable best efforts to develop and commercialize licensed products. We are obligated under the license agreement to make milestone payments upon the treatment of the first subject treated in a U.S. Phase 3, or a foreign equivalent, clinical trial and upon the first commercial sale for the first licensed product in each of four indications. These milestone payments range from \$125,000 to \$5.0 million, and would, in the aggregate, reach a maximum of \$7.1 million if all milestones are achieved. In addition, we are obligated to pay CHOP a low-single-digit royalty on a country-by-country basis on net sales of licensed products covered by a valid licensed patent claim. Following the expiration of our royalty obligations as to a licensed product in a country, we will retain a perpetual, full and unrestricted right to make, use and commercialize the licensed product in such country under the licensed intellectual property rights. CHOP controls the prosecution and maintenance of the licensed patent rights. We have agreed to reimburse CHOP for fees and expenses incurred in connection with the prosecution and maintenance of the licensed patent rights, including those fees and expenses incurred prior to the effective date of the license agreement. Unless sooner terminated, the term of the license agreement continues until the expiration of the last to expire of the licensed patent rights, the latest of which is currently expected to expire in 2034. If we oppose or contest the grant or validity of any licensed patent right, or any claims thereof, CHOP may terminate the license granted to us with respect to such patent right. CHOP may terminate this license upon uncured material breaches by us of the terms of the license or if such action is legally necessary to comply with applicable federal laws or regulations relating to government march-in rights and we may terminate the license at any time upon giving 90 days' prior written notice to CHOP.

We also have entered into a master research services agreement with CHOP under which CHOP supplies us with viral vectors. Under this master research services agreement, we expect to maintain a sufficient supply of clinical-grade gene therapy vectors produced in CHOP's cGMP clinical facility to meet both our clinical needs and, at our option, our commercial batches to support the commercial launch of SPK-RPE65, if approved. The term of the agreement extends until October 14, 2028 as to services relating to the supply of RPE65 vectors and until July 1, 2015 as to other services, and continues beyond such expiration dates as to work orders executed by the parties prior to the applicable expiration date until the completion of such work orders. We may terminate this agreement upon 30 days' written notice for any reason, and CHOP may terminate this agreement upon 30 days' written notice upon uncured material breaches by us of the terms of the agreement or if it reasonably determines that continuation of this agreement will have a materially adverse effect on its legal, regulatory or tax status.

**University of Pennsylvania**

In October 2013, we entered into a license agreement with Penn. Under this license agreement, Penn granted us a co-exclusive, worldwide license, with the right to sublicense, to certain patent rights owned by Penn or jointly owned by Penn, Cornell University and/or the University of Florida related to a method of treating and retarding the development of blindness to manufacture and commercialize products covered by the licensed patent rights in the field of research, development, manufacture and commercialization for the diagnosis, treatment, amelioration and prevention of human and animal diseases. Penn, on behalf of the other joint owners, has the right to grant one additional co-exclusive license to the licensed patent rights. This additional license could grant a third party the same scope of rights that we have received under our license agreement with Penn, including a right to commercialize products covered by the licensed patent rights. However, we believe that the potential one-time nature of a gene therapy treatment could enable a company that receives the first FDA approval for a disease or

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condition, and which also has obtained orphan product exclusivity for such disease or condition, to treat a substantial portion of the addressable patient population during the period of orphan product exclusivity.

Under the terms of the license agreement, we are obligated to use commercially reasonable efforts to develop and commercialize licensed products, and to use such efforts to accomplish specified development and commercial launch objectives in accordance with a specified timeline as well as to expend specified resources in the development and commercialization of licensed products. If our total expenditures on development and commercialization of the licensed products in any 12-month period do not meet or exceed the applicable diligence minimum, then we must pay Penn the amount of the shortfall. Under the terms of the agreement, we are obligated to make commercial milestone payments related to the licensed products, which could, in the aggregate, reach a maximum of \$3.8 million per licensed product if all milestones are achieved for such licensed product. In addition, we are obligated to pay Penn a low- to mid-single-digit royalty on a country-by-country basis on net sales of licensed products covered by a valid licensed patent claim. Penn controls the prosecution and maintenance of the licensed patent rights. We made an initial cash payment to Penn to cover 50% of Penn's previously incurred patent expenses relating to the licensed patent rights, with the exception of one patent for which we agreed to reimburse Penn for all such expenses. With respect to that specific patent, we agreed to reimburse Penn for patent expenses arising during the term of the license, with such reimbursement obligation reduced to 50% of applicable expenses if there is another co-exclusive licensee of the licensed patent rights. This license will expire upon the expiration or abandonment of all of the patents and patent applications subject to the license, the latest of which is currently expected to expire in 2022. Penn may terminate the license upon uncured material breaches by us of the terms of the license or upon the occurrence of certain events, including specified bankruptcy and insolvency events relating to us, or if we commence an action against Penn or any of the co-owners of the licensed patent rights to declare or render invalid or unenforceable the patent rights. We may terminate the license at any time upon giving 60 days' prior written notice to Penn.

In December 2014, we entered into a license agreement with Penn, under which Penn granted us an exclusive, worldwide license, with the right to sublicense, to certain patent rights owned by Penn related to certain proviral plasmids that are useful in the manufacture of certain gene therapy products for the treatment of CHM.

Under the terms of the license agreement, we are obligated to use commercially reasonable efforts to develop and commercialize licensed products, and to use such efforts to accomplish development and commercial launch objectives as well as to expend specified resources in the development and commercialization of licensed products. If our total expenditures in any 12-month period do not meet or exceed the applicable diligence minimum, then we must pay Penn the amount of the shortfall. Under the terms of the agreement, we issued shares of our common stock to Penn and we are obligated to make milestone payments upon the achievement of certain regulatory milestones relating to the licensed products, which could, in the aggregate, reach a maximum of \$5.5 million per licensed product if all milestones are achieved for such licensed product. Upon mutual agreement between Penn and us, we could elect to pay up to 100% of such amounts with shares of our common stock. In addition, we are obligated to pay Penn a mid-single-digit royalty on a country-by-country basis on net sales of licensed products covered by a licensed patent claim so long as the licensed product achieves and retains orphan designation, and if the licensed product does not receive or retain orphan product designation, we are obligated to pay Penn a low-single digit royalty on a country-by-country basis. We are obligated to pay Penn specified percentages of certain non-royalty payments and other consideration we may receive from any sublicense of our rights under the license agreements, with the specified percentage dependent on the timing of the sublicense grant. Penn controls the prosecution and maintenance of the licensed patent rights. We also made an initial cash payment to Penn to cover all of Penn's previously incurred patent expenses relating to the licensed patent rights. This license will expire upon the expiration or abandonment of all of the patents and patent applications subject to the license, the latest of which, if it issues as a patent, is currently expected to expire in 2032. Penn may terminate the license upon uncured material

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breaches by us of the terms of the license and upon the occurrence of certain events, including specified bankruptcy and insolvency events relating to us, or if we commence an action against Penn to declare or render invalid or unenforceable the patent rights, and we may terminate the license at any time upon giving 60 days prior written notice to Penn.

### **University of Iowa Research Foundation**

In October 2013, we entered into a license agreement with UIRF. Under this license agreement, UIRF granted us an exclusive worldwide license, with the right to sublicense, to a portfolio of approximately 50 gene therapy patents and patent applications owned by UIRF or jointly owned by UIRF and Massachusetts General Hospital related to RNA interference and gene therapy technologies, and to the results of a certain research collaboration among UIRF, Howard Hughes Medical Institute and CHOP, to manufacture and commercialize products covered by the licensed patent rights or discovered, developed, manufactured or commercialized through the use of the research collaboration results. Under the terms of the license agreement, we are obligated to use reasonable efforts to develop and commercialize licensed products. In connection with the agreement, we issued shares of our common stock and made a cash payment of approximately \$157,000 to UIRF, and we are obligated to make milestone payments upon the achievement of certain regulatory milestones relating to the licensed products, which could, in the aggregate, reach a maximum of \$1.3 million if all milestones are achieved. In addition, we are obligated to pay UIRF a low-single-digit royalty on a country-by-country basis on net sales of licensed products covered by a valid licensed patent claim. Commencing in 2017, we are obligated to pay an aggregate of \$40,000 in annual license maintenance fees to UIRF, which are creditable against specified milestone and royalty payment obligations accruing in the same year. The license maintenance fees and royalty rates are subject to increase if we, or any person or entity acting on our behalf, bring any action or claim challenging the validity or enforceability of the licensed patent rights. UIRF is responsible for prosecution and maintenance of the licensed patent rights and we have agreed to reimburse UIRF for reasonable expenses incurred in prosecution and maintenance of the licensed patent rights. Upon mutual agreement between UIRF and us, we could elect to pay some or all of our payment obligations under the license with shares of our common stock.

The license agreement and our obligation to pay royalties expire, unless earlier terminated, on a country-by-country and licensed product-by-licensed product basis, upon the expiration of the last to expire valid claim, as defined in the agreement in the licensed patent rights (including patent applications) covering the manufacture, use, sale or importation of such licensed product in such country. Following the expiration of our obligation to pay royalties on a licensed product in a country, we will retain a fully paid-up, non-royalty-bearing, perpetual license to the results of the collaboration relating to such licensed product in such country. UIRF may terminate this license or render it non-exclusive at any time after October 14, 2018 if we have both (i) not put the licensed product into commercial use in any country and (ii) are not demonstrably engaged in a program directed toward achieving commercial use of the product, and if we fail to eliminate such conditions within a specified cure period following notice from UIRF. UIRF may also terminate this license upon uncured material breaches by us of the terms of the license, subject to a specified notice and cure period. The license agreement automatically terminates if we undergo certain bankruptcy or insolvency events. We may terminate the license at any time upon giving 90 days prior written notice to UIRF.

## **Competition**

The biotechnology and pharmaceutical industries, including the gene therapy field, are characterized by rapidly changing technologies, significant competition and a strong emphasis on intellectual property. We face substantial competition from many different sources, including large and specialty pharmaceutical and biotechnology companies, academic research institutions, government agencies and public and private research institutions.

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We are aware of several companies focused on developing gene therapies in various indications, including bluebird bio, AGTC, Asklepios, Audentes, Avalanche, Dimension, GenSight, NighstaRx, ReGenX and uniQure, as well as several companies addressing other methods for modifying genes and regulating gene expression. Any advances in gene therapy technology made by a competitor may be used to develop therapies that could compete against any of our product candidates.

For our particular product candidates, the main competitors include:

**RPE65.** While no approved pharmacologic agents exist for patients with RPE65-mediated IRDs, Second Sight Medical Products has received approval from FDA and other foreign regulatory authorities for a retinal prosthesis medical device, which is being marketed to RP patients with limited or no light perception. Another retinal prosthesis medical device from Retina Implant has obtained a CE Certificate of Conformity from its notified body, and is similarly indicated for blinded patients. QLT is in Phase 1b clinical development with a vitamin A derivative to treat RP and LCA. In the gene therapy space, AGTC, as well as several academic institutions, have conducted clinical trials involving RPE65-based product candidates, but none has completed a Phase 1 trial of injection of the second eye or initiated a Phase 3 trial, and we believe we are the furthest along in development of any gene therapy product to treat this disease.

**Choroideremia.** We are aware that NightstaRx is developing an AAV-based gene therapy for the treatment of choroideremia. NightStaRx has obtained orphan product designation in the European Union for this product candidate for the treatment of choroideremia and a Phase 1/2 trial of this product candidate is being conducted in Europe.

**Hemophilia B.** Hemophilia B patients typically are treated by a variety of plasma-derived, recombinant or long-acting products that are produced by a number of companies, including Pfizer. Many other companies are developing gene therapies to treat hemophilia B, including Baxter, uniQure and Dimension.

Many of our potential competitors, alone or with their strategic partners, have substantially greater financial, technical and other resources than we do, such as larger research and development, clinical, marketing and manufacturing organizations. Mergers and acquisitions in the biotechnology and pharmaceutical industries may result in even more resources being concentrated among a smaller number of competitors. Our commercial opportunity could be reduced or eliminated if 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. 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. Additionally, technologies developed by our competitors may render our potential product candidates uneconomical or obsolete, and we may not be successful in marketing our product candidates against competitors.

## **Government regulation**

In the United States, FDA, regulates biologic products including gene therapy products under the Federal Food, Drug, and Cosmetic Act, or FDCA, the Public Health Service Act, or PHSA, and regulations and guidance implementing these laws. The FDCA, PHSA and their corresponding regulations govern, among other things, the testing, manufacturing, safety, efficacy, labeling, packaging, storage, record keeping, distribution, reporting, advertising and other promotional practices involving biologic products. Applications to FDA are required before conducting human clinical testing of biologic products. Additionally, each clinical trial protocol for a gene therapy product candidate is reviewed by FDA and, in limited instances NIH, through its RAC. FDA approval also must be obtained before marketing of biologic products.

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Within FDA, CBER regulates gene therapy products. Within CBER, the review of gene therapy and related products is consolidated in the Office of Cellular, Tissue and Gene Therapies, or OCTGT, and FDA has established the Cellular, Tissue and Gene Therapies Advisory Committee, or CTGTAC, to advise CBER on its reviews. CBER works closely with NIH and the RAC, which makes recommendations to NIH on gene therapy issues and engages in a public discussion of scientific, safety, ethical and societal issues related to proposed and ongoing gene therapy protocols. Although FDA has not yet approved any human gene therapy product for sale, it has provided guidance for the development of gene therapy products. This guidance includes a growing body of guidance documents on chemistry, manufacturing and control, or CMC, clinical investigations and other areas of gene therapy development, all of which are intended to facilitate the industry's development of gene therapy products.

### *U.S. biologic products development process*

The process required by FDA before a biologic product candidate may be marketed in the United States generally involves the following:

completion of preclinical laboratory tests and *in vivo* studies in accordance with FDA's current Good Laboratory Practice, or GLP, regulations and applicable requirements for the humane use of laboratory animals or other applicable regulations;

submission to FDA of an application for an Investigational New Drug exemption, or IND, which allows human clinical trials to begin unless FDA objects within 30 days;

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

performance of adequate and well-controlled human clinical trials according to FDA's GCP regulations, and any additional requirements for the protection of human research subjects and their health information, to establish the safety and efficacy of the proposed biologic product candidate for its intended use;

preparation and submission to FDA of a BLA for marketing approval that includes substantial evidence of safety, purity and potency from results of nonclinical testing and clinical trials;

satisfactory completion of an FDA inspection of the manufacturing facility or facilities where the biologic product candidate is produced to assess compliance with cGMP and to assure that the facilities, methods and controls are adequate to preserve the biologic product candidate's identity, safety, strength, quality, potency and purity;

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

payment of user fees and FDA review and approval, or licensure, of the BLA.

Before testing any biologic product candidate in humans, including a gene therapy product candidate, the product candidate must undergo preclinical testing. Preclinical tests, also referred to as nonclinical studies, include laboratory evaluations of product chemistry, toxicity and formulation, as well as *in vivo* studies to assess the potential safety and activity of the product candidate. The conduct of the preclinical tests must comply with federal regulations and requirements including GLPs.

If a gene therapy trial is conducted at, or sponsored by, institutions receiving NIH funding for recombinant DNA research, prior to the submission of an IND to FDA, a protocol and related documents must be submitted to, and the study registered with, the NIH Office of Biotechnology Activities, or OBA, pursuant to the NIH Guidelines for





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Research Involving Recombinant DNA Molecules, or NIH Guidelines. Compliance with the NIH Guidelines is mandatory for investigators at institutions receiving NIH funds for research involving recombinant DNA. However, many companies and other institutions, not otherwise subject to the NIH Guidelines, voluntarily follow them. NIH is responsible for convening the RAC that discusses protocols that raise novel or particularly important scientific, safety or ethical considerations at one of its quarterly public meetings. The OBA will notify FDA of the RAC's decision regarding the necessity for full public review of a gene therapy protocol. RAC proceedings and reports are posted to the OBA website and may be accessed by the public.

The clinical trial sponsor must submit the results of the preclinical tests, together with manufacturing information, analytical data, any available clinical data or literature and a proposed clinical protocol, to FDA as part of the IND. Some preclinical testing may continue even after the IND is submitted. The IND automatically becomes effective 30 days after receipt by FDA, unless FDA places the clinical trial on a clinical hold. In such a case, the IND sponsor and FDA must resolve any outstanding concerns before the clinical trial can begin. With gene therapy protocols, if FDA allows the IND to proceed, but the RAC decides that full public review of the protocol is warranted, FDA will request at the completion of its IND review that sponsors delay initiation of the protocol until after completion of the RAC review process. FDA also may impose clinical holds on a biologic product candidate at any time before or during clinical trials due to safety concerns or non-compliance. If FDA imposes a clinical hold, trials may not recommence without FDA authorization and then only under terms authorized by FDA.

### *Human clinical trials under an IND*

Clinical trials involve the administration of the biologic product candidate to healthy volunteers or patients under the supervision of qualified investigators which generally are physicians not employed by, or under, the control of the trial sponsor. Clinical trials are conducted under protocols detailing, among other things, the objectives of the clinical trial, dosing procedures, subject selection and exclusion criteria and the parameters to be used to monitor subject safety, including stopping rules that assure a clinical trial will be stopped if certain adverse events should occur. Each protocol and any amendments to the protocol must be submitted to FDA as part of the IND. Clinical trials must be conducted and monitored in accordance with FDA's regulations comprising the GCP requirements, including the requirement that all research subjects provide informed consent.

Further, each clinical trial must be reviewed and approved by an IRB at or servicing each institution at which the clinical trial will be conducted. An IRB is charged with protecting the welfare and rights of trial participants and considers items such as whether the risks to individuals participating in the clinical trials are minimized and are reasonable in relation to anticipated benefits. The IRB also approves the form and content of the informed consent that must be signed by each clinical trial subject, or his or her legal representative, and must monitor the clinical trial until completed. Clinical trials involving recombinant DNA also must be reviewed by an institutional biosafety committee, or IBC, a local institutional committee that reviews and oversees basic and clinical research that utilizes recombinant DNA at that institution. The IBC assesses the safety of the research and identifies any potential risk to public health or the environment.

Human clinical trials typically are conducted in three sequential phases that may overlap or be combined:

*Phase 1.* The biologic product candidate initially is introduced into healthy human subjects and tested for safety, dosage tolerance, absorption, metabolism, distribution, excretion and, if possible, to gain an early understanding of its effectiveness. In the case of some product candidates for severe or life-threatening diseases, especially when the product candidate may be too inherently toxic to ethically administer to healthy volunteers, the initial human testing is often conducted in patients.

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*Phase 2.* The biologic product candidate is evaluated in a limited patient population to identify possible adverse effects and safety risks, to preliminarily evaluate the efficacy of the product candidate for specific targeted diseases and to determine dosage tolerance, optimal dosage and dosing schedule.

*Phase 3.* The biologic product candidate is administered to an expanded patient population at geographically dispersed clinical trial sites in adequate and well-controlled clinical trials to generate sufficient data to statistically confirm the potency and safety of the product for approval. These clinical trials are intended to establish the overall risk/benefit ratio of the product candidate and provide an adequate basis for product labeling.

Post-approval clinical trials, sometimes referred to as Phase 4 clinical trials, may be conducted after initial approval. These clinical trials are used to gain additional experience from the treatment of patients in the intended therapeutic indication, particularly for long-term safety follow-up.

During all phases of clinical development, regulatory agencies require extensive monitoring and auditing of all clinical activities, clinical data and clinical trial investigators. Annual progress reports detailing the results of the clinical trials must be submitted to FDA.

Written IND safety reports must be promptly submitted to FDA, NIH and the investigators for: serious and unexpected adverse events; any findings from other trials, *in vivo* laboratory tests or *in vitro* testing that suggest a significant risk for human subjects; or any clinically important increase in the rate of a serious suspected adverse reaction over that listed in the protocol or investigator brochure. The sponsor must submit an IND safety report within 15 calendar days after the sponsor determines that the information qualifies for reporting. The sponsor also must notify FDA of any unexpected fatal or life-threatening suspected adverse reaction within seven calendar days after the sponsor's initial receipt of the information.

FDA or the sponsor or its data safety monitoring board may suspend a clinical trial at any time on various grounds, including a finding that the research subjects or patients are being exposed to an unacceptable health risk. Similarly, an IRB can suspend or terminate approval of a clinical trial at its institution if the clinical trial is not being conducted in accordance with the IRB's requirements or if the biologic product candidate has been associated with unexpected serious harm to patients.

### *Additional regulation for gene therapy clinical trials*

In addition to the regulations discussed above, there are a number of additional standards that apply to clinical trials involving the use of gene therapy. FDA has issued various guidance documents regarding gene therapies, which outline additional factors that FDA will consider at each of the above stages of development and relate to, among other things: the proper preclinical assessment of gene therapies; the CMC information that should be included in an IND application; the proper design of tests to measure product potency in support of an IND or BLA application; and measures to observe delayed adverse effects in subjects who have been exposed to investigational gene therapies when the risk of such effects is high. Further, FDA usually recommends that sponsors observe subjects for potential gene therapy-related delayed adverse events for a 15-year period, including a minimum of five years of annual examinations followed by 10 years of annual queries, either in person or by questionnaire.

NIH and FDA have a publicly accessible database, the Genetic Modification Clinical Research Information System, which includes information on gene therapy trials and serves as an electronic tool to facilitate the reporting and analysis of adverse events on these trials.

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### *Compliance with cGMP requirements*

Manufacturers of biologics must comply with applicable cGMP regulations, including quality control and quality assurance and maintenance of records and documentation. Manufacturers and others involved in the manufacture and distribution of such products also must register their establishments with FDA and certain state agencies. Both domestic and foreign manufacturing establishments must register and provide additional information to FDA upon their initial participation in the manufacturing process. Establishments may be subject to periodic, unannounced inspections by government authorities to ensure compliance with cGMP requirements and other laws. Discovery of problems may result in a government entity placing restrictions on a product, manufacturer or holder of an approved BLA, and may extend to requiring withdrawal of the product from the market. 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 specification.

Concurrent with clinical trials, companies usually complete additional preclinical studies and must also develop additional information about the physical characteristics of the biologic product candidate as well as finalize a process for manufacturing the product candidate in commercial quantities in accordance with cGMP requirements. To help reduce the risk of the introduction of adventitious agents or of causing other adverse events with the use of biologic products, the PHSA emphasizes the importance of manufacturing control for products whose attributes cannot be precisely defined. The manufacturing process must be capable of consistently producing quality batches of the product candidate and, among other requirements, the sponsor must develop methods for testing the identity, strength, quality, potency and purity of the final biologic product. Additionally, appropriate packaging must be selected and tested and stability studies must be conducted to demonstrate that the biologic product candidate does not undergo unacceptable deterioration over its shelf life.

### *U.S. review and approval processes*

The results of the preclinical tests and clinical trials, together with detailed information relating to the product's CMC and proposed labeling, among other things, are submitted to FDA as part of a BLA requesting approval to market the product for one or more indications.

For gene therapies, selecting patients with applicable genetic defects is a necessary condition to effective treatment. For the therapies we are currently developing, we believe that diagnoses based on symptoms, in conjunction with existing genetic tests developed and administered by laboratories certified under the Clinical Laboratory Improvement Amendments, or CLIA, are sufficient to select appropriate patients and will be permitted by FDA. For future therapies, however, it may be necessary to use FDA-cleared or FDA-approved diagnostic tests to select patients or to assure the safe and effective use of therapies in appropriate patients. FDA refers to such tests as *in vitro* companion diagnostic devices. On July 31, 2014, FDA announced the publication of a final guidance document describing the agency's current thinking about the development and regulation of *in vitro* companion diagnostic devices. The final guidance articulates a policy position that, when safe and effective use of a therapeutic product depends on a diagnostic device, FDA generally will require approval or clearance of the diagnostic device at the same time that FDA approves the therapeutic product. The final guidance allows for two exceptions to the general rule of concurrent drug/device approval, namely, when the therapeutic product is intended to treat serious and life-threatening conditions for which no alternative exists, and when a serious safety issue arises for an approved therapeutic agent, and no FDA-cleared or FDA-approved companion diagnostic test is yet available. At this point, it is unclear how FDA will apply this policy to our future gene therapy candidates, or even to our current products. Should FDA deem genetic tests used for selecting appropriate patients for our therapies to be *in vitro* companion diagnostics requiring FDA clearance or approval, we may face significant delays or obstacles in obtaining approval for a BLA.

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In addition, under the Pediatric Research Equity Act, or PREA, a BLA or supplement to a BLA must contain data to assess the safety and effectiveness of the biologic product candidate for the claimed indications in all relevant pediatric subpopulations and to support dosing and administration for each pediatric subpopulation for which the product candidate is safe and effective. FDA may grant deferrals for submission of data or full or partial waivers. Unless otherwise required by regulation, PREA does not apply to any biologic product candidate for an indication for which orphan designation has been granted.

Under the Prescription Drug User Fee Act, or PDUFA, as amended, each BLA must be accompanied by a user fee. FDA adjusts the PDUFA user fees on an annual basis. According to FDA's fee schedule, effective through September 30, 2015, the user fee for an application requiring clinical data, such as a BLA, is \$2,335,200. PDUFA also imposes an annual product fee for biologics (\$110,370) and an annual establishment license fee (\$569,200) on facilities used to manufacture prescription biologics. Fee waivers or reductions are available in certain circumstances, including a waiver of the application fee for the first application filed by a small business. Additionally, no user fees are assessed on BLAs for product candidates designated as orphan drugs, unless the product candidate also includes a non-orphan indication.

FDA reviews a BLA within 60 days of submission to determine if it is substantially complete before the agency accepts it for filing. FDA may refuse to file any BLA that it deems incomplete or not properly reviewable at the time of submission and may request additional information. In that event, the BLA must be resubmitted with the additional information. The resubmitted application also is subject to review before FDA accepts it for filing. Once the submission is accepted for filing, FDA begins an in-depth, substantive review of the BLA.

FDA reviews the BLA to determine, among other things, whether the proposed product candidate is safe and potent, or effective, for its intended use, has an acceptable purity profile and whether the product candidate is being manufactured in accordance with cGMP to assure and preserve the product candidate's identity, safety, strength, quality, potency and purity. FDA may refer applications for novel biologic products or biologic products that present difficult questions of safety or efficacy to an advisory committee, typically a panel that includes clinicians and other experts, for review, evaluation and a recommendation as to whether the application should be approved and under what conditions. FDA is not bound by the recommendations of an advisory committee, but it considers such recommendations carefully when making decisions. During the product approval process, FDA also will determine whether a REMS is necessary to assure the safe use of the product candidate. A REMS could include medication guides, physician communication plans and elements to assure safe use, such as restricted distribution methods, patient registries and other risk minimization tools. If FDA concludes a REMS is needed, the sponsor of the BLA must submit a proposed REMS; FDA will not approve the BLA without a REMS, if required.

Before approving a BLA, FDA will inspect the facilities at which the product candidate is manufactured. FDA will not approve the product candidate unless it determines that the manufacturing processes and facilities are in compliance with cGMP requirements and adequate to assure consistent production of the product candidate within required specifications. Additionally, before approving a BLA, FDA typically will inspect one or more clinical sites to assure that the clinical trials were conducted in compliance with IND trial requirements and GCP requirements.

On the basis of the BLA and accompanying information, including the results of the inspection of the manufacturing facilities, FDA may issue an approval letter or a complete response letter. An approval letter authorizes commercial marketing of the biologic 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 FDA to reconsider the application. If and when those deficiencies have been addressed to FDA's satisfaction in a resubmission of the BLA, FDA will issue an approval letter.

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If a product candidate receives regulatory approval, the approval may be significantly limited to specific diseases and dosages or the indications for use may otherwise be limited. Further, FDA may require that certain contraindications, warnings or precautions be included in the product labeling. FDA may impose restrictions and conditions on product distribution, prescribing or dispensing in the form of a REMS, or otherwise limit the scope of any approval. In addition, FDA may require post-marketing clinical trials, sometimes referred to as Phase 4 clinical trials, designed to further assess a biologic product's safety and effectiveness, and testing and surveillance programs to monitor the safety of approved products that have been commercialized.

FDA has agreed to specified performance goals in the review of BLAs under the PDUFA. One such goal is to review 90% of standard BLAs in 10 months after FDA accepts the BLA for filing, and 90% of priority BLAs in six months, whereupon a review decision is to be made. The FDA does not always meet its PDUFA goal dates for standard and priority BLAs and its review goals are subject to change from time to time. The review process and the PDUFA goal date may be extended by three months if the FDA requests or the BLA sponsor otherwise provides additional information or clarification regarding information already provided in the submission within the last three months before the PDUFA goal date.

### *Orphan drug designation*

Under the Orphan Drug Act, FDA may designate a biologic 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 biologic product available in the United States for treatment of the disease or condition will be recovered from sales of the product). Orphan product designation must be requested before submitting a BLA. After FDA grants orphan product designation, the identity of the therapeutic agent and its potential orphan use are disclosed publicly by FDA. Orphan product designation does not convey any advantage in, or shorten the duration of, the regulatory review and approval process.

If a product with orphan status receives the first FDA approval for the disease or condition for which it has such designation, the product is entitled to orphan product exclusivity, meaning that FDA may not approve any other applications to market the same drug or biologic product for the same indication for seven years, except in limited circumstances, such as a showing of clinical superiority to the product with orphan exclusivity or if the party holding the exclusivity fails to assure the availability of sufficient quantities of the drug to meet the needs of patients with the disease or condition for which the drug was designated. Competitors, however, may receive approval of different products for the same indication for which the orphan product has exclusivity or obtain approval for the same product but for a different indication for which the orphan product has exclusivity. Orphan medicinal product status in the European Union has similar, but not identical, benefits.

### *Expedited development and review programs*

FDA is authorized to expedite the review of BLAs in several ways. Under the Fast Track program, the sponsor of a biologic product candidate may request FDA to designate the product for a specific indication as a Fast Track product concurrent with or after the filing of the IND. Biologic products are eligible for Fast Track designation if they are intended to treat a serious or life-threatening condition and demonstrate the potential to address unmet medical needs for the condition. Fast Track designation applies to the combination of the product candidate and the specific indication for which it is being studied. In addition to other benefits, such as the ability to have greater interactions with FDA, FDA may initiate review of sections of a Fast Track BLA before the application is complete, a process known as rolling review.

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Any product submitted to FDA for marketing, including under a Fast Track program, may be eligible for other types of FDA programs intended to expedite development and review, such as breakthrough therapy designation, priority review and accelerated approval.

*Breakthrough therapy designation.* To qualify for the breakthrough therapy program, product candidates must be intended to treat a serious or life-threatening disease or condition and preliminary clinical evidence must indicate that such product candidates may demonstrate substantial improvement on one or more clinically significant endpoints over existing therapies. FDA will seek to ensure the sponsor of a breakthrough therapy product candidate receives: intensive guidance on an efficient drug development program; intensive involvement of senior managers and experienced staff on a proactive, collaborative and cross-disciplinary review; and rolling review.

*Priority review.* A product candidate is eligible for priority review if it treats a serious condition and, if approved, it would be a significant improvement in the safety or effectiveness of the treatment, diagnosis or prevention of a serious condition compared to marketed products. FDA aims to complete its review of priority review applications within six months as opposed to 10 months for standard review.

*Accelerated approval.* Drug or biologic products studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit over existing treatments may receive accelerated approval. Accelerated approval means that a product candidate may be approved on the basis of adequate and well-controlled clinical trials establishing that the product candidate has an effect on a surrogate endpoint that is reasonably likely to predict a clinical benefit, or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity and prevalence of the condition and the availability or lack of alternative treatments. As a condition of approval, 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. In addition, FDA currently requires as a condition for accelerated approval pre-approval of promotional materials.

Fast Track designation, breakthrough therapy designation, priority review and accelerated approval do not change the standards for approval but may expedite the development or approval process.

### *Post-approval requirements*

Rigorous and extensive FDA regulation of biologic products continues after approval, particularly with respect to cGMP requirements. Manufacturers are required to comply with applicable requirements in the cGMP regulations, including quality control and quality assurance and maintenance of records and documentation. Other post-approval requirements applicable to biologic products include reporting of cGMP deviations that may affect the identity, potency, purity and overall safety of a distributed product, record-keeping requirements, reporting of adverse effects, reporting updated safety and efficacy information and complying with electronic record and signature requirements. After a BLA is approved, the product also may be subject to official lot release. If the product is subject to official release by FDA, the manufacturer submits samples of each lot of product to FDA, together with a release protocol, showing a summary of the history of manufacture of the lot and the results of all tests performed on the lot. FDA also may perform certain confirmatory tests on lots of some products before releasing the lots for distribution. In addition, FDA conducts laboratory research related to the regulatory standards on the safety, purity, potency and effectiveness of biologic products.

A sponsor also must comply with FDA's advertising and promotion requirements, such as those related to direct-to-consumer advertising, the prohibition on promoting products for uses or in patient populations that

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are not described in the product's approved labeling (known as off-label use), industry-sponsored scientific and educational activities and promotional activities involving the Internet. Discovery of previously unknown problems or the failure to comply with the applicable regulatory requirements may result in restrictions on the marketing of a product or withdrawal of the product from the market as well as possible civil or criminal sanctions. In addition, changes to the manufacturing process or facility generally require prior FDA approval before being implemented and other types of changes to the approved product, such as adding new indications and additional labeling claims, are also subject to further FDA review and approval.

Failure to comply with the applicable U.S. requirements at any time during the product development process, approval process or after approval, may subject an applicant or manufacturer to administrative or judicial civil or criminal actions and adverse publicity. These actions could include refusal to approve pending applications or supplemental applications, withdrawal of an approval, clinical hold, suspension or termination of clinical trial by an IRB, warning or untitled letters, product recalls, product seizures, total or partial suspension of production or distribution, injunctions, fines or other monetary penalties, refusals of government contracts, mandated corrective advertising or communications with healthcare providers, debarment, restitution, disgorgement of profits or other civil or criminal penalties.

### *U.S. patent term restoration and marketing exclusivity*

Depending upon the timing, duration and specifics of FDA approval of product candidates, some of a sponsor's U.S. patents may be eligible for limited patent term extension under the Drug Price Competition and Patent Term Restoration Act of 1984. The Hatch-Waxman Amendments permit a patent restoration term of up to five years as compensation for patent term lost during product development and FDA regulatory review process. However, patent term restoration cannot extend the remaining term of a patent beyond a total of 14 years from the product's approval date. The patent term restoration period generally is one-half the time between the effective date of an IND and the submission date of a BLA plus the time between the submission date of a BLA and the approval of that application. Only one patent applicable to an approved biologic product is eligible for the extension and the application for the extension must be submitted prior to the expiration of the patent. The USPTO, in consultation with FDA, reviews and approves the application for any patent term extension or restoration.

### *Pediatric exclusivity*

Pediatric exclusivity is a type of non-patent marketing exclusivity in the United States that, 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 a BLA sponsor submits pediatric data that fairly respond to a written request from 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 FDA's request, the additional protection is granted. If reports of requested pediatric studies are submitted to, and accepted by, FDA within the statutory time limits, whatever statutory or regulatory periods of exclusivity or patent protection that cover the product are extended by six months. This is not a patent term extension, but it effectively extends the regulatory period during which FDA cannot accept or approve a biosimilar application.

### *Biosimilars and exclusivity*

The PPACA created an abbreviated approval pathway for biologic products shown to be similar to, or interchangeable with, an FDA-licensed reference biologic product, referred to as biosimilars. In order for FDA to approve a biosimilar product, it must find that there are no clinically meaningful differences between the



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reference product and proposed biosimilar product. Interchangeability requires that a product is biosimilar to the reference product and the product must demonstrate that it can be expected to produce the same clinical results as the reference product and, for products administered multiple times, the biologic and the reference biologic may be switched after one has been previously administered without increasing safety risks or risks of diminished efficacy relative to exclusive use of the reference biologic.

A reference biologic is granted 12 years of exclusivity from the time of first licensure of the reference product. An application for a biosimilar product may not be submitted to FDA until four years following approval of the reference product, and it may not be approved until 12 years thereafter. These exclusivity provisions only apply to biosimilars companies that rely on their own data and file a full BLA may be approved earlier than 12 years. We currently plan to rely on our own data and to file a full BLA for all of our current and future products.

### *Government regulation outside of the United States*

In addition to regulations in the United States, sponsors are subject to a variety of regulations in other jurisdictions governing, among other things, clinical trials and any commercial sales and distribution of biologic products. Because biologically sourced raw materials are subject to unique contamination risks, their use may be restricted in some countries.

Whether or not a sponsor obtains FDA approval for a product, a sponsor must obtain the requisite approvals from regulatory authorities in foreign countries prior to the commencement of clinical trials or marketing of the product in those countries. Certain countries outside of the United States have a similar process that requires the submission of a clinical trial application, much like the IND, prior to the commencement of human clinical trials. In the European Union, for example, a request for a Clinical Trial Authorization, or CTA, must be submitted to the competent regulatory authorities and the competent Ethics Committees in the European Union Member States in which the clinical trial takes place, much like FDA and the IRB, respectively. Once the CTA request is approved in accordance with the European Union and the European Union Member States requirements, clinical trial development may proceed.

The requirements and processes governing the conduct of clinical trials, product licensing, pricing and reimbursement vary from country to country. In all cases, the clinical trials are conducted in accordance with GCPs and the applicable regulatory requirements and the ethical principles that have their origin in the Declaration of Helsinki.

Failure to comply with applicable foreign regulatory requirements may result in, among other things, fines, suspension, variation or withdrawal of regulatory approvals, product recalls, seizure of products, operating restrictions and criminal prosecution.

### *European Union regulation and exclusivity*

To obtain regulatory approval of an investigational biologic product under European Union regulatory systems, applicants must submit an MAA. The grant of marketing authorization in the European Union for products containing viable human tissues or cells such as gene therapy medicinal products is governed by Regulation 1394/2007/EC on advanced therapy medicinal products, read in combination with Directive 2001/83/EC of the European Parliament and of the Council, commonly known as the Community code on medicinal products. Regulation 1394/2007/EC lays down specific rules concerning the authorization, supervision and pharmacovigilance of gene therapy medicinal products, somatic cell therapy medicinal products and tissue engineered products. Manufacturers of advanced therapy medicinal products must demonstrate the quality, safety and efficacy of their products to EMA which provides an opinion regarding the application for marketing authorization. European Commission grants or refuses marketing authorization in light of the opinion delivered by EMA.

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Innovative medicinal products are authorized in the European Union on the basis of a full marketing authorization application (as opposed to an application for marketing authorization that relies on data in the marketing authorization dossier for another, previously approved medicinal product). Applications for marketing authorization for innovative medicinal products must contain the results of pharmaceutical tests, preclinical tests and clinical trials conducted with the medicinal product for which marketing authorization is sought. Innovative medicinal products for which marketing authorization is granted are entitled to eight years of data exclusivity. During this period, applicants for approval of generics or biosimilars of these innovative products cannot rely on data contained in the marketing authorization dossier submitted for the innovative medicinal product to support their application. Innovative medicinal products for which marketing authorization is granted are also entitled to 10 years of market exclusivity. During these 10 years of market exclusivity, no generic or biosimilar medicinal product may be placed on the European Union market even if a generic or biosimilar marketing authorization can be submitted to the competent regulatory authorities in the European Union Member States. The overall 10-year period will be extended to a maximum of 11 years if, during the first eight years of those 10 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 a new chemical entity and the innovator is able to gain the period of data exclusivity, another company, nevertheless, could also market another competing medicinal product for the same therapeutic indication if such company obtained marketing authorization based on an MAA with a complete independent data package of pharmaceutical tests, preclinical tests and clinical trials.

Products receiving orphan designation in the European Union can receive 10 years of market exclusivity. During this 10-year period, the competent authorities of the European Union Member States and European Commission may not accept applications or grant marketing authorization for other similar medicinal product for the same orphan indication. There are, however, three exceptions to this principle. Marketing authorization may be granted to a similar medicinal product for the same orphan indication if:

The second applicant can establish in its application that its medicinal product, although similar to the orphan medicinal product already authorized, is safer, more effective or otherwise clinically superior;

The holder of the marketing authorization for the original orphan medicinal product consents to a second orphan medicinal product application; or

The holder of the marketing authorization for the original orphan medicinal product cannot supply sufficient quantities of orphan medicinal product.

An orphan product can also obtain an additional two years of market exclusivity in the European Union for the conduct of pediatric trials. The 10-year market exclusivity may be reduced to six years if, at the end of the fifth year, it is established that the product no longer meets the criteria for orphan designation; for example, if the product is sufficiently profitable not to justify maintenance of market exclusivity.

The criteria for designating an orphan medicinal product in the European Union are similar, in principle, to those in the United States. Orphan medicinal products are eligible for financial incentives such as reduction of fees or fee waivers. The application for orphan medicinal product designation must be submitted before the application for marketing authorization. Orphan medicinal product designation does not convey any advantage in, or shorten the duration of, the regulatory review and approval process.

### *Other healthcare laws and regulations*

Healthcare providers, physicians and third-party payors play a primary role in the recommendation and use of pharmaceutical products that are granted marketing approval. Arrangements with third-party payors, existing

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or potential customers and referral sources are subject to broadly applicable fraud and abuse and other healthcare laws and regulations, and these laws and regulations may constrain the business or financial arrangements and relationships through which manufacturers market, sell and distribute the products for which they obtain marketing approval. Such restrictions under applicable federal and state healthcare laws and regulations include the following:

the federal Anti-Kickback Statute, which prohibits, among other things, persons from knowingly and willfully soliciting, receiving, offering or paying remuneration, directly or indirectly, in cash or kind, in exchange for, or to induce, either the referral of an individual for, or the purchase, order or recommendation of, any good or service for which payment may be made under federal healthcare programs such as the Medicare and Medicaid programs. This statute has been interpreted to apply to arrangements between pharmaceutical manufacturers, on the one hand, and prescribers, purchasers and formulary managers on the other. The PPACA amends the intent requirement of the federal Anti-Kickback Statute. A person or entity no longer needs to have actual knowledge of this statute or specific intent to violate it;

the federal False Claims Act or FCA, which prohibits, among other things, individuals or entities from knowingly presenting, or causing to be presented, claims for payment from Medicare, Medicaid or other third-party payors that are false or fraudulent. Federal Anti-Kickback Statute violations and certain marketing practices, including off-label promotion, also may implicate the FCA;

federal criminal laws that prohibit executing a scheme to defraud any healthcare benefit program or making false statements relating to healthcare matters;

the federal Physician Payment Sunshine Act, which requires certain manufacturers of drugs, devices, biologics and medical supplies to report annually to CMS information related to payments and other transfers of value to physicians, other healthcare providers and teaching hospitals, and ownership and investment interests held by physicians and other healthcare providers and their immediate family members;

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, which governs the conduct of certain electronic healthcare transactions and protects the security and privacy of protected health information; and

state and foreign law equivalents of each of the above federal laws, such as anti-kickback and false claims laws which may apply to: items or services reimbursed by any third-party payor, including commercial insurers; state laws that require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government or otherwise restrict payments that may be made to healthcare providers and other potential referral sources; state laws that require drug manufacturers to report information related to payments and other transfers of value to physicians and other healthcare providers or marketing expenditures; and state laws governing the privacy and security of health information in certain circumstances, many of which differ from each other in significant ways and may not have the same effect, thus complicating compliance efforts.

Violation of any of the laws described above or any other governmental laws and regulations may result in penalties, including civil and criminal penalties, damages, fines, the curtailment or restructuring of operations, the exclusion from participation in federal and state healthcare programs and imprisonment. Furthermore, efforts to ensure that business activities and business arrangements comply with applicable healthcare laws and regulations can be costly for manufacturers of branded prescription products.

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*Coverage and reimbursement*

Significant uncertainty exists as to the coverage and reimbursement status of any products for which we may obtain regulatory approval. In the United States and markets in other countries, sales of any product candidates for which regulatory approval for commercial sale is obtained will depend in part on the availability of coverage and reimbursement from third-party payors. Third-party payors include government authorities, managed care providers, private health insurers and other organizations. The process for determining whether a payor will provide coverage for a drug product may be separate from the process for setting the reimbursement rate that the payor will pay for the drug product. Third-party payors may limit coverage to specific drug products on an approved list, or formulary, which might not include all of FDA-approved drugs for a particular indication. Moreover, a payor's decision to provide coverage for a drug product does not imply that an adequate reimbursement rate will be approved.

Third-party payors are increasingly challenging the price and examining the medical necessity and cost-effectiveness of medical products and services, in addition to their safety and efficacy. New metrics frequently are used as the basis for reimbursement rates, such as ASP, AMP and Actual Acquisition Cost. In order to obtain coverage and reimbursement for any product that might be approved for sale, it may be necessary to conduct expensive pharmacoeconomic studies in order to demonstrate the medical necessity and cost-effectiveness of the products, in addition to the costs required to obtain regulatory approvals. If third-party payors do not consider a product to be cost-effective compared to other available therapies, they may not cover the product after approval as a benefit under their plans or, if they do, the level of payment may not be sufficient to allow a company to sell its products at a profit. Health Technology Assessment, or HTA, which is intended to take account of medical, social, economic and ethical issues when determining the suitability of a medicinal product for reimbursement is increasingly become an element of the pricing and reimbursement decisions of the competent authorities in European Union Member States.

The United States government, state legislatures and foreign governments have shown significant interest in implementing cost containment programs to limit the growth of government-paid health care costs, including price controls, restrictions on reimbursement and requirements for substitution of generic products for branded prescription drugs. By way of example, the PPACA contains provisions that may reduce the profitability of drug products, including, for example, increasing the minimum rebates owed by manufacturers under the Medicaid Drug Rebate Program, extending the rebate program to individuals enrolled in Medicaid managed care plans, addressing 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 and establishing annual fees based on pharmaceutical companies' share of sales to federal health care programs. Adoption of government controls and measures, and tightening of restrictive policies in jurisdictions with existing controls and measures, could limit payments for pharmaceuticals.

*Additional regulation*

In addition to the foregoing, state and federal laws regarding environmental protection and hazardous substances, including the Occupational Safety and Health Act, the Resource Conservation and Recovery Act and the Toxic Substances Control Act, affect our business. These and other laws govern the use, handling and disposal of various biologic, chemical and radioactive substances used in, and wastes generated by, operations. If our operations result in contamination of the environment or expose individuals to hazardous substances, we could be liable for damages and governmental fines. Equivalent laws have been adopted in third countries that impose similar obligations.

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### *U.S. Foreign Corrupt Practices Act*

The U.S. Foreign Corrupt Practices Act, or FCPA, prohibits U.S. corporations and individuals from engaging in certain activities to obtain or retain business abroad or to influence a person working in an official capacity. It is illegal to pay, offer to pay or authorize the payment of anything of value to any foreign government official, government staff member, political party or political candidate in an attempt to obtain or retain business or to otherwise influence a person working in an official capacity. The scope of the FCPA includes interactions with certain healthcare professionals in many countries. Equivalent laws have been adopted in other foreign countries that impose similar obligations.

## **Employees**

As of January 15, 2015, we had 47 full-time employees, including a total of 23 employees with M.D. or Ph.D. degrees. Of our workforce, 27 employees are engaged in research and development, nine employees are engaged in manufacturing and eleven employees are engaged in finance, legal, human resources and general management. None of our employees is represented by a labor union or covered by a collective bargaining agreement. We consider our relationship with our employees to be good.

## **Facilities**

We occupy approximately 28,000 square feet of office, laboratory and manufacturing space in Philadelphia, Pennsylvania, under a lease that expires in 2025, with our option for early termination in 2021.

## **Legal proceedings**

We are not currently a party to any material legal proceedings.

**Table of Contents****Management****Executive officers, key employees and directors**

The following table sets forth the name, age and position of each of our executive officers, key employees and directors as of January 15, 2015.

<b>Name</b>	<b>Age</b>	<b>Position</b>
Jeffrey D. Marrazzo	36	Co-founder, Chief Executive Officer and Director
Katherine A. High, M.D.(4)	63	Co-founder, President, Chief Scientific Officer and Director
Rog�erio Vivaldi, M.D.	51	Chief Commercial Officer
Stephen W. Webster	53	Chief Financial Officer
Joseph W. La Barge	43	General Counsel and Head of Business Administration
J. Fraser Wright, Ph.D.	56	Co-founder and Chief Technology Officer
Daniel F. Takefman, Ph.D.	47	Head of Regulatory Affairs
Diane I. Blumenthal	56	Head of Technical Operations
Carol Greve-Philips	62	Head of Business Development and Strategy
Lisa Dalton	41	Head of Human Resources
Guang Qu, Ph.D.	56	Head of Process Development
Jennifer Wellman	37	Co-founder and Head of Regulatory Strategy
Romuald Corbau	47	Translational Research Lead
Steven Altschuler, M.D.(3)	61	Chairman of the Board of Directors
A. Lorris Betz, M.D., Ph.D.	67	Director
Lars Ekman, M.D., Ph.D.(1)(3)(4)	64	Director
Anand Mehra, M.D.(1)(2)(4)	39	Director
Vincent J. Milano(1)(2)	51	Director
Elliott Sigal, M.D., Ph.D.(2)(3)(4)	62	Director

(1) Member of the audit committee.

(2) Member of the compensation committee.

(3) Member of the nominating and corporate governance committee.

(4) Member of the scientific and technology committee.

**Executive officers and key employees*****Jeffrey D. Marrazzo***

Jeffrey D. Marrazzo is a co-founder and has served as Chief Executive Officer of Spark and as a member of our board of directors since our founding in 2013. Prior to founding Spark, Mr. Marrazzo launched and was Chief Business Officer of the U.S. division of Molecular Health,

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Inc. from 2011 to 2013. Mr. Marrazzo was part of the founding management of Generation Health from 2009 to 2011, up to and through the acquisition of a majority of the company's shares by CVS Caremark. From 2008 to 2009, Mr. Marrazzo served as an employee and independent consultant to the business development and finance teams at Tengion Inc. and, from 2011 to 2013, Mr. Marrazzo served as an independent consultant to CHOP. Previously, Mr. Marrazzo served as healthcare

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advisor to former Pennsylvania Governor Edward G. Rendell and as an IBM management consultant to global pharmaceutical companies. Mr. Marrazzo holds a B.S.E. and B.A. in systems science and engineering and economics from the University of Pennsylvania and a dual M.B.A./M.P.A. from The Wharton School and Harvard University. We believe that Mr. Marrazzo is qualified to serve on our board of directors because of his extensive leadership experience in the life sciences industry and his extensive knowledge of our company based on his role as co-founder and Chief Executive Officer.

***Katherine A. High, M.D.***

Dr. Katherine A. High has served as our President and Chief Scientific Officer and a member of our board of directors since September 2014. Prior to serving as our President, Dr. High provided advice to Spark and subsequently served as an independent consultant to Spark from December 2013 to September 2014. Dr. High was previously a Professor at the Perelman School of Medicine at the University of Pennsylvania and an Investigator of the Howard Hughes Medical Institute. She served as the Director of the Center for Cellular and Molecular Therapeutics at CHOP from 2004 to 2014, where her team's research led to the discovery of new gene and cell therapies for genetic diseases. Dr. High began her independent research career at Yale University and the University of North Carolina studying the molecular basis of blood coagulation and the development of novel therapeutics for the treatment of bleeding disorders. Dr. High's studies at CHOP established the first proof of principle of gene therapy for hemophilia in preclinical models and led to a series of studies that characterized the human immune response to AAV vectors in a variety of target tissues. Dr. High served a five-year term from 2000 to 2005 on the FDA Advisory Committee on Cell, Tissue and Gene Therapies and is a past-president of the American Society of Gene & Cell Therapy. Dr. High holds an A.B. in chemistry from Harvard, an M.D. from the University of North Carolina School of Medicine, a business certification from the University of North Carolina Business School Management Institute for Hospital Administrators and an honorary M.A. from Penn. We believe that Dr. High is qualified to serve on our board of directors because of her extensive executive and scientific leadership in the life sciences industry and her extensive knowledge of our company based on her role as co-founder, President and Chief Scientific Officer.

***Rogério Vivaldi, M.D.***

Dr. Rogério Vivaldi has served as our Chief Commercial Officer since December 2014. Prior to joining Spark, Dr. Vivaldi was Chief Executive Officer and President of Minerva Neurosciences, Inc. from November 2013 to December 2014. Prior to joining Minerva, Dr. Vivaldi served as Senior Vice President - Head of the Rare Diseases business unit at Genzyme Corporation, from October 2011 to October 2013. From July 2010 to September 2011, he was the Senior Vice President - Head of the Renal and Endocrinology business unit at Genzyme and from January 2004 to June 2010 he was the Senior Vice President - Head of Genzyme Latin America. Prior to 2004, Dr. Vivaldi founded Genzyme Brazil in 1997. Dr. Vivaldi served on our board of directors from April 2014 to December 2014 and served on the board of directors of Minerva Neurosciences from November 2013 to December 2014. Dr. Vivaldi holds a medical degree from the University of Rio de Janeiro and his M.B.A. from Federal University of Rio de Janeiro. Dr. Vivaldi completed his residency in metabolism and endocrinology at Rio de Janeiro State University and his fellowship at Mount Sinai Hospital Center in New York, department of genetics, with an emphasis on Gaucher's disease.

***Stephen W. Webster***

Stephen W. Webster has served as our Chief Financial Officer since July 2014. From June 2012 to November 2013, he served as Senior Vice President, Finance and Chief Financial Officer at Optimer Pharmaceuticals. From June 2008 to December 2011, Mr. Webster served as Senior Vice President, Finance and Chief Financial Officer at Adolor Corporation. Mr. Webster has served on the board of directors of Viking Therapeutics Inc. since June



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2014 as well as the Pennsylvania Biotech Association. Mr. Webster holds an A.B. in economics from Dartmouth College and an M.B.A. in finance from The Wharton School at the University of Pennsylvania.

### ***Joseph W. La Barge***

Joseph W. La Barge has served as our General Counsel and Head of Business Administration since November 2013. Prior to joining Spark, Mr. La Barge was of counsel at Ballard Spahr LLP from April 2012 to April 2013, where he advised biotechnology companies in private and public financings, mergers and acquisitions and collaboration and licensing transactions. He also served as the Deputy General Counsel to the Kennedy Health System from April 2013 to November 2013. Mr. La Barge was the Vice President, General Counsel and Chief Compliance Officer at Tengion, Inc., serving in increasing roles of responsibility from November 2006 to December 2011, where he oversaw legal affairs, compliance and quality assurance. Mr. La Barge serves on the board of directors of the Pennsylvania Biotech Association. Mr. La Barge holds a B.A. from Bucknell University and a J.D. from Temple University.

### ***J. Fraser Wright, Ph.D.***

Dr. J. Fraser Wright has served as our Chief Technology Officer since January 2015. From July 2013 until he joined Spark, Dr. Wright served as our Chief Technology Advisor. Dr. Wright established and had been the director of the Clinical Vector Core Laboratory at CHOP from 2004 to January 2015. Dr. Wright also was a Professor at the Perelman School of Medicine at the University of Pennsylvania. Dr. Wright previously served as Director of Development and Clinical Manufacturing at Avigen, Inc. from 1999 to 2004, and as scientist with Sanofi Pasteur and as scholar investigator with the Canadian blood services. Dr. Wright received his B.S. and Ph.D. in biochemistry from the University of Toronto.

### ***Daniel M. Takefman, Ph.D.***

Dr. Daniel M. Takefman has served as our Head of Regulatory Affairs since November 2014. Prior to joining Spark, Dr. Takefman served as the Chief, Gene Therapy Branch of the Division of Cellular and Gene Therapies within CBER at FDA. Dr. Takefman began his career at FDA in 1999 as a Postdoctoral Fellow and became a Staff Fellow shortly thereafter. He served as a Microbiologist at FDA from 2001 to 2006. He had oversight of the chemistry, manufacturing and control review process of several hundred gene therapy INDs and three BLAs. Dr. Takefman holds a B.S. in microbiology from the University of Iowa and a Ph.D. in microbiology from Rush University.

### ***Diane I. Blumenthal***

Diane I. Blumenthal has served as our Head of Technical Operations since October 2014. Prior to joining Spark, Ms. Blumenthal served as Vice President of Technical Services and Manufacturing Sciences for Eli Lilly and Company, following the acquisition of ImClone Systems. Prior to her time at Lilly, Ms. Blumenthal served as a Scientific and Manufacturing Consultant to multiple start-up biotechnology companies and held scientific leadership positions at Zymquest, Inc., Scios, Inc. and the Eastman Kodak Company. Ms. Blumenthal holds a B.S.E. in bioengineering from the University of Pennsylvania and an M.S.E. in chemical engineering from Lehigh University.

### ***Carol Greve-Philips***

Carol Greve-Philips has served as our Head of Business Development and Strategy since January 2014.

Ms. Greve-Philips was previously Chief Business Officer at Pronota B.V. from February 2012 to January 2014 and before that was Vice President of Corporate Development of Genzyme Corporation from 2009 to 2011. Ms. Greve-Philips also has held roles in direct sales, sales management and marketing for Amersham

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Corporation, Chemsyn Science Laboratories, Watson Laboratories and Toxikon Corporation. She is a member of the Whitehead Connects Advisory Board and the Licensing Executive Society. Ms. Greve-Philips has a B.Sc. in zoology from the University of Massachusetts at Amherst.

### ***Lisa Dalton***

Lisa Dalton has served as our Head of Human Resources since July 2014. Prior to joining Spark, Ms. Dalton served as Vice President, Human Resources at Shire Pharmaceutical, where she most recently led human resources merger and acquisition activity and implementation. Ms. Dalton also has held roles in compensation and human resources business partnering with Franklin Templeton and Applied Biosystems. Ms. Dalton holds a B.A. in psychology from Penn State University and an M.B.A. from Rutgers University School of Business.

### ***Guang Qu, Ph.D***

Dr. Guang Qu has served as our Head of Process Development since October 2013. Prior to joining Spark, Dr. Qu served as Technical Director for the Clinical Vector Core Laboratory at CHOP. Dr. Qu previously held a role in process development at Avigen, Inc. Dr. Qu is a member of the American Society for Gene Therapy. Dr. Qu holds a B.S. from Liaoning General University, an M.S. from Academia Sinica, both in China, and a Ph.D. from The Ohio State University.

### ***Jennifer Wellman***

Jennifer Wellman has served as our Head of Regulatory Strategy since October 2013. Prior to joining Spark, Ms. Wellman was the Director of Regulatory Interactions for Gene Therapy Studies at the Center for Cellular and Molecular Therapeutics at CHOP. Ms. Wellman also previously held a role as Associate Scientist at Avigen, Inc. Ms. Wellman holds a B.S. in microbiology and immunology from Queen's University and an M.S. from the University of New Haven.

### ***Romuald Corbau***

Romuald Corbau has served as our Translational Research Lead since September 2014. Prior to joining Spark, Mr. Corbau served as Associate Director at the Center for Cellular and Molecular at CHOP, where he focused on AAV-mediated gene transfer in the central nervous system. Mr. Corbau also has held gene therapy drug discovery roles at the Center for Innovation and Stimulation of Drug Discovery at the Catholic University of Leuven in Belgium and Pfizer.

## **Non-Employee Directors**

### ***Steven M. Altschuler, M.D.***

Dr. Steven M. Altschuler has served on our board of directors and has been the Chairman of our board since October 2013. Dr. Altschuler has been Chief Executive Officer of CHOP and the Children's Hospital of Philadelphia Foundation, or the CHOP Foundation, since 2000. Previously, Dr. Altschuler served in many leadership roles at CHOP including: Division Chief of Gastroenterology, Physician-in-Chief, inaugural holder of the Leonard and Madlyn Abramson Endowed Chair in Pediatrics and Professor and Chair of the Department of Pediatrics at the Perelman School of Medicine at the University of Pennsylvania, where he was a faculty member from 1985 to 2000. Dr. Altschuler has served on the board of directors for Mead Johnson Nutrition Company since 2009 and Weight Watchers International since 2012. Dr. Altschuler holds a B.A. in mathematics and an M.D., both from Case Western Reserve University. He completed his pediatric internship and residency at Children's Hospital Medical Center-Boston and fellowship training in gastroenterology and nutrition at CHOP and the University of Pennsylvania School of Medicine. We believe that Dr. Altschuler is qualified to serve on our board of directors because of his extensive experience in the medical industry, his service on the boards of directors of other another life sciences company and his extensive leadership experience.

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### ***A. Lorris Betz, M.D., Ph.D.***

Dr. A. Lorris Betz has served on our board of directors since January 2015. Dr. Betz served as Senior Vice President for Health Sciences and Dean of the School of Medicine at The University of Utah, where he also was a faculty member, and as Chief Executive Officer of the University of Utah Health Care, from 1999 to 2011. Dr. Betz also served twice as the Interim President of the University of Utah from January 2004 to August 2004 and from May 2011 to March 2012. Dr. Betz previously held various faculty positions at the University of Michigan from 1979 to 1998. Dr. Betz has served on the Board of Directors of the Association of Medical Colleges since 2012, including as Chairman from 2013 to 2014, and currently serves as a member of the Board of Trustees and Executive Committee of CHOP and the CHOP Foundation. Dr. Betz holds a B.S., M.D. and Ph. D. in biochemistry and physiology from the University of Wisconsin. He completed his pediatric residency and a research fellowship in pediatric neurology at the University of California, San Francisco. We believe that Dr. Betz is qualified to serve on our board of directors because of his extensive experience in medicine and the medical industry and his extensive leadership experience.

### ***Lars Ekman, M.D., Ph.D.***

Dr. Lars Ekman has served on our board of directors since May 2014. He has served as Executive Partner at Sofinnova Ventures since 2008. Prior to joining Sofinnova Ventures, Dr. Ekman was President of Research and Development at Elan Corporation (now Perrigo) from January 2001 to December 2007. Prior to Elan, he was Executive Vice President, Research and Development, at Schwarz Pharma AG and, before that, held a variety of senior scientific and clinical roles at Pharmacia (now Pfizer). Dr. Ekman is Chairman of Amarin Corporation, Chairman of Prothena Biosciences and Chairman of Sophiris Bioscience. He co-founded and served as Chief Executive Officer of Cebix, Inc., and has served on their board since 2009 as well as on the board of directors of InterMune, Inc. and Ocera Therapeutics, Inc. Dr. Ekman is a board-certified surgeon and holds an M.D. and a Ph.D. in experimental biology from the University of Gothenburg, Sweden. We believe that Dr. Ekman is qualified to serve on our board of directors because of his extensive experience in the life sciences industry, both as an executive and as a venture capital investor, and his extensive leadership experience.

### ***Anand Mehra, M.D.***

Dr. Anand Mehra has served on our board of directors since May 2014. Dr. Mehra is currently a General Partner of Sofinnova Ventures, which he joined in 2007. Prior to joining Sofinnova, Dr. Mehra worked in J.P. Morgan's private equity and venture capital group, and before that, Dr. Mehra was a consultant in McKinsey & Company's pharmaceutical practice. Dr. Mehra has served on the board of directors of Aerie Pharmaceuticals since August 2010 and Marinus Pharmaceuticals since October 2007 and several private companies. Dr. Mehra holds a B.A. from the University of Virginia and an M.D. from Columbia University's College of Physicians and Surgeons. We believe that Dr. Mehra is qualified to serve on our board of directors because of his extensive experience in the life sciences industry, his service on the boards of directors of other life sciences companies and his extensive leadership experience.

### ***Vincent J. Milano***

Vincent J. Milano has served on our board of directors since June 2014. Mr. Milano is currently the Chief Executive Officer of Idera Pharmaceuticals Inc. Prior to joining Idera, Mr. Milano served as President, Chief Executive Officer and Chairman of the board of directors of ViroPharma Incorporated, or ViroPharma, from 2006 to 2014, which was acquired by Shire Pharmaceuticals in January 2014. Mr. Milano joined ViroPharma in 1996 and served as Vice President, Chief Financial Officer and Treasurer from 1997 to 2006. Prior to joining ViroPharma, Mr. Milano served as a Senior Manager at KPMG LLP, independent certified public accountants.

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Mr. Milano has served on the board of directors of Vanda Pharmaceuticals since 2010. Mr. Milano holds a B.S. in accounting from Rider College. We believe that Mr. Milano is qualified to serve on our board of directors because of his extensive experience in the life sciences industry, his financial expertise and his extensive leadership experience.

### ***Elliott Sigal, M.D., Ph.D.***

Dr. Elliott Sigal has served on our board of directors since January 2014. Dr. Sigal served as Executive Vice President and Chief Scientific Officer and President of R&D at Bristol-Myers Squibb from 2004 until his retirement in 2013. Dr. Sigal previously held positions of increasing responsibility in drug discovery at Syntex and also was Vice President of R&D and Chief Executive Officer for the genomics firm Mercator Genetics Inc. Dr. Sigal served on the board of directors of Bristol Myers-Squibb from 2011 to 2013 and currently serves as a member of the board of directors for the Mead Johnson Nutrition Company, the Melanoma Research Alliance and the University of California San Francisco, or UCSF, Nina Ireland Program for Lung Health. Dr. Sigal is an advisor to the life sciences venture firm, New Enterprise Associates, and consults for select biopharmaceutical companies. Dr. Sigal holds B.S., M.S. and Ph.D. degrees in industrial engineering from Purdue University and an M.D. from the University of Chicago. He completed his training in internal medicine and pulmonary medicine at the UCSF. He received his research training at the Cardiovascular Research Institute at UCSF, where he served on the faculty of the UCSF Department of Medicine. We believe that Dr. Sigal is qualified to serve on our board of directors because of his extensive experience in the life sciences industry and his extensive leadership experience.

## **Composition of the board of directors**

Our board of directors currently is authorized to have nine members. In accordance with the terms of our restated certificate of incorporation and amended and restated 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 Drs. Betz and Mehra, and their term will expire at the annual meeting of stockholders to be held in 2016;

the class II directors will be Drs. Altschuler, Ekman and High, and their term will expire at the annual meeting of stockholders to be held in 2017; and

the class III directors will be Messrs. Marrasso and Milano and Dr. Sigal, and their term will expire at the annual meeting of stockholders to be held in 2018.

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. In accordance with the terms of our restated certificate of incorporation and amended and restated bylaws that will become effective upon the closing of this offering, our directors may be removed only for cause by the affirmative vote of the holders of at least 75% of the votes that all our stockholders would be entitled to cast in an annual election of directors.

## **Director independence**

Rule 5605 of the NASDAQ Listing Rules requires a majority of a listed company's board of directors to be comprised of independent directors within one year of listing. In addition, the NASDAQ Listing Rules require that, subject to specified exceptions, each member of a listed company's audit, compensation and nominating

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and corporate governance committees be independent and that audit committee members also satisfy independence criteria set forth in Rule 10A-3 under the Securities Exchange Act of 1934, as amended, or the Exchange Act.

Under Rule 5605(a)(2) of the NASDAQ Listing Rules, a director will only qualify as an independent director if, in the opinion of our 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: (1) accept, directly or indirectly, any consulting, advisory or other compensatory fee from the listed company or any of its subsidiaries; or (2) be an affiliated person of the listed company or any of its subsidiaries. In addition, in affirmatively determining the independence of any director who will serve on a company's compensation committee, Rule 10C-1 under the Exchange Act requires that a company's board of directors consider 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 December 2014, 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 Mr. Marrazzo and Dr. High, is an independent director as defined under Rule 5605(a)(2) of the NASDAQ Listing Rules. Our board of directors also determined that Mr. Milano and Drs. Ekman and Mehra who will comprise our audit committee following this offering, Mr. Milano and Drs. Mehra and Sigal, who will comprise our compensation committee following this offering, and Drs. Ekman, Altschuler and Sigal, who will comprise our nominating and corporate governance committee following this offering, satisfy the independence standards for such committees established by the Securities and Exchange Commission and the NASDAQ Listing Rules, as applicable. In making such determinations, our board of directors considered the relationships that each such non-employee director has with our company and all other facts and circumstances our board of directors deemed relevant in determining independence, including the beneficial ownership of our capital stock by each non-employee director.

There are no family relationships among any of our directors or executive officers.

## **Board committees**

Our board has established four standing committees—audit, compensation, nominating and corporate governance and science and technology—each of which will, upon the date of this offering, operate under a charter that has been approved by our board.

### ***Audit committee***

The members of our audit committee are Mr. Milano and Drs. Ekman and Mehra. Mr. Milano 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;

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overseeing the work of our registered public accounting firm, including through the receipt and consideration of reports from such firm;

reviewing and discussing with management and the 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;

assessing our risk management policies;

establishing policies regarding hiring employees from the registered public accounting firm;

procedures for the receipt and retention of accounting related complaints and concerns;

meeting independently with our internal auditing staff, 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 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 Mr. Milano is an audit committee financial expert as defined by applicable SEC rules.

***Compensation committee***

The members of our compensation committee are Mr. Milano and Drs. Mehra and Sigal. Mr. Milano is the chair of the compensation committee. Our compensation committee's responsibilities include:

annually reviewing and approving corporate goals and objectives relevant to compensation for the CEO and our other executive officers;

determining our CEO's compensation as well as the compensation of 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 with respect to director compensation;

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reviewing and discussing annually with management our Compensation Discussion and Analysis ; and

preparing the annual compensation committee report required by SEC rules.

### ***Nominating and corporate governance committee***

The members of our nominating and corporate governance committee are Drs. Ekman, Altschuler and Sigal. Dr. Ekman is the chair of the nominating and corporate governance committee. Our nominating and corporate governance committee s responsibilities include:

identifying individuals qualified to become board members;

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recommending to our board the persons to be nominated for election as directors and to each of the Board's committees;

reviewing and making recommendations to the board with respect to management succession planning;

developing and recommending to the board corporate governance principles; and

overseeing periodic evaluations of the board.

### ***Science and technology committee***

The members of our science and technology committee are Drs. High, Ekman, Mehra and Sigal. Dr. High is the chair of the science and technology committee. Our science and technology committee's responsibilities include:

reviewing, evaluating and advising the board of directors and management regarding the long-term strategic goals and objectives and the quality and direction of our research and development programs;

monitoring and evaluating trends in research and development, and recommending to the board of directors and management emerging technologies for building our technological strength;

recommending approaches to acquiring and maintaining technology positions; advising the board of directors and management on the scientific aspects of business development transactions; and

regularly reviewing our research and development pipeline.

### **Compensation committee interlocks and insider participation**

None of our executive officers serves as a director or a member of a 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 director or member of our compensation committee. None of the members of our current 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 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 intend to post on our website, [www.sparktx.com](http://www.sparktx.com), a current copy of the code and all disclosures that are required by law or NASDAQ stock market listing standards concerning any amendments to, or waivers from, any provision of the code.



Table of Contents**Executive compensation**

This section describes the material elements of compensation awarded to, earned by or paid to each of our named executive officers. Our named executive officers for 2014 were Jeffrey D. Marrazzo, who serves as our Chief Executive Officer, Dr. Katherine A. High, M.D., who serves as our President and Chief Scientific Officer and Stephen W. Webster, who serves as our Chief Financial Officer. This section also provides qualitative information regarding the manner and context in which compensation is awarded to and earned by our executive officers and is intended to place in perspective the data presented in the tables and narrative that follow.

**Summary compensation table**

The following table sets forth information regarding compensation awarded to, earned by or paid to our named executive officers during 2013 and 2014.

Name and principal position	Year	Salary	Equity awards (1)	Non-equity incentive plan compensation (2)	All other compensation (3)	Total
Jeffrey D. Marrazzo	2014	\$ 349,604	\$ 1,292,156	\$ 63,801	\$ 32,709	\$ 1,738,270
<i>Chief Executive Officer</i>	2013	\$ 196,319	\$ 1,680,000	\$ 78,699	\$ 9,969	\$ 1,964,987
Dr. Katherine A. High, M.D.	2014	\$ 108,538(4)	\$ 467,966	\$	\$ 5,213	\$ 581,717
<i>President and Chief Scientific Officer</i>	2013		\$ 1,680,000	\$	\$	\$ 1,680,000
Stephen W. Webster	2014	\$ 147,528(5)	\$ 550,967		8,738	\$ 707,233
<i>Chief Financial Officer</i>						

- (1) The amounts reported in the Equity awards column reflect the aggregate fair value of share-based compensation awarded during the year computed in accordance with the provisions of Financial Accounting Standards Board Accounting Standard Codification Topic 718. See Note 6 to our audited financial statements appearing at the end of this prospectus regarding assumptions underlying the valuation of equity awards.
- (2) The amounts reported in the Non-equity incentive plan compensation column represent signing bonuses as well as prorated portions of bonuses awarded in July 2014 to Mr. Marrazzo to reflect performance from July 1, 2013 to June 30, 2014. Our compensation committee and our chief executive officer, as applicable, have not yet determined the amounts of performance-based cash bonuses payable to our named executive officers for the second half of 2014. Performance-based cash bonuses, if any, for the second half of 2014 will be determined by our compensation committee and chief executive officer and paid during the first quarter of 2015.
- (3) The compensation included in the All other compensation column consists of premiums we paid with respect to each of our named executive officers for: (a) medical, dental and vision insurance; (b) personal accident insurance; (c) life insurance; (d) long-term disability insurance; (e) short-term disability insurance and (f) matching contributions to our 401(k) plan. Each of the named executive officers may be eligible to receive additional safe harbor contributions to our 401(k) plan for 2014, with such amounts to be determined during the first quarter of 2015.
- (4) Dr. High joined us on September 16, 2014. Dr. High's annualized base salary for 2014 was \$367,171.
- (5) Mr. Webster joined us on July 7, 2014. Mr. Webster's annualized base salary for 2014 was \$300,000. In 2013, we paid a base salary of \$300,000 to Mr. Marrazzo. For 2014, we paid annualized base salaries of \$300,000, which was increased to \$392,000 in June, to Mr. Marrazzo, \$367,171 to Dr. High and \$300,000 to Mr. Webster. Base salaries recognize the experience, skills, knowledge and responsibilities required of all our employees, including our named executive officers. None of our named executive officers currently is party to an employment agreement or other agreement or arrangement that provides for automatic or scheduled increases in base salary.

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In 2013, we paid a signing bonus of \$30,000 to Mr. Marrazzo upon his hiring. We also paid a performance-based bonus of \$112,500 to Mr. Marrazzo in July of 2014, covering performance from July 1, 2013 to June 30, 2014. 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. For 2014, under the terms of our employee agreement with her, Dr. High will receive a bonus of \$45,896.

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Although we do not have a formal policy with respect to the grant of equity incentive awards to our named 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 incentivizes our executives 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 or other equity awards. In October 2013, in recognition of his role as a co-founder, we granted Mr. Marrazzo restricted common membership units, which converted into 400,000 shares of common stock. Of Mr. Marrazzo's restricted common shares, 25% vested in October 2013 and the remainder vested upon the closing of our Series B financing on May 23, 2014.

**2014 outstanding option awards at fiscal year-end**

The following table sets forth information concerning outstanding equity awards at December 31, 2014 for each of our named executive officers.

Name	Option Awards				Stock Awards Market	
	Number of securities underlying unexercised options exercisable (#)	Number of securities underlying unexercised options unexercisable (#)	Option exercise price (\$/share)	Option expiration date	Number of shares or units of stock that have not vested (#)	value of shares or units of stock that have not vested (\$)
Jeffery D. Marrazzo (2)	0	437,071	3.45	7/2/2024	0	0
Dr. Katherine A. High, M.D. (3)	0	158,249	3.45	7/2/2024	225,000	4,500,000
Stephen W. Webster (4)	0	186,015	3.45	7/6/2024	0	0

- (1) There was no public market for our common stock at December 31, 2014. We have estimated the fair market value of the unvested stock awards as \$20.00 per share, the midpoint of the price range set forth on the cover of this prospectus.
- (2) Mr. Marrazzo's option to purchase 437,071 shares of common stock vests as follows: 25% vests on May 24, 2015 and the remainder vests in equal quarterly installments over the following three years.
- (3) Dr. High's restricted stock vests as follows: 25% of the shares vested on March 13, 2014 with the remaining shares vesting in equal quarterly installments over the following three years. Dr. High's option to purchase 158,249 shares of common stock vests as follows: 25% vests on May 24, 2015 and the remainder vests in equal quarterly installments over the following three years.
- (4) Mr. Webster's option to purchase 186,015 shares of common stock vests as follows: 25% vests on July 7, 2015 and the remainder vests in equal quarterly installments over the following three years.

**Employment agreements with executive officers**

We have written employment agreements with each of our executive officers—Mr. Marrazzo, Dr. High, Dr. Vivaldi and Mr. Webster. The agreements with each of Mr. Marrazzo, Dr. High, Dr. Vivaldi and Mr. Webster provide for at-will employment. In addition, each of our executive officers is subject to invention assignment, non-disclosure, non-competition and non-solicitation agreements through separate agreements that were executed and delivered by the executives in connection with their employment agreements.

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Pursuant to these agreements, each of our executive officers is entitled to receive an annual base salary following completion of this offering as follows: Mr. Marrazzo: \$450,000; Dr. High: \$405,000; Dr. Vivaldi: \$405,000; and Mr. Webster: \$350,000.

Following the end of each calendar year, each executive is eligible to receive an annual bonus based on the achievement of individual and company performance objectives. The amount of the annual bonus, if any, for

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Mr. Marrazzo will be determined by our board of directors in its sole discretion; the amount of the annual bonus, if any, for Dr. High, Dr. Vivaldi and Mr. Webster will be determined by our board of directors and our Chief Executive Officer in their sole discretion. For each of our executive officers, the bonus is calculated as a percentage of the executive's annual base salary. Following completion of this offering, the target bonus percentages for each executive officer is as follows: Mr. Marrazzo: 50%; Dr. High: 45%; Dr. Vivaldi: 40%; and Mr. Webster: 40%.

***Potential payments upon termination or change in control***

Upon execution and effectiveness of a separation agreement and release of claims, each executive officer is entitled to severance payments if his or her employment is terminated under specified circumstances. If we terminate any of our executive officers' employment without cause, or if such executive officer terminates his or her employment with us for good reason, each as defined in his or her employment agreement, such executive officer is entitled to continue receiving his or her base salary and insurance benefits for a period of 12 months following the date of termination of employment, the amount of any bonus determined by our board of directors to be payable to the executive officer for the immediately preceding year that has not yet been paid and a payment in an amount equal to the pro rata portion of such executive officer's target bonus for the fiscal year in which the termination occurs. Moreover, if we terminate any of our executive officers' employment without cause, or if any such executive officer terminates his or her employment with us for good reason, such executive officer's unvested equity awards will vest on a monthly basis for the period from the last vesting date of each equity award through the date of termination of his or her employment.

If, within 24 months following a change in control, as defined in such executive officer's employment agreement, we terminate such executive officer's employment without cause or such executive officer terminates his or her employment with us for good reason, such executive officer is entitled to continue receiving his or her base salary and insurance benefits for a period of 18 months following the date of termination of employment, the amount of any bonus determined by our board of directors to be payable to the executive for the immediately preceding year that has not yet been paid, a payment in an amount equal to the pro rata portion of such executive officer's target bonus for the fiscal year in which the termination occurs and an additional payment equal to 1.5 times his or her target bonus for the fiscal year in which the termination occurs. In addition, if there occurs a change of control, any unvested equity granted prior to the corporate conversion will become vested. Additionally, 50% of the unvested portion of each of our executive officers' unvested equity awards that were outstanding at the time of the change of control will vest immediately, and the remaining 50% will vest in equal quarterly installments over the following two years or, if shorter, over the remaining period of the award's original vesting schedule; provided, however, that the new vesting schedule will not replace any more favorable vesting acceleration provision provided for in any equity award agreement governing an equity award held by such executive officer. Following a termination without cause or for good reason within 24 months of the change of control, such executive officer's unvested equity awards that were outstanding at the time of the change of control will vest in full.

To the extent that any severance or other compensation payment to any of our executive officers pursuant to an employment agreement or any other agreement constitutes an excess parachute payment within the meaning of Sections 280G and 4999 of the Internal Revenue Code of 1986, as amended, then such executive officer will receive the full amount of such severance and other payments, or a reduced amount intended to avoid the application of Sections 280G and 4999, whichever provides the executive with the highest amount on an after-tax basis.

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### **Stock option and other compensation plans**

In this section we describe our 2014 stock incentive plan, as amended to date, or the 2014 plan, our 2015 stock incentive plan, or the 2015 plan and our 2015 employee stock purchase plan. Prior to this offering, we granted awards to eligible participants under the 2014 plan. Following the closing of this offering, we expect to grant awards to eligible participants under the 2015 plan.

#### ***2014 plan***

The 2014 plan was adopted by our board of directors and approved by our stockholders in May 2014. The 2014 plan provides for the grant of incentive stock options, nonstatutory stock options, restricted stock awards, restricted stock unit awards, stock appreciation rights and other stock-based awards. Our employees, officers, directors, consultants and advisors are eligible to receive awards under our 2014 plan; however, incentive stock options may only be granted to our employees. A maximum of 2,543,299 shares of our common stock are authorized for issuance under the 2014 plan.

The type of award granted under our 2014 plan and the terms of such award are set forth in the applicable award agreement.

Pursuant to the terms of the 2014 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, measurement price, 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).

*Effect of certain changes in capitalization.*

Upon the occurrence of any of a 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, our board of directors shall equitably adjust:

the number and class of securities available under the 2014 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;



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the number of shares subject to, and the repurchase price per share subject to, each outstanding restricted stock award; and

the share and per-share related provisions and the purchase price, if any, of each other stock-based award.

*Effect of certain corporate transactions*

Upon a merger or other reorganization event (as defined in our 2014 plan), our board of directors may, in its sole discretion, take any one or more of the following actions pursuant to the 2014 plan as to some or all outstanding awards other than restricted stock:

provide that all outstanding awards shall be assumed, or substantially equivalent awards shall be substituted, by the acquiring or successor corporation (or an affiliate thereof);

upon written notice to a participant, provide that all of the participant's vested but unexercised awards will terminate immediately prior to the consummation of such reorganization event unless exercised by the participant;

provide that outstanding awards shall become exercisable, realizable or deliverable, or restrictions applicable to an award shall 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 the 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; and/or

provide that, in connection with a liquidation or dissolution, awards shall convert into the right to receive liquidation proceeds (if applicable, net of the exercise, measurement or purchase price thereof and any applicable tax withholdings).

Our board of directors does not need to take the same action with respect to all awards and may take different actions with respect to portions of the same award.

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 a liquidation or dissolution, the repurchase and other rights with respect to outstanding awards of restricted stock will continue for the benefit of the successor company and will, unless the board of directors may otherwise determine, apply to the cash, securities or other property into which shares of our common stock are converted or exchanged pursuant to the reorganization event. Upon the occurrence of a reorganization event involving a liquidation or dissolution, all restrictions and conditions on each outstanding restricted stock award will automatically be deemed terminated or satisfied, unless otherwise provided in the agreement evidencing the restricted stock award.

At any time, our board of directors may, in its sole discretion, provide that any award under the 2014 plan will become immediately exercisable in full or in part, free of some or all restrictions or conditions, or otherwise realizable in full or in part.



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As of January 15, 2015, there were options to purchase 2,264,497 shares of our common stock outstanding under the 2014 plan, at a weighted-average exercise price of \$4.52 per share, and no options to purchase shares of our common stock had been exercised.

No award may be granted under the 2014 plan on or after the effectiveness of the registration statement for this offering. Our board of directors may amend, suspend or terminate the 2014 plan at any time, except that stockholder approval may be required to comply with applicable law or stock market requirements.

***2015 plan***

Our board of directors has adopted, and our stockholders have approved, the 2015 plan, which will become effective immediately prior to the effectiveness of the registration statement for this offering. The 2015 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. Upon effectiveness of the 2015 plan, the number of shares of our common stock that will be reserved for issuance under the 2015 plan will be the sum of: (1) 1,830,000 plus; (2) the number of shares (up to 2,543,299 shares) equal to the sum of the number of shares of our common stock then available for issuance under the 2014 plan and the number of shares of our common stock subject to outstanding awards under the 2014 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, 2016 and continuing until, and including, the fiscal year ending December 31, 2025, equal to the lowest of 1,724,000 shares of our common stock, 4% of the number of shares of our common stock outstanding on the first day of such fiscal year and an amount determined by our board of directors.

Our employees, officers, directors, consultants and advisors will be eligible to receive awards under the 2015 plan. Incentive stock options, however, may only be granted to our employees. We expect to grant options to purchase an aggregate of 146,000 shares to our recently appointed director and certain recently hired employees upon the commencement of trading of our common stock on the NASDAQ Global Select Market under the 2015 plan.

Pursuant to the terms of the 2015 plan, our board of directors (or a committee delegated by our board of directors) will administer the plan and, subject to any limitations in the plan, will select the recipients of awards and determine:

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 an executive officer to grant awards under the 2015 plan, the executive officer will have the power to make awards to all of our employees, except executive officers. Our board of directors will fix the terms of the awards to be granted by such executive officer, including the exercise

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price of such awards (which may include a formula by which the exercise price will be determined), and the maximum number of shares subject to awards that such executive officer may make.

*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, our board of directors shall equitably adjust:

the number and class of securities available under the 2015 plan;

the share counting rules under the 2015 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; and

the share and per-share related provisions and the purchase price, if any, of each other stock-based award.

*Effect of certain corporate transactions*

Upon a merger or other reorganization event (as defined in our 2015 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 2015 plan as to some or all outstanding awards, other than restricted stock awards:

provide that all outstanding awards shall be assumed, or substantially equivalent awards shall be substituted, by the acquiring or successor corporation (or an affiliate thereof);

upon written notice to a participant, provide that all of the participant's unvested and/or vested but unexercised awards will terminate immediately prior to the consummation of such reorganization event unless exercised by the participant (to the extent then exercisable);

provide that outstanding awards shall become exercisable, realizable or deliverable, or restrictions applicable to an award shall 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 the 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; and/or

provide that, in connection with a liquidation or dissolution, awards shall convert into the right to receive liquidation proceeds (if applicable, net of the exercise, measurement or purchase price thereof and any applicable tax withholdings).

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Our board of directors does not need to take the same action with respect to all awards, all awards held by a participant or all awards of the same type.

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 a liquidation or dissolution, the repurchase and other rights with respect to outstanding restricted stock awards will continue for the benefit of the successor company and will, unless the board of directors may otherwise determine, apply to the cash, securities or other property into which shares of our common stock are converted or exchanged pursuant to the reorganization event. Upon the occurrence of a reorganization event involving a liquidation or dissolution, all restrictions and conditions on each outstanding restricted stock award will automatically be deemed terminated or satisfied, unless otherwise provided in the agreement evidencing the restricted stock award or any other agreement between the participant and us.

The 2015 plan provides that, except to the extent specifically provided to the contrary in an award agreement or any other agreement between the participant and us, immediately prior to a change in control event (as defined in our 2015 plan), the vesting schedule of each outstanding option and restricted stock award shall be accelerated in part so that 50% of the unvested portion of such award shall immediately become exercisable or free from forfeiture or repurchase, as applicable, and the remaining 50% shall vest in substantially equal quarterly installments over the following two years, or, if shorter, in accordance with the original vesting schedule set forth in the award agreement governing such award. Additionally, each such option or restricted stock award shall vest in full and become exercisable or free from forfeiture or repurchase, as applicable, if, on or prior to the second anniversary of the change in control event, the participant's employment with the company or the acquiring company is terminated for good reason by the participant or is terminated without cause by the company or the acquiring corporation (as such terms are defined in the 2015 plan). However, if the acquiring corporation does not provide for the assumption or substitution of unvested options or restricted stock awards in connection with the change in control event, each such option and restricted stock award shall vest in full and become exercisable or free from forfeiture or repurchase, as applicable, immediately prior to the change in control event. Our board of directors may specify in an award agreement at the time of grant the effect of a change in control event on an restricted stock units, stock appreciation rights or other stock-based awards.

At any time, our board of directors may, in its sole discretion, provide that any award under the 2015 plan will become immediately exercisable in full or in part, free of some or all restrictions or conditions, or otherwise realizable in whole or in part as the case may be.

No award may be granted under the 2015 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 2015 plan at any time, except that stockholder approval may be required to comply with applicable law or stock market requirements.

***2015 employee stock purchase plan***

Our board of directors has adopted, and our stockholders have approved, our 2015 employee stock purchase plan, or the 2015 ESPP, which will become effective immediately prior to the closing of this offering. The 2015 ESPP will be administered by our board of directors or by a committee appointed by our board of directors. The 2015 ESPP initially will provide participating employees with the opportunity to purchase an aggregate of 220,000 shares of our common stock. The number of shares of our common stock reserved for issuance under the 2015 ESPP automatically will increase on the first day of each fiscal year, beginning with the fiscal year

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ending December 31, 2016 and continuing until, and including, the fiscal year ending December 31, 2026, in an amount equal to the lowest of: (1) 440,000 shares of our common stock; (2) 1% of the total number of shares of our common stock outstanding on the first day of the applicable fiscal year; and (3) an amount determined by our board of directors.

All of our employees and employees of any of our designated subsidiaries, as defined in the 2015 ESPP, are eligible to participate in the 2015 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 six months prior to enrolling in the 2015 ESPP; and

such person was our employee or an employee of a designated subsidiary at least fifteen business days prior to the first day of the applicable offering period under the 2015 ESPP.

No employee may purchase shares of our common stock under the 2015 ESPP and any of our other employee stock purchase plans in excess of \$25,000 of the fair market value of our common stock (as of the date of the option grant) in any calendar year. In addition, no employee may purchase shares of our common stock under the 2015 ESPP that would result in the employee owning 5% or more of the total combined voting power or value of our stock.

We expect to make one or more offerings to our eligible employees to purchase stock under the 2015 ESPP beginning at such time as our board of directors may determine. 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 may, at its discretion, choose a different period of not more than 12 months for offerings.

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 2015 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 buy, not in excess of the maximum numbers set forth above. Under the terms of the 2015 ESPP, the purchase price shall be determined by our board of directors for each offering period and will be at least 85% of the applicable closing price of our common stock. If our board of directors 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 for any reason withdraw from participation in an offering prior to the end of an offering period 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 made and the balance in the employee's account will be paid to the employee.

We will be required to make equitable adjustments to the number and class of securities available under the 2015 ESPP, the share limitations under the 2015 ESPP and the purchase price for an offering period under the 2015 ESPP to reflect stock splits, reverse stock splits, stock dividends, recapitalizations, combinations of shares,

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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 2015 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 2015 ESPP on such terms as our board or committee determines:

provide that options shall be assumed, or substantially equivalent options shall be substituted, by the acquiring or succeeding corporation (or an affiliate thereof);

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 our board or committee in such notice, which date shall 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 acquisition price 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 2015 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 shall convert into the right to receive liquidation proceeds (net of the purchase price thereof).

The 2015 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) retirement plan***

We maintain a 401(k) retirement plan that is intended to be a tax-qualified defined contribution plan under Section 401(k) of the Internal Revenue Code. In general, all of our employees are eligible to participate, beginning on the first day of the month following commencement of their employment. The 401(k) plan includes a salary deferral arrangement pursuant to which participants may elect to reduce their current compensation by up to the statutorily prescribed limit, equal to \$18,000 in 2015, and have the amount of the reduction contributed to the 401(k) plan. Participants who are at least 50 years old also can make catch-up contributions, which in 2015 may be up to an additional \$5,500 above the statutory limit. We also currently make discretionary matching contributions to our 401(k) plan equal to 50% of the employee contributions up to 6% of the employee's salary, subject to the statutorily prescribed limit, equal to \$18,000 in 2015. The match immediately vests in full.

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### **Limitation of liability and indemnification**

Our restated 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 DGCL and provides that no director will have personal liability to us or to our stockholders for monetary damages for breach of fiduciary duty or other 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 which involve intentional misconduct or a knowing violation of law;

for voting 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 restated 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 certain liabilities of our directors and executive officers arising out of claims based on acts or omissions in their capacities as directors or executive officers. In addition, we intend to enter into indemnification agreements with each of our directors and executive officers. 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.

Certain of our non-employee directors may, through their relationships with their employers, be insured and/or indemnified against certain liabilities incurred in their capacity as members of our board of directors.

Insofar as indemnification for liabilities arising under the Securities Act of 1933, as amended, 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.

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### **Director compensation**

Neither Mr. Marrazzo nor Dr. High, our directors who also serve as our Chief Executive Officer and our President and Chief Scientific Officer, respectively, receive any additional compensation for his or her service as a director.

In August 2014, we granted options to purchase 37,203 shares of our common stock to each of Drs. Altschuler, Ekman and Mehra and Mr. Milano and an option to purchase 17,203 shares of our common stock to Dr. Sigal. Each of these options has an exercise price of \$3.45 per share and expires ten years after the date of grant. Dr. Altschuler holds his option as a nominee of the CHOP Foundation, which shall receive any economic benefit associated with such option.

In June 2014, we granted an option to purchase 25,786 shares of our common stock to Dr. Sigal with an exercise price of \$3.45 per share and expires ten years after the date of grant. Subject to Dr. Sigal's continued service on our board, this stock option vests as follows: 25% vests upon the first anniversary of the grant date with the remainder vesting in equal quarterly installments over the following three years.

In February 2014, we issued 6,214 shares of restricted common stock to Dr. Sigal. Subject to Dr. Sigal's continued service on our board, these restricted shares vest as follows: 25% vest upon the first anniversary of the grant date with the remaining shares vesting in equal quarterly installments over the following three years.

Dr. Ekman and Mr. Milano each receive a prorated annual retainer of \$25,000 in connection with his service on our board of directors during 2014.

Following this offering, our non-employee directors will be compensated for their services on our board of directors as follows:

each non-employee director will receive an annual retainer of \$35,000;

the chairman of the board will receive an additional annual retainer of \$25,000; and

each non-employee director who serves as member of a committee of our board of directors will receive additional compensation as follows:

audit committee an annual retainer of \$7,500; chair an additional annual retainer of \$15,000;

compensation committee an annual retainer of \$5,000; chair an additional annual retainer of \$10,000; and

nominating and corporate governance committee an annual retainer of \$3,500; chair an additional annual retainer of \$7,500; and

science and technology committee an annual retainer of \$5,000; chair an additional annual retainer of \$10,000.

In addition, upon the commencement of trading of our common stock on the NASDAQ Global Select Market, Dr. Betz will receive an option to purchase 27,000 shares of our common stock with an exercise price equal to the public offering price for shares in this offering. Subject to Dr. Betz's continued service on our board, this stock option will vest in equal quarterly installments over the following three years. Dr. Betz will hold his option as a nominee of the CHOP Foundation, which shall receive any economic benefit associated with such option.

Each annual retainer will be payable in arrears in four equal quarterly installments on the last day of each quarter, provided that the amount of each payment will be prorated for any portion of a quarter that a director is not serving on our board.





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In connection with Dr. Altschuler's employment by the CHOP Foundation and Dr. Betz's role as a member of the CHOP Foundation's board of trustees, all compensation received, or receivable, by Dr. Altschuler and Dr. Betz in consideration for their services rendered to us will be paid to the CHOP Foundation.

Each member of our board of directors also will continue to be entitled to be reimbursed for reasonable travel and other expenses incurred in connection with attending meetings of the board of directors and any committee of the board of directors on which he or she serves.

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## **Certain relationships and related-person transactions**

Since our inception on March 13, 2013, we have engaged in the following transactions with our directors, executive officers and holders of more than 5% of our voting securities and affiliates of our directors, executive officers and holders of more than 5% of our voting securities. We believe that all of the transactions described below were made on terms no less favorable to us than could have been obtained from unaffiliated third parties.

### **Collaboration with CHOP**

In October 2013, we entered into a licensing agreement with CHOP, which we amended in December 2013 and May 2014. We also entered into a technology assignment agreement, a master research service agreement and an administrative services agreement with CHOP in October 2013, a sponsored research agreement with CHOP in October 2014 and multiple clinical trial agreements with CHOP at various times regarding the conduct of our various clinical trials. See [Business Collaboration and license agreements The Children's Hospital of Philadelphia](#). Pursuant to these agreements, we paid CHOP \$3.8 million for the period from inception to December 31, 2013 and \$4.6 million for the nine months ended September 30, 2014.

Additionally, in 2013, we issued equity interests, since converted into 4,943,629 shares of our common stock, to CHOP as consideration for entry into certain technology and license agreements from CHOP that we determined to have a fair market value of \$49.4 million. All equity interests issued to CHOP currently are held by the CHOP Foundation.

Steven Altschuler, M.D., chairman of our board of directors, is the chief executive officer of CHOP and the CHOP Foundation.

### **Series A financing**

In October 2013, we issued and sold equity interests, since converted into 5,000,000 shares of our Series A preferred stock, to CHOP for a purchase price of \$10.0 million.

### **Consulting agreement with Katherine A. High, M.D.**

In December 2013, we entered into a consulting agreement with Katherine A. High, M.D., whereby Dr. High provided consulting and advisory services related to, among other things, clinical studies of various AAV vectors. In compensation for her services, Dr. High received common units in Spark LLC, which were subsequently converted into 400,000 shares of restricted common stock of Spark Inc. Pursuant to the related employment agreement in September 2014, Dr. High became President and Chief Scientific Officer. Dr. High's restricted stock vests as follows: 25% of the grant vested on March 13, 2014, with the remainder vesting in equal quarterly installments over the subsequent three year period.

**Table of Contents****Series B financing**

In May 2014, we issued and sold an aggregate of 45,186,334 shares of our Series B Stock, at a price per share of \$1.61, for an aggregate purchase price of approximately \$72.7 million. The following table sets forth the number of shares of our Series B Stock purchased by our directors, executive officers and 5% stockholders and their affiliates pursuant to this transaction.

<b>Purchaser(1)</b>	<b>Shares of series B</b>	<b>Total</b>
	<b>preferred stock</b>	<b>purchase price</b>
CHOP(2)	13,975,155	\$ 22,500,000
Sofinnova Venture Partners VIII, L.P.(3)	9,316,770	\$ 15,000,000
Entities affiliated with Baker Bros. Advisors LP	6,211,180	\$ 10,000,000
Sigal Family Investments, LLC(4)	155,279	\$ 250,000

(1) See Principal stockholders for more information about the shares held by these entities.

(2) Dr. Steven Altschuler, chairman of our board of directors, is the chief executive officer of CHOP and the CHOP Foundation, a holder of more than 5% of our voting securities.

(3) Dr. Anand Mehra, a member of our board of directors, is a managing member of Sofinnova Management VIII, L.L.C., the sole general partner of Sofinnova Venture Partners VIII, L.P., a holder of more than 5% of our voting securities. Dr. Mehra may be deemed to have voting and investment power over the shares held by Sofinnova Venture Partners VIII, L.P. Dr. Mehra disclaims beneficial ownership of such shares except to the extent of any respective pecuniary interest therein.

(4) Dr. Elliott Sigal, a member of our board of directors, is a manager of Sigal Family Investments, LLC. Dr. Sigal may be deemed to have voting and investment power over the shares held by Sigal Family Investments, LLC. Dr. Sigal disclaims beneficial ownership of such shares except to the extent of any pecuniary interest therein.

In connection with the issuance and sale of shares of our Series B Stock, each of the purchasers has the right to elect to purchase up to, at a per share purchase price equal to the public offering price of the shares offered hereby, a number of shares of our common stock necessary to maintain their pro rata ownership interests in us, either by purchasing shares in this public offering, or at our determination, in a concurrent private placement.

**Investor rights agreement**

We are a party to an investors' rights agreement, dated May 23, 2014, which we refer to as the Investors' Rights Agreement, with holders of our Series A Stock and Series B Stock, which includes our 5% stockholders and entities affiliated with two of our directors. The Investors' Rights Agreement provides these holders the right, following the completion of this offering, to demand that we file a registration statement or 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 arrangements**

Our current certificate of incorporation and our restated certificate of incorporation, which will become effective as of 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 have entered into indemnification agreements with certain of our directors and executive officers and expect to enter into indemnification agreements with each of our directors and executive officers that may be broader in scope than the specific indemnification provisions contained in the DGCL. See the Executive compensation Limitation of liability and indemnification section of this prospectus for a further discussion of these arrangements.

**Policies and procedures for related-person transactions**

On December 29, 2014 our board of directors adopted written policies and procedures for the review of any transaction, arrangement or relationship in which we are a participant, the amount involved exceeds \$120,000

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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. The policy calls for the proposed related-person transaction to be reviewed and, if deemed appropriate, approved by the audit committee of our board of directors. Whenever practicable, the reporting, review and approval will occur prior to entry into the transaction. If advance review and approval is not practicable, the committee will review and, in its discretion, may ratify the related-person transaction. The policy also permits the chair 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 committee after full disclosure of the related person's interest in the transaction. As appropriate for the circumstances, the 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 related-person 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.

The audit committee may approve or ratify the transaction only if the audit committee determines that, under all of the circumstances, the transaction is not inconsistent with our best interests. The 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, the 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 such entity) that is a participant in the transaction, where (a) the related person and all other related persons own in the aggregate less than a 10% equity interest in such entity; (b) 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; (c) the amount involved in the transaction equals less than the greater of \$200,000 or 5% of the annual gross revenues of the company receiving payment under the transaction; and

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a transaction that is specifically contemplated by provisions of our charter or bylaws. The policy provides that transactions involving compensation of executive officers shall be reviewed and approved by the compensation committee in the manner specified in its charter.

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## Principal stockholders

The following table sets forth information with respect to the beneficial ownership of our common stock, as of January 15, 2015 by:

each person known by us to beneficially own more than 5% of our common stock;

each of our directors;

each of our named executive officers; and

all of our executive officers and directors as a group.

The column entitled "Percentage of shares beneficially owned - Before offering" is based on 16,490,367 shares of our common stock outstanding as of January 15, 2015, assuming the automatic conversion of all outstanding shares of our preferred stock, including shares of preferred stock that are issuable as accrued dividends, into an aggregate of 10,200,050 shares of our common stock upon the closing of this offering, assuming such closing occurs on February 4, 2015. The column entitled "Percentage of shares beneficially owned - After offering" is based on shares of our common stock to be outstanding after this offering, including the shares of our common stock that we are selling in this offering, but not including any additional shares issuable upon exercise of outstanding options.

The number of shares beneficially owned by each stockholder is determined under rules issued by the SEC and includes voting or investment power with respect to securities. Under these rules, beneficial ownership includes any shares as to which the individual or entity has sole or shared voting power or investment power. In computing the number of shares beneficially owned by an individual or entity and the percentage ownership of that person, shares of common stock subject to options, warrants or other rights held by such person that are currently exercisable, or will become exercisable within 60 days of January 15, 2015, are considered outstanding, although these shares are not considered outstanding for purposes of computing the percentage ownership of any other person. Unless otherwise indicated, the address of all listed stockholders is 3737 Market Street, Suite 1300, Philadelphia, PA 19104. Each of the stockholders listed has sole voting and investment power with respect to the shares beneficially owned by the stockholder unless noted otherwise, subject to community property laws where applicable.

Our principal stockholders have indicated an interest in purchasing an aggregate of up to approximately \$15 million of shares of common stock in this offering at the initial public offering price. However, because indications of interest are not binding agreements or commitments to purchase, these stockholders may determine to purchase fewer shares than they indicate an interest in purchasing or not to purchase in this offering. It also is possible that these stockholders could indicate an interest in purchasing more shares of our common stock. In addition, the underwriters could determine to sell fewer shares to any of these stockholders than the stockholders indicate an interest in purchasing or not to sell any shares to these stockholders. Accordingly, the following table does not reflect any potential purchases by these existing principal stockholders or their affiliated entities. If any shares are purchased by these stockholders, the number and percentage of shares of our common stock beneficially owned by them after this offering will differ from those set forth in the following table.



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Name of beneficial owner	Number of shares beneficially owned	Percentage of shares beneficially owned	
		Before offering	After offering
<b>Named Executive Officers and Directors</b>			
Jeffrey D. Marrazzo	380,000	2.3%	2.1%
Katherine A. High, M.D.	340,000	2.1%	1.9%
Stephen W. Webster		*	*
Steven Altschuler, M.D.(1)	8,800,212	53.4%	49.5%
A. Lorris Betz, M.D., Ph.D.		*	*
Lars Ekman, M.D., Ph.D.		*	*
Anand Mehra, M.D.(2)	1,893,576	11.5%	10.6%
Vincent J. Milano		*	*
Elliott Sigal, M.D., Ph.D. (3)	44,219	*	*
All executive officers and directors as a group (10 persons)	11,461,890	69.5%	64.4%
<b>5% Stockholders</b>			
CHOP Foundation(4)	8,800,212	53.4%	49.5%
Sofinnova Venture Partners VIII, L.P.(5)	1,893,576	11.5%	10.6%
Entities affiliated with Baker Bros. Advisors LP(6)	1,262,382	7.7%	7.1%

\* Less than 1%.

- (1) Consists of the shares described in note 4 below. Dr. Altschuler, chairman of our board of directors is chief executive officer of the CHOP Foundation and may be deemed to have voting and investment power over the shares held by the CHOP Foundation. Dr. Altschuler disclaims beneficial ownership over such shares.
- (2) Consists of the shares described in note 5 below. Dr. Mehra is a managing member of Sofinnova Management VIII, L.L.C., the sole general partner of Sofinnova Venture Partners VIII, L.P. Dr. Mehra may be deemed to have voting and investment power over the shares held by Sofinnova Venture Partners VIII, L.P. Dr. Mehra disclaims beneficial ownership of such shares except to the extent of any pecuniary interest therein.
- (3) Consists of (a) 6,214 shares of common stock owned by Dr. Sigal, (b) 31,056 shares of common stock issuable upon conversion of Series B Stock owned by Sigal Family Investments, LLC, (c) 6,446 shares of common stock underlying options that are exercisable as of January 15, 2015 or will become exercisable within 60 days after such date and (d) 503 shares of common stock issuable upon the automatic conversion of the outstanding shares of preferred stock related to the preferred stock dividend, including shares of preferred stock issuable as accrued stock dividends, assuming the closing of this offering and the conversion of such shares occurs on February 4, 2015. Dr. Sigal is a manager of Sigal Family Investments, LLC. Dr. Sigal may be deemed to have voting and investment power over the shares held by Sigal Family Investments, LLC. Dr. Sigal disclaims beneficial ownership of such shares except to the extent of any pecuniary interest therein.
- (4) Consists of: (a) 4,943,629 shares of common stock; (b) 1,000,000 shares of common stock issuable upon conversion of Series A Stock, (c) 2,795,031 shares of common stock issuable upon conversion of Series B Stock and (d) 61,552 shares of common stock issuable upon the automatic conversion of the outstanding shares of preferred stock related to the preferred stock dividend, including shares of preferred stock issuable as accrued stock dividends, assuming the closing of this offering and the conversion of such shares occurs on February 4, 2015. The CHOP Foundation's board of trustees, or a committee designated by the board of trustees, has voting and investment power of their shares. Dr. Altschuler, chairman of our board of directors is chief executive officer of the CHOP Foundation and may be deemed to have voting and investment power over the shares held by the CHOP Foundation. Dr. Altschuler disclaims beneficial ownership over such shares. The address of each of Dr. Altschuler and the CHOP Foundation is 34<sup>th</sup> Civic Center Boulevard, Philadelphia, PA 19104. CHOP has engaged Perella Weinberg Partners ( Perella Weinberg ) to serve as its financial advisor in connection with its investment in Spark. Perella Weinberg will receive fees from CHOP in connection with this service. The services provided by Perella Weinberg include customary business and financial analysis, assistance in reviewing information materials regarding the offering and advising CHOP with respect to the structuring of its investment in Spark.

(5)

## Edgar Filing: Spark Therapeutics, Inc. - Form S-1/A

Consists of (a) 1,863,354 shares of common stock issuable upon conversion of Series B Stock and (b) 30,222 shares of common stock issuable upon the automatic conversion of the outstanding shares of preferred stock related to the preferred stock dividend, including shares of preferred stock issuable as accrued stock dividends, assuming the closing of this offering and the conversion of such shares occurs on February 4, 2015. Dr. Mehra, a member of our board of directors, is a managing member of Sofinnova Management VIII, L.L.C., the sole general partner of Sofinnova Venture Partners VIII, L.P. Dr. Mehra may be deemed to have voting and investment power over the shares held by Sofinnova Venture Partners VIII, L.P. Dr. Mehra disclaims beneficial ownership of such shares except to the extent of any pecuniary interest therein. The address of Sofinnova Venture Partners VIII, L.P. is 3000 Sand Hill Road, Bldg. 4, Suite 250, Menlo Park, CA 94025.

- (6) Consists of (a) 69,223 shares of common stock issuable upon conversion of Series B Stock purchased by 667, L.P. ( 667 LP ) (account #1), (b) 49,966 shares of common stock issuable upon conversion of Series B Stock purchased by 667 LP (account #2), (c) 27,163 shares of common stock issuable upon conversion of Series B Stock purchased by 14159, L.P. ( 14159 LP ), (d) 1,095,882 shares of common stock issuable upon conversion of Series B Stock purchased by Baker Brothers Life Sciences, L.P. ( Baker Brothers Life Sciences ) and together with 667 LP and 14159 LP, the Baker Bros. Funds ) and (e) 20,148 shares of common stock issuable upon the automatic conversion of the outstanding shares of preferred stock related to the preferred stock dividend, including shares of preferred stock issuable as accrued stock dividends, assuming the closing of this offering and the conversion of such shares occurs on February 4, 2015. Baker Bros. Advisors LP ( Baker Bros. Advisors ) is the investment adviser to each of the Baker Bros. Funds and, pursuant to amended and restated management agreements between Baker Bros. Advisors, the Baker Bros. Funds and the respective general partners of the Baker Bros. Funds. Baker Bros. Advisors has complete and unlimited discretion and authority with respect to Baker Bros. Funds investments and voting power over investments. Baker Bros. Advisors disclaims beneficial ownership of all shares held by the Baker Bros. Funds except to the extent of any pecuniary interest therein. The address of each of the Baker Bros. Funds is 667 Madison Ave. 21st Floor, New York, NY 10065.

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## **Description of capital stock**

### **General**

Following the closing of this offering, our authorized capital stock will consist of shares of 150,000,000 common stock, par value \$0.001 per share, and 5,000,000 shares of preferred stock, par value \$0.001 per share. The following description of our capital stock and provisions of our restated certificate of incorporation and amended and restated bylaws are summaries and are qualified by reference to the restated certificate of incorporation and amended and restated bylaws that will become effective upon the closing of this offering. Copies of these documents have been filed with the SEC as exhibits to the registration statement, of which this prospectus forms a part. The description of our common stock reflects changes to our capital structure that will occur upon the closing of this offering.

As of January 15, 2015, we had issued and outstanding:

6,290,317 shares of our common stock held of record by 28 stockholders;  
5,000,000 shares of our Series A Stock that are convertible into 1,000,000 shares of common stock; and  
45,186,334 shares of our Series B Stock that are convertible into 9,037,255 shares of our common stock.

Upon the closing of this offering, all of the outstanding shares of our preferred stock, including shares of preferred stock that are issuable as accrued dividends, will automatically convert into an aggregate of 10,200,050 shares of our common stock, assuming the closing of this offering occurred on February 4, 2015. The number of shares of common stock issuable upon the automatic conversion of the outstanding shares of our preferred stock will continue to increase if the closing occurs after February 4, 2015 as a result of the issuance of additional shares of preferred stock accruing as stock dividends at a rate of 8% per annum. For each day occurring between February 4, 2015 and the closing of this offering, if any, the number of shares of common stock issuable upon the automatic conversion of the outstanding shares of our preferred stock will increase by approximately 2,200 shares.

### **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. An election of directors by our stockholders shall 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 any series of preferred stock that we may designate and issue in the future.

In the event of our liquidation or dissolution, the holders of common stock are entitled to receive proportionately our net assets available for distribution to stockholders after the payment of all debts and other liabilities and subject to the prior rights of any outstanding preferred stock. Holders of common stock have no preemptive, subscription, redemption or conversion rights. Our outstanding shares of common stock are, and the shares offered by us in this offering will be, when issued and paid for, validly issued, fully paid and nonassessable. The rights, preferences and privileges of holders of common stock are subject to and may be adversely affected by the rights of the holders of shares of any series of preferred stock that we may designate and issue in the future.

### **Preferred stock**

Under the terms of our restated certificate of incorporation, our board of directors is authorized to direct us to issue shares of preferred stock in one or more series without stockholder approval. Our board of directors has

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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**

As of January 15, 2015, options to purchase 2,264,497 shares of our common stock at a weighted-average exercise price of \$4.52 per share were outstanding.

## **Registration rights**

Pursuant to the terms of the Investors' Rights Agreement, upon the completion of this offering, holders of a total of 10,200,050 shares of our common stock, including shares issuable upon conversion of our preferred stock (which includes shares issuable as accrued stock dividends assuming the closing of this offering occurs on February 4, 2015), will have the right to require us to register these shares under the Securities Act of 1933, as amended, or Securities Act, and to participate in future registrations of securities by us, under the circumstances described below. After registration pursuant to these rights, these shares will become freely tradable without restriction under the Securities Act. If not otherwise exercised, the rights described below will expire three years after the closing of this offering.

### ***Demand registration rights***

Beginning six months after the closing of this offering, subject to specified limitations set forth in the Investors' Rights Agreement, at any time, the holders of a majority of the then outstanding shares having rights under the Investors' Rights Agreement, which we refer to as registrable shares, may at any time demand in writing that we register all or a portion of the registrable shares under the Securities Act if the total amount of registrable shares registered have an aggregate offering price of at least \$10 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 Investors' Rights Agreement, at any time after we become eligible to file a registration statement on Form S-3, holders of the registrable shares then outstanding may request that we register their registrable securities on Form S-3 for purposes of a public offering if the total amount of registrable shares registered have an aggregate offering price of at least \$2 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 file a registration statement to register any of our securities under the Securities Act in connection with a public offering of such securities solely for cash, other than pursuant to certain specified registrations, including relating to company stock option plans and rule 145 transactions, the holders of our registrable securities are entitled to notice of registration and, subject to

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specified exceptions, including market conditions, we will be required, upon the holder's request, to use our best efforts to register their then held registrable securities.

In the event that any registration in which the holders of registrable shares participate pursuant to our Investors' Rights Agreement is an underwritten public offering, we agree to enter into an underwriting agreement containing customary terms for such offering.

### ***Expenses***

Pursuant to the Investors' Rights Agreement, we are required to pay all registration and filing fees, exchange listing fees, printing expenses, fees and expenses of one counsel 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 and the fees and expenses of selling stockholders' own counsel (other than the counsel selected to represent all selling stockholders). We are not required to pay registration expenses if a demand registration request under the Investors' Rights Agreement is withdrawn at the request of holders who exercise their demand right to register the registrable securities, unless the withdrawal is due to discovery of a materially adverse change in our business.

The Investors' 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 applicable registration statement attributable to us, and the selling stockholders are obligated to indemnify us for material misstatements or omissions in the registration statement attributable to them.

### **Anti-takeover provisions**

#### ***DGCL***

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 the interested stockholder attained such status with the approval of our board of directors or unless the business combination is approved in a prescribed manner. 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.

#### ***Staggered board; removal of directors***

Our restated certificate of incorporation and our amended and restated bylaws divide our board of directors into three classes with staggered three-year terms. In addition, a director may be removed only for cause and only by the affirmative vote of the holders of at least 75% of the votes that all our stockholders would be entitled to cast in an annual election of directors. 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.

The classification of our board of directors and the limitations on the removal of directors and filling of 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.

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### ***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 by-laws may be amended or repealed by a majority vote of our board of directors or the affirmative vote of the holders of at least two-thirds of the votes that all our stockholders would be entitled to cast in an annual election of directors. In addition, the affirmative vote of the holders of at least two-thirds of the votes which all our stockholders would be entitled to cast in an election of directors is required to amend or repeal or to adopt any provisions inconsistent with any of the provisions of our restated certificate of incorporation described in the prior two paragraphs.

### ***Stockholder action; special meeting of stockholders***

Our restated certificate of incorporation provides that any action required or permitted to be taken by our stockholders must be effected at a duly called annual or special meeting of such stockholders and may not be effected by any consent in writing by such stockholders. Our restated certificate of incorporation and our amended and restated bylaws also provide that, except as otherwise required by law, special meetings of our stockholders can only be called by our chairman of the board, our chief executive officer or our board of directors.

### ***Authorized but unissued shares***

The authorized but unissued shares of common stock and preferred stock are available for future issuance without stockholder approval, subject to any limitations imposed by the listing standards of the NASDAQ Global Select Market. These additional shares may be used for a variety of corporate finance transactions, acquisitions and employee benefit plans. The existence of authorized but unissued and unreserved common stock and preferred stock could make more difficult or discourage an attempt to obtain control of us by means of a proxy contest, tender offer, merger or otherwise.

## **Transfer agent and registrar**

The transfer agent and registrar for our common stock will be American Stock Transfer & Trust Company, LLC.

## **NASDAQ Global Select Market**

Our common stock has been approved for listing on the NASDAQ Global Select Market under the symbol ONCE.

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## **Shares eligible for future sale**

Immediately prior to this offering, there was no public market for our common stock. Future sales of substantial amounts of common stock in the public market, or the perception that such sales may occur, could adversely affect the market price of our common stock. Although we have been approved to have our common stock listed on the NASDAQ Global Select Market, we cannot assure you that there will be an active public market for our common stock.

Upon the closing of this offering, we will have outstanding an aggregate of 22,990,367 shares of common stock, assuming the issuance of 6,500,000 shares of common stock offered by us in this offering, assuming no exercise by the underwriters of their option to purchase additional shares and no exercise of options outstanding as of January 15, 2015.

Of these shares, all shares sold in this offering will be freely tradable without restriction or further registration under the Securities Act, except for any shares purchased by our affiliates, as that term is defined in Rule 144 under the Securities Act, the sale of which would be subject to the Rule 144 resale restrictions described below, other than the holding period requirement.

The remaining 16,490,367 shares of common stock will be restricted securities, as that term is defined in Rule 144 under the Securities Act and will further be subject to either restrictions on transfer under the lock-up agreements described below or restrictions on transfer for a period of 180 days from the effectiveness of the registration statement of which this prospectus forms a part under stock option and restricted stock agreements entered into between us and the holders of those shares. Following the expiration of these restrictions, these shares will become eligible for public sale if they are registered under the Securities Act or if they qualify for an exemption from registration under Rules 144 or 701 under the Securities Act, which are summarized below. These restricted securities are eligible for public sale only if they are registered under the Securities Act or if they qualify for an exemption from registration under Rules 144 or 701 under the Securities Act, which are summarized below.

In addition, of the 2,264,497 shares of our common stock that were subject to stock options outstanding as of January 15, 2015, options to purchase 45,124 shares of common stock were vested as of January 15, 2015 and, upon exercise, these shares will be eligible for sale subject to the lock-up agreements described below and Rules 144 and 701 under the Securities Act.

### **Lock-up agreements**

We, and each of our directors and executive officers and holders of substantially all of our outstanding capital stock, who collectively own 16,489,332 shares of our common stock, based on shares outstanding as of January 15, 2015, including shares issuable upon conversion of our preferred stock (which includes shares issuable as accrued stock dividends assuming the closing of this offering occurs on February 4, 2015), have agreed that, without the prior written consent of J.P. Morgan Securities LLC and Credit Suisse Securities (USA) 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, subject to extension in specified circumstances:

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 our common stock or any securities convertible into or exercisable or exchangeable for common stock; or

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

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whether any transaction described above is to be settled by delivery of our 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 "Underwriting."

Upon the expiration of the applicable lock-up periods, substantially all of the shares subject to such lock-up restrictions will become eligible for sale, subject to the limitations discussed above.

## **Rule 144**

### *Affiliate resales of restricted securities*

In general, beginning 90 days after the effective date of the registration statement of which this prospectus is a part, a person who is an affiliate of ours, or who was an affiliate at any time during the 90 days before a sale, who has beneficially owned shares of our common stock for at least six months would be entitled to sell in "broker's transactions" or certain "riskless principal transactions" or to market makers, 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 229,904 shares immediately after this offering; or

the average weekly trading volume in our common stock on the NASDAQ Global Select Market during the four calendar weeks preceding the filing of a notice on Form 144 with respect to such sale.

Affiliate resales under Rule 144 also are subject to the availability of current public information about us. In addition, if the number of shares being sold under Rule 144 by an affiliate during any three-month period exceeds 5,000 shares or has an aggregate sale price in excess of \$50,000, the seller must file a notice on Form 144 with the Securities and Exchange Commission and NASDAQ concurrently with either the placing of a sale order with the broker or the execution directly with a market maker.

### *Non-affiliate resales of restricted securities*

In general, beginning 90 days after the effective date of the registration statement of which this prospectus is a part, a person who is not an affiliate of ours at the time of sale, and has not been an affiliate at any time during the three months preceding a sale, and who has beneficially owned shares of our common stock for at least six months but less than a year, is entitled to sell such shares subject only to the availability of current public information about us. If such person has held our shares for at least one year, such person can resell under Rule 144(b)(1) without regard to any Rule 144 restrictions, including the 90-day public company requirement and the current public information requirement.

Non-affiliate resales are not subject to the manner of sale, volume limitation or notice filing provisions of Rule 144.

## **Rule 701**

In general, under Rule 701, any of an issuer's employees, directors, officers, consultants or advisors who purchases shares from the issuer in connection with a compensatory stock or option plan or other written agreement before the effective date of a registration statement under the Securities Act is entitled to sell such shares 90 days after such effective date in reliance on Rule 144. An affiliate of the issuer can resell shares in reliance on Rule 144 without having to comply with the holding period requirement, and non-affiliates of the



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issuer can resell shares in reliance on Rule 144 without having to comply with the current public information and holding period requirements.

The SEC has indicated that Rule 701 will apply to typical stock options granted by an issuer before it becomes subject to the reporting requirements of the Exchange Act, along with the shares acquired upon exercise of such options, including exercises after an issuer becomes subject to the reporting requirements of the Exchange Act.

## **Equity plans**

We intend to file one or more registration statements on Form S-8 under the Securities Act to register all shares of common stock subject to outstanding stock options and shares of common stock issued or issuable under our stock plans. We expect to file the registration statement covering shares offered pursuant to our stock plans on or shortly after the date of this prospectus, permitting the resale of such shares by nonaffiliates in the public market without restriction under the Securities Act and the sale by affiliates in the public market, subject to compliance with the resale provisions of Rule 144.

## **Registration rights**

Upon the closing of this offering, the holders of 10,200,050 shares of common stock, or their transferees, will be entitled to various rights with respect to the registration of these shares under the Securities Act. Registration of these shares under the Securities Act would result in these shares becoming fully tradable without restriction under the Securities Act immediately upon the effectiveness of the registration, except for shares purchased by affiliates. See [Description of capital stock](#) [Registration rights](#) for additional information. Shares covered by a registration statement will be eligible for sale in the public market upon the expiration or release from the terms of the lock-up agreement.

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## **Material U.S. federal income and estate tax considerations for non-U.S. holders of common stock**

The following is a discussion of the material U.S. federal income and estate tax considerations applicable to non-U.S. holders with respect to their ownership and disposition of shares of our common stock. For purposes of this discussion, a non-U.S. holder means a beneficial owner 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 any other organization taxable as a corporation for U.S. federal income tax purposes, created or organized in or under the laws of the United States or of any state thereof or the District of Columbia;

an estate, the income of which is subject to U.S. federal income tax regardless of its source; or

a trust if (1) a U.S. court is able to exercise primary supervision over the trust's administration and one or more U.S. persons have the authority to control all of the trust's substantial decisions 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 that hold their common stock through partnerships or other pass-through entities. 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 acquiring, holding and disposing 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, all of which are subject to change or to differing interpretation, possibly with retroactive effect. Any change could alter the tax consequences to non-U.S. holders described in this prospectus. There can be no assurance that the Internal Revenue Service, which we refer to as the IRS, will not challenge one or more of the tax consequences described herein. We assume in this discussion that a non-U.S. holder holds shares of our common stock as a capital asset, generally property held for investment.

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:

insurance companies;

tax-exempt organizations;

financial institutions;

brokers or dealers in securities;

pension plans;

controlled foreign corporations;

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passive foreign investment companies;

persons deemed to sell our common stock under the constructive sale provisions of the Code;

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

certain former citizens or residents of the United States.

**All prospective non-U.S. holders of our common stock should consult their own tax advisors with respect to the U.S. federal, state, local and non-U.S. tax consequences of the purchase, ownership and disposition of our common stock.**

## **Distributions on our common stock**

Distributions on our common stock, if any, 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 such holder's tax basis in the common stock. Any remaining excess will be treated as capital gain, subject to the tax treatment described below in "Gain on sale, exchange or other disposition of our common stock." Any such distributions will also be subject to the discussion below under the section titled "Withholding and information reporting requirements - 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.

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, including providing a Form W-8ECI. However, such U.S. effectively connected income, net of specified deductions and credits, is taxed at the same graduated U.S. federal income tax rates applicable to United States persons (as defined in the Code). Any U.S. effectively connected income received by a non-U.S. holder that is a corporation may also, under certain circumstances, be subject to an additional "branch profits tax" at a 30% rate or such lower rate as may be specified by an applicable income tax treaty between the United States and such holder's country of residence.

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

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 a U.S. tax return with the IRS.

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### **Gain on sale, exchange or other disposition of our common stock**

In general (subject to the discussion below under the section titled "Withholding and information reporting requirements (FATCA)"), a non-U.S. holder will not be subject to any U.S. federal income tax on any gain realized upon such holder's sale, exchange or other disposition of shares of our common stock unless:

the gain is effectively connected with the non-U.S. holder's conduct of a U.S. trade or business and, if an applicable income tax treaty so provides, is attributable to a permanent establishment or a fixed base maintained by such 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 graduated U.S. federal income tax rates applicable to United States persons (as defined in the Code) and, if the non-U.S. holder is a foreign corporation, the branch profits tax described above in "Distributions on our common stock" also may apply;

the non-U.S. holder is a nonresident alien individual who is present in the United States for 183 days or more in the taxable year of the disposition and certain other conditions are met, in which case the non-U.S. holder will be subject to a 30% tax (or such lower rate as may be specified by an applicable income tax treaty 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 holds no more than 5% of our outstanding common stock, directly, indirectly or constructively, 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 a purchaser may withhold 10% of the proceeds payable to a non-U.S. holder from a sale of our common stock (if our common stock is not regularly traded on an established securities market) and the non-U.S. holder generally will be taxed on its net gain derived from the disposition at the graduated U.S. federal income tax rates applicable to United States 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 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, or that we are likely to become one in the future. We also expect that our common stock will continue to be regularly traded on an established securities market, although no assurance can be provided.

### **U.S. federal estate tax**

Shares of our common stock that are owned or treated as owned at the time of death by an individual who is not a citizen or resident of the United States, as specifically defined for U.S. federal estate tax purposes, 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.

### **Backup withholding and information reporting**

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 may have to comply with specific certification procedures to establish that the holder is not a United States person (as defined in the Code) in order to avoid backup withholding at the applicable rate with respect

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to dividends on our common stock. Dividends paid to non-U.S. holders subject to withholding of U.S. federal income tax, as described above in Distributions on our common stock, generally will 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 foreign, unless the holder certifies its status as a non-U.S. holder and satisfies certain other requirements, or otherwise establishes an exemption. Generally, information reporting and backup withholding will not apply to a payment 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. 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.

## **Withholding and information reporting requirements FATCA**

The Foreign Account Tax Compliance Act, or FATCA, generally imposes a U.S. federal withholding tax at a rate of 30% on payments of dividends on, or gross proceeds from the sale or other disposition of, our common stock paid to a foreign entity unless: (i) if the foreign entity is a foreign financial institution, such foreign entity undertakes certain due diligence, reporting, withholding and certification obligations, including collecting and providing to U.S. tax authorities substantial information regarding the U.S. account holders of such institution; (ii) if the foreign entity is not a foreign financial institution, such foreign entity identifies certain of its U.S. investors, if any; or (iii) the foreign entity is otherwise exempt under FATCA. Under applicable U.S. Treasury regulations, withholding under FATCA will apply (1) currently to payments of dividends on our common stock, and (2) to payments of gross proceeds from a sale or other disposition of our common stock made after December 31, 2016. Under certain circumstances, a non-U.S. holder may be eligible for refunds or credits of the tax. An intergovernmental agreement between the United States and an applicable foreign country may modify the requirements described in this paragraph. Non-U.S. holders should consult their own tax advisors regarding the possible implications of this legislation 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.

**Table of Contents****Underwriting**

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

<b>Name</b>	<b>Number of shares</b>
J.P. Morgan Securities LLC	
Credit Suisse Securities (USA) LLC	
Cowen and Company, LLC	
Sanford C. Bernstein & Co., LLC	
<b>Total</b>	<b>6,500,000</b>

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

Our principal stockholders have indicated an interest in purchasing an aggregate of up to approximately \$15 million in shares of our common stock in this offering at the initial public offering price. However, because indications of interest are not binding agreements or commitments to purchase, these stockholders may determine to purchase fewer shares than they indicate an interest in purchasing or not to purchase any shares in this offering. It also is possible that these stockholders could indicate an interest in purchasing more shares of our common stock. In addition, the underwriters could determine to sell fewer shares to any of these stockholders than the stockholders indicate an interest in purchasing or not to sell any shares to these stockholders.

The underwriters propose to offer the common shares directly to the public at the initial public offering price set forth on the cover page of this prospectus and to certain dealers at that price less a concession not in excess of \$ per share. Any such dealers may resell shares to certain other brokers or dealers at a discount of up to \$ per share from the initial public offering price. After the initial public offering of the shares, the offering price and other selling terms may be changed by the underwriters. Sales of shares made outside of the United States may be made by affiliates of the underwriters.

The underwriters have an option to buy up to 975,000 additional shares of common stock from us to cover sales of shares by the underwriters which exceed the number of shares specified in the table above. The underwriters have 30 days from the date of this prospectus to exercise this option. If any shares are purchased with this option, the underwriters will purchase shares in approximately the same proportion as shown in the table above. If any additional shares of common stock are purchased, the underwriters will offer the additional shares on the same terms as those on which the shares are being offered.

At our request, the underwriters have reserved for sale, at the initial public offering price, up to 2% of the shares offered hereby for employees, directors and other persons associated with us who have expressed an interest in purchasing common stock in the offering. Our officers and directors who are participating in this program have agreed that any shares purchased through this program will be subject to a 180-day lock-up restriction. The number of shares available for sale to the general public in the offering will be reduced to the extent these persons purchase the reserved shares. Any reserved shares not so purchased will be offered by the underwriters to the general public on the same terms as the other shares.

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

	<b>Without option exercise</b>	<b>With full option exercise</b>
Per share	\$	\$
Total	\$	\$

We estimate that the total expenses of this offering payable by us, including registration, filing and listing fees, printing fees and legal and accounting expenses, but excluding the underwriting discounts and commissions, will be approximately \$3.0 million. We have agreed to reimburse the underwriters for expenses of up to \$35,000 related to clearance of this offering with the Financial Industry Regulatory Authority, Inc., or FINRA.

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

We have agreed that we will not (i) 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 or otherwise transfer or dispose of, directly or indirectly, or file with the SEC a registration statement under the Securities Act relating to, any shares of our common stock or any securities convertible into or exercisable or exchangeable for any shares of our common stock, or publicly disclose the intention to make any offer, sale, pledge, disposition or filing or (ii) enter into any swap or other agreement that transfers all or a portion of any of the economic consequences of ownership of any shares of common stock or any such other securities (regardless of whether any of the transactions described above are to be settled by the delivery of shares of common stock or such other securities, in cash or otherwise), in each case without the prior written consent of J.P. Morgan Securities LLC and Credit Suisse Securities (USA) LLC for a period of 180 days after the date of this prospectus, other than (A) the shares of our common stock to be sold hereunder; (B) any shares of our common stock issued upon the exercise of options granted under our existing management incentive plans; (C) any options and other awards granted under our existing management incentive plans; (D) our filing of a registration statement on Form S-8 or a successor form thereto relating to the shares of our common stock granted pursuant to or reserved for issuance under our existing management incentive plans; and (E) shares of our common stock or other securities issued in connection with a transaction that includes a commercial relationship (including joint ventures, marketing or distribution arrangements, collaboration agreements or intellectual property license agreements) or any acquisition of assets or not less than a majority or controlling portion of the equity of another entity; provided that the aggregate number of shares of our common stock issued pursuant to clause (E) shall not exceed 10.0% of the total number of outstanding shares of our common stock immediately following the issuance and sale of the underwritten shares pursuant to the underwriting agreement; provided, further, the recipient of any such shares of our common stock and securities issued pursuant to clauses (C) or (E) during the 180-day restricted period described above shall enter into an agreement substantially in the form described below.

Our directors and executive officers, and each of our significant shareholders, have entered into lock-up agreements with the underwriters pursuant to which each of these persons or entities, with limited exceptions, for a period of 180 days after the date of this prospectus, may not, without the prior written consent of J.P. Morgan Securities LLC and Credit Suisse Securities (USA) LLC: (1) offer, pledge, sell, contract to sell, sell any



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option or contract to purchase, purchase any option or contract to sell, grant any option, right or warrant to purchase or otherwise transfer or dispose of, directly or indirectly, any shares of our common stock or any securities convertible into or exercisable or exchangeable for our common stock (including, without limitation, common stock or such other securities which may be deemed to be beneficially owned by such directors, executive officers, managers and members in accordance with the rules and regulations of the SEC and securities which may be issued upon exercise of a stock option or warrant), or publicly disclose the intention to make my offer, sale, pledge, disposition or filing; (2) enter into any swap or other agreement that transfers, in whole or in part, any of the economic consequences of ownership of shares of our common stock or such other securities, whether any such transaction described in clause (1) or (2) above is to be settled by delivery of common stock or such other securities, in cash or otherwise; or (3) make any demand for or exercise any right with respect to the registration of any shares of our common stock or any security convertible into or exercisable or exchangeable for shares of our common stock in each case subject to certain exceptions, including: (A) shares of our common stock to be sold pursuant to the underwriting agreement; (B) transfers of shares of our common stock or other securities as bona fide gifts; (C) transfers or dispositions of shares of our common stock or other securities to any trust for the direct or indirect benefit of the director, officer or stockholder or the immediate family members of such person in a transaction not involving a disposition for value; (D) transfers or dispositions of shares of our common stock or other securities to any affiliate of the director, officer or stockholder or to any investment fund or other entity controlled or managed by such director, officer or stockholder or under common control of such director, officer or stockholder, or if such director, officer or stockholder is an investment company registered under the Investment Company Act of 1940, as amended (a Mutual Fund), pursuant to a merger or reorganization with or into another Mutual Fund that shares the same investment adviser registered pursuant to the requirements of the Investment Advisers Act of 1940, as amended; (E) transfers or dispositions of shares of our common stock or other securities by will, other testamentary document or intestate succession to the legal representative, heir, beneficiary or a member of the immediate family of the director, officer or stockholder; (F) distributions of shares of our common stock or other securities to any of the director's, officer's or stockholder's partners, members or stockholders; (G) transfers of shares of our common stock or other securities in connection with the conversion of our outstanding preferred stock into shares of our common stock in connection with the consummation of this offering, it being understood that such shares of common stock received by the director, officer or stockholder upon such conversion will be subject to these restrictions; (H) transfers or other dispositions prior to the first public filing of this prospectus with a price range set forth on the cover; and certain other exceptions. In the case of any transfer, disposition or distribution pursuant to clause (B), (C), (D), (E), (F) or (H), each donee or distributee shall execute and deliver to J.P. Morgan Securities LLC and Credit Suisse Securities (USA) LLC a lock-up agreement. In addition, in the case of any transfer, disposition or distribution pursuant to clause (B), (C), (D), (E), (F) or (H), no filing by any party under the Exchange Act, or other public announcement reporting a reduction in the beneficial ownership of shares of our common stock held by the director, officer or stockholder, shall be required or voluntarily made in connection with such transfer or distribution, other than a filing on a Form 5 made after the expiration of the 180-day period referred to above and any required Schedule 13G (or 13G/A) or 13F filing. In addition, notwithstanding the foregoing restrictions, the director, officer or stockholder may: (i) exercise an option to purchase shares of our common stock granted under any of our stock incentive plans or stock purchase plans, provided that the underlying shares of common stock continue to be subject to the restrictions on transfer set forth in the lock-up agreement; (ii) transfer such director's, officer's or stockholder's 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 that provides for the repurchase of such director's, officer's or stockholder's shares of our common stock or such other securities by us, pursuant to the terms of any of our stock incentive plans or stock purchase plans to satisfy tax withholding obligations or in connection with the termination of such director's or officer's employment with us; (iii) establish a trading plan pursuant to Rule 10b5-1 under the Exchange Act for the

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transfer of shares of our common stock, provided that such plan does not provide for any transfers of shares of our common stock, and no filing under the Exchange Act or other public announcement shall be required or voluntarily made by the director, officer or stockholder or any other person in connection therewith, in each case during the 180-day restricted period pursuant to the lock-up agreement; and (iv) transfer or dispose of shares of common stock acquired in the offering, subject to certain restrictions with respect to company directed shares, or on the open market following the offering, provided that certain limitations on filings under the Exchange Act or other public announcements reporting a reduction in the beneficial ownership of common stock held by the director, officer or stockholder apply in connection with such transfer or disposition.

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

Our common stock has been approved for listing/quotation on the NASDAQ Global Select Market under the symbol ONCE.

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

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

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

Prior to this offering, there has been no public market for our common stock. The initial public offering price will be determined by negotiations between us and the representatives of the underwriters. In determining the initial public offering price, we and the representatives of the underwriters expect to consider a number of factors including:

the information set forth in this prospectus and otherwise available to the representatives;

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our prospects and the history and prospects for the industry in which we compete;

an assessment of our management;

our prospects for future earnings;

the general condition of the securities markets at the time of this offering;

the recent market prices of, and demand for, publicly traded common stock of generally comparable companies; and

other factors deemed relevant by the underwriters and us.

Neither we nor the underwriters can assure investors that an active trading market will develop for our common shares, or that the shares will trade in the public market at or above the initial public offering price.

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

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

This document is only being distributed to, and is only directed at: (i) persons who are outside the United Kingdom; (ii) investment professionals falling within Article 19(5) of the Financial Services and Markets Act 2000 (Financial Promotion) Order 2005 (the Order); or (iii) high net worth entities, and other persons to whom it may lawfully be communicated, falling within Article 49(2)(a) to (d) of the Order (all such persons together being referred to as relevant persons). The securities are only available to, and any invitation, offer or agreement to subscribe, purchase or otherwise acquire such securities will be engaged in only with, relevant persons. Any person who is not a relevant person should not act or rely on this document or any of its contents.

## **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, from and including the date on which the European Union Prospectus Directive, the EU Prospectus Directive, was implemented in that Relevant Member State, the Relevant Implementation Date, an offer of securities described in this prospectus may not be made to the public in that Relevant Member State prior to the publication of a prospectus in relation to the shares which has been approved by the competent authority in that Relevant Member State or, where appropriate, approved in

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another Relevant Member State and notified to the competent authority in that Relevant Member State, all in accordance with the EU Prospectus Directive, except that, with effect from and including the Relevant Implementation Date, an offer of securities described in this prospectus may be made to the public in that Relevant Member State at any time:

to any legal entity which is a qualified investor as defined under the EU Prospectus Directive;

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 EU Prospectus Directive); or

in any other circumstances falling within Article 3(2) of the EU Prospectus Directive, provided that no such offer of securities described in this prospectus shall result in a requirement for the publication by us of a prospectus pursuant to Article 3 of the EU Prospectus Directive. For the purposes of this provision, the expression an offer of securities to the public in relation to any securities in any Relevant Member State means the communication in any form and by any means of sufficient information on the terms of the offer and the securities to be offered so as to enable an investor to decide to purchase or subscribe for the securities, as the same may be varied in that Member State by any measure implementing the EU Prospectus Directive in that Member State. The expression EU Prospectus Directive means Directive 2003/71/EC (and any amendments thereto, including the 2010 PD Amending Directive, to the extent implemented in the Relevant Member State) and includes any relevant implementing measure in each Relevant Member State, and the expression 2010 PD Amending Directive means Directive 2010/73/EU.

### ***United Kingdom***

Each of the underwriters has:

only communicated or caused to be communicated and only will 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, or FSMA) received by it in connection with the issue or sale of the securities in circumstances in which Section 21(1) of the FSMA does not apply to us; and

complied and will comply with all applicable provisions of the FSMA with respect to anything done by it in relation to the securities in, from or otherwise involving the United Kingdom.

### ***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 document 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 document, nor any other offering or marketing material relating to the shares or the offering, may be publicly distributed or otherwise made publicly available in Switzerland.

Neither this document nor any other offering or marketing material relating to the offering, the Company, the shares has been or will be filed with or approved by any Swiss regulatory authority. In particular, this document 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

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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.

***United Arab Emirates***

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.

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## **Legal matters**

The validity of the shares of common stock offered hereby will be passed upon for us by Wilmer Cutler Pickering Hale and Dorr LLP, New York, New York. Davis Polk & Wardwell LLP, New York, New York, has acted as counsel for the underwriters in connection with certain legal matters related to this offering.

## **Experts**

The financial statements of Spark Therapeutics, Inc. (formerly Spark Therapeutics, LLC), as of December 31, 2013, and for the period from March 13, 2013 (inception) through December 31, 2013 have been included in this prospectus in reliance upon the report of KPMG LLP, independent registered public accounting firm, appearing elsewhere herein, and upon the authority of said firm as experts in accounting and auditing.

## **Where you can find more information**

We have filed with the SEC a registration statement on Form S-1 under the Securities Act with respect to the shares of common stock offered hereby. This prospectus, which constitutes a part of the registration statement, does not contain all of the information set forth in the registration statement or the exhibits and schedules filed therewith. For further information about us and the common stock offered hereby, we refer you to the registration statement and the exhibits and schedules filed thereto. Statements contained in this prospectus regarding the contents of any contract or any other document that is filed as an exhibit to the registration statement are not necessarily complete, and each such statement is qualified in all respects by reference to the full text of such contract or other document filed as an exhibit to the registration statement. Upon completion of this offering, we will be required to file periodic reports, proxy statements, and other information with the SEC pursuant to the Securities Exchange Act of 1934. You may read and copy this information at the Public Reference Room of the Securities and Exchange Commission, 100 F Street, N.E., Room 1580, Washington, D.C. 20549. You may obtain information on the operation of the public reference rooms by calling the SEC at 1-800-SEC-0330. The SEC also maintains an Internet website that contains reports, proxy statements and other information about registrants, like us, that file electronically with the Securities SEC. The address of that site is [www.sec.gov](http://www.sec.gov).

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## **Report of Independent Registered Public Accounting Firm**

The Board of Directors and Stockholders

Spark Therapeutics, Inc.:

We have audited the accompanying balance sheet of Spark Therapeutics, Inc. (formerly Spark Therapeutics, LLC) as of December 31, 2013, and the related statements of operations, members' equity and cash flows for the period from March 13, 2013 (inception) through December 31, 2013. These financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on these financial statements based on our audit.

We conducted our audit in accordance with the standards of the Public Company Accounting Oversight Board (United States). Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement. An audit includes examining, on a test basis, evidence supporting the amounts and disclosures in the financial statements. An audit also includes assessing the accounting principles used and significant estimates made by management, as well as evaluating the overall financial statement presentation. We believe that our audit provides a reasonable basis for our opinion.

In our opinion, the financial statements referred to above present fairly, in all material respects, the financial position of Spark Therapeutics, Inc. as of December 31, 2013, and the results of its operations and its cash flows for the period from March 13, 2013 (inception) through December 31, 2013, in conformity with U.S. generally accepted accounting principles.

/s/ KPMG LLP

Philadelphia, Pennsylvania

September 23, 2014, except as to

Note 3(h), which is as of January 16, 2015



Table of Contents**Spark Therapeutics, LLC****Balance sheet****December 31, 2013**

<b>Assets</b>	
Current assets:	
Receivable from related party	\$ 4,861,285
Total current assets	4,861,285
Total assets	\$ 4,861,285
<b>Liabilities and Members Equity</b>	
Current liabilities:	
Accrued expenses	\$ 1,492,497
Total current liabilities	1,492,497
Total liabilities	1,492,497
Commitments and contingencies (Note 5)	
Members equity:	
Series A convertible preferred units, no par value. Authorized, 5,000,000 units; issued and outstanding, 5,000,000 units	10,000,000
Common units, no par value. Authorized, 35,000,000 units; issued and outstanding, 30,870,000 units	50,646,585
Accumulated deficit	(57,277,797)
Total members equity	3,368,788
Total liabilities and members equity	\$ 4,861,285

*See accompanying notes to financial statements*

Table of Contents**Spark Therapeutics, LLC****Statement of operations****Period from March 13, 2013 (inception) through December 31, 2013**

Operating expenses:	
Research and development	\$ 4,897,152
Acquired in-process research and development	50,000,000
General and administrative	2,380,645
<b>Total operating expenses</b>	<b>57,277,797</b>
Net loss	\$ (57,277,797)
<b>Basic and diluted net loss per common unit</b>	<b>\$ (8.44)</b>
Weighted average basic and diluted common units outstanding	6,788,396
<b>Unaudited pro forma net loss</b>	<b>\$ (57,277,797)</b>
Unaudited pro forma basic and diluted net loss per common share	\$ (35.27)
<b>Unaudited pro forma weighted average basic and diluted common shares outstanding</b>	<b>1,623,891</b>

*See accompanying notes to financial statements*

Table of Contents**Spark Therapeutics, LLC****Statement of members' equity****Period from March 13, 2013 (inception) through December 31, 2013**

	Series A convertible preferred		Common		Accumulated deficit	Total
	Units	Amount	Units	Amount		
Balance, March 13, 2013 (inception)		\$		\$	\$	\$
Issuance of common units in connection with license and technology agreements			25,000,000	50,000,000		50,000,000
Issuance of Series A convertible preferred units	5,000,000	10,000,000				10,000,000
Issuance of restricted common units Common membership units			5,870,000			
compensation expense				646,585		646,585
Net loss					(57,277,797)	(57,277,797)
Balance, December 31, 2013	5,000,000	\$ 10,000,000	30,870,000	\$ 50,646,585	\$ (57,277,797)	\$ 3,368,788

*See accompanying notes to financial statements*

Table of Contents**Spark Therapeutics, LLC****Statement of cash flows****Period from March 13, 2013 (inception) through December 31, 2013**

Cash flows from operating activities:	
Net loss	\$ (57,277,797)
Adjustments to reconcile net loss to net cash used in operating activities:	
Acquired in-process research and development	50,000,000
Common membership units compensation expense	646,585
Changes in operating assets and liabilities:	
Accrued expenses	1,492,497
Net cash used in operating activities	(5,138,715)
Cash flows from investing activities	
Net cash used in investing activities	
Cash flows from financing activities:	
Proceeds from issuance of Series A convertible preferred units	5,138,715
Net cash provided by financing activities	5,138,715
Net increase (decrease) in cash and cash equivalents	
Cash and cash equivalents, beginning of period	
Cash and cash equivalents, end of period	\$

*See accompanying notes to financial statements*

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# Spark Therapeutics, LLC

## Notes to financial statements

### December 31, 2013

#### **(1) Background**

Spark Therapeutics, LLC was formed on March 13, 2013 in the state of Delaware as AAvenue Therapeutics, LLC and amended its Certificate of Formation in October 2013 to change its name from AAvenue Therapeutics, LLC to Spark Therapeutics, LLC. In May 2014, the Company converted from a limited liability company (LLC) to a C corporation, Spark Therapeutics, Inc. (the Company). The Company is a gene therapy company, seeking to transform the lives of patients suffering from debilitating genetic diseases by developing one-time, life-altering treatments. The Company's product candidates have the potential to provide long-lasting effects, dramatically and positively changing the lives of patients with conditions where no, or only palliative, therapies exist. The Company operates in one segment and has its principal offices in Philadelphia, Pennsylvania.

#### **(2) Development-stage risks and liquidity**

The Company has incurred losses and negative cash flows from operations since inception and had an accumulated deficit of \$57.3 million at December 31, 2013. The Company anticipates incurring additional losses until such time, if ever, that it can generate significant sales of its product candidates in development. Substantial additional financing will be needed by the Company to fund its operations and to commercially develop its product candidates.

In May 2014, the Company issued shares of Series B convertible preferred stock (Series B Stock) for \$72.4 million, net of transaction costs (Note 6). Management believes that the proceeds from the sale of Series B Stock, the cash received from the related-party receivable of \$4.9 million as of December 31, 2013 and the cash proceeds from a collaboration agreement (Note 8), are sufficient to fund the Company's planned operations through 2015.

The Company's future operations are highly dependent on a combination of factors, including: (i) the success of its research and development; (ii) regulatory approval and market acceptance of the Company's proposed future products; (iii) the timely and successful completion of additional financing; and (iv) the development of competitive therapies by other biotechnology and pharmaceutical companies.

#### **(3) Summary of significant accounting policies**

##### *(a) Use of estimates*

The preparation of financial statements in conformity with U.S. generally accepted accounting principles (GAAP) requires management to make estimates and assumptions that affect the reported amounts of assets and liabilities and disclosure of contingent assets and liabilities at the date of the financial statements and the reported amounts of expenses during the reporting period. Actual results could differ from such estimates.

##### *(b) Fair value of financial instruments*

Management believes that the carrying amounts of the Company's financial instruments, including the receivable from the related party and accrued expenses, approximate fair value due to the short-term nature of those instruments.

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**Spark Therapeutics, LLC**

**Notes to financial statements**

**December 31, 2013**

***(c) Receivable from related party***

The receivable from related party represents amounts due from The Children's Hospital of Philadelphia (CHOP) (Note 7). These amounts were received in 2014.

***(d) Research and development and in-process research and development***

Research and development costs are expensed as incurred. Research and development expenses consist of internal and external expenses. Internal expenses include compensation and overhead. External expenses include development, clinical trials, statistical analysis and report writing and regulatory compliance costs incurred with clinical research organizations and other third-party vendors. At the end of the reporting period, the Company compares payments made to third-party service providers to the estimated progress toward completion of the research or development objectives. Such estimates are subject to change as additional information becomes available. Depending on the timing of payments to the service providers and the progress that the Company estimates has been made as a result of the service provided, the Company may record net prepaid or accrued expense relating to these costs.

Upfront and milestone payments made to third parties who perform research and development services on the Company's behalf are expensed as services are rendered. Costs incurred in obtaining technology licenses are charged to research and development expense as acquired in-process research and development if the technology licensed has not reached technological feasibility and has no alternative future use (Notes 5 and 7).

***(e) Income taxes***

The Company is a Delaware LLC for federal and state income tax purposes. The Company's taxable losses are allocated to the members in accordance with the LLC operating agreement. Accordingly, income taxes have not been provided, as the losses will be included in the members' federal income tax returns.

The Company evaluates tax positions taken or expected to be taken in the course of preparing tax returns to determine whether the tax positions will more likely than not be sustained by the Company upon challenge by the applicable tax authority. Tax positions not deemed to meet the more-likely-than-not threshold and that would result in a tax benefit or expense to the Company would be recorded as a tax benefit or expense in the current period. The Company has not recognized any amounts for unrecognized tax benefits. A reconciliation is not provided herein, as the beginning and ending amounts of unrecognized benefits are \$0, with no interim additions, reductions or settlements. The tax year 2013 remains subject to examination by the U.S. taxing authorities.

***(f) Net loss per common unit***

Basic and diluted net loss per common unit is determined by dividing net loss by the weighted average number of common units outstanding during the period. The outstanding Series A convertible preferred units (Series A Units) and unvested restricted units have been excluded from the calculation of net loss per common unit because their effect would be anti-dilutive. Therefore, the weighted average units used to calculate both basic and diluted loss per unit are the same.

Table of Contents**Spark Therapeutics, LLC****Notes to financial statements****December 31, 2013**

The following potentially dilutive securities have been excluded from the computations of diluted weighted average units outstanding as of December 31, 2013 as they would be anti-dilutive:

Convertible preferred units	5,000,000
Unvested restricted common units	5,370,000

Amounts in the table above reflect the common unit equivalents of the noted instruments.

The unaudited pro forma net loss per common share is computed using the weighted average number of common shares outstanding and assumes the conversion of all outstanding Series A Units into 5,000,000 common shares upon the closing of the Company's contemplated initial public offering (IPO), and reflects the reverse stock split described in note 3(h) below as if they had occurred at the later of the beginning of the period or date of issuance. The Company believes the unaudited pro forma net loss per common share provides material information to investors, as the conversion of the Company's preferred shares to common stock will occur upon the closing of an IPO, and the disclosure of pro forma net loss per common share provides an indication of net loss per common share that is comparable to the net loss per common share that will be reported by the Company as a public company following the closing of an IPO.

The following table summarizes the calculation of unaudited pro forma basic and diluted net loss per common share:

	<b>Period from March 13, 2013 (inception) through December 31, 2013</b>
<b>Numerator:</b>	
Pro forma net loss	\$ (57,277,797)
<b>Denominator:</b>	
Weighted average common shares outstanding	1,357,679
Conversion of convertible preferred shares	266,212
Shares used in computing unaudited pro forma weighted average basic and diluted common shares outstanding	1,623,891
Unaudited pro forma basic and diluted net loss per common share	\$ (35.27)

***(g) Recent accounting pronouncements***

In June 2014, the Financial Accounting Standards Board (FASB) issued Accounting Standards Update (ASU) No. 2014-10, *Elimination of Certain Financial Reporting Requirements, Including an Amendment to Variable Interest Entities Guidance in Topic 810, Consolidation*, which eliminates all incremental financial reporting requirements for development stage entities by removing Accounting Standards Codification (ASC) Topic 915, *Development Stage Entities*, from the FASB ASC. ASC Topic 915 is removed effective for annual periods beginning after December 15, 2014 and early adoption is permitted. The Company adopted the ASU effective with the issuance of the December 31, 2013 financial statements.



Table of Contents**Spark Therapeutics, LLC****Notes to financial statements****December 31, 2013*****(h) Recapitalization***

On January 16, 2015, the Company effected a reverse stock split of the Company's common stock at a ratio of one share for every five shares previously held. All common stock share and common stock per share data included in these financial statements reflect the reverse stock split. The unit and per unit data included in these financial statements do not reflect the reverse stock split as the reverse split was not applicable to the units.

**(4) Accrued expenses**

Accrued expenses consist of the following at December 31, 2013:

Compensation and benefits	\$ 138,761
Consulting and professional fees	518,485
Research and development	799,585
Other	35,666
	<b>\$ 1,492,497</b>

**(5) Commitments and contingencies*****(a) Lease***

In March 2014, the Company entered into an operating lease for laboratory and office space in Philadelphia, PA, through October 2025. Future minimum lease payments under this lease are as follows:

Year ending December 31:	
2014	\$
2015	500,000
2016	1,200,000
2017	1,200,000
2018	1,300,000
2019 and thereafter	9,400,000

Total \$ 13,600,000

***(b) License agreements***

See Note 7 for a discussion of the CHOP license agreement.

In October 2013, the Company entered into a patent license agreement with The Trustees of the University of Pennsylvania (Penn) for certain intellectual property licenses to be provided by Penn to the Company in the fields of research, development, manufacture and commercialization. The license agreement requires the Company to reimburse Penn for the patent costs related to the underlying licensed rights. In 2013, the Company recorded \$94,501 of general and administrative expenses related to the reimbursement of such patent costs in the accompanying statement of operations. The Company is obligated to make payments to Penn upon the

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## Spark Therapeutics, LLC

### Notes to financial statements

#### December 31, 2013

occurrence of first commercial sale for certain licensed products in both the United States and Europe. The Company must pay a low-single-digit royalty based on net sales of licensed products by territory, which royalties will be reduced if the Company is required to license patents or intellectual property from third parties.

In October 2013, the Company entered into a license agreement with the University of Iowa Research Foundation (UIRF) for certain intellectual property licenses. The license agreement requires the Company to reimburse UIRF for the patent costs related to the underlying licensed rights. In 2013 the Company recorded \$0.3 million of general and administrative expenses related to the reimbursement of such patent costs in the accompanying statement of operations. The Company is obligated to make payments to UIRF upon the occurrence of various development and commercialization milestones. The Company must pay a low-single-digit royalty to UIRF based on net sales of licensed products by territory. In connection with the license agreement, the Company issued 281,854 Series 1 common units (Series 1 Units) to UIRF. The fair value of these units of \$0.6 million has been recorded as acquired in-process research and development expense in 2013.

*(c) Litigation*

Liabilities for loss contingencies arising from claims, assessments, litigation, fines, penalties and other sources are recorded when it is probable that a liability has been incurred and the amount can be reasonably estimated. Legal costs incurred in connection with loss contingencies are expensed as incurred. In the opinion of management, the ultimate disposition of any open matters will not have a material adverse effect on the Company's financial position, results of operation or liquidity.

*(d) Employment agreements*

The Company has employment agreements with certain of its executive officers and several key employees, which provide for potential salary adjustments, bonuses, as defined, and severance benefits upon termination of employment, as defined.

#### **(6) Members' equity**

The Company's operating agreement contained the terms of the LLC and the rights, preferences and privileges of the members and their respective units.

*(a) Convertible preferred*

*October 2013 Series A financing*

In October 2013, the Company entered into an agreement with CHOP to sell 5,000,000 Series A Units at \$2.00 per unit for proceeds of \$10.0 million. As discussed in Note 7, the Company recorded a receivable from CHOP for the Series A Units, as CHOP managed the Company's expenditures during 2013. The remaining proceeds from the sale of the Series A Units are reflected on the accompanying balance sheet as receivable from related party. The receivable was collected by the Company in 2014.

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## Spark Therapeutics, LLC

### Notes to financial statements

#### December 31, 2013

Each Series A Unit was convertible into one Series 1 Unit (subject to certain antidilution adjustments) at any time at the option of the holder. The Series A Units were mandatorily convertible into common stock in the event of an IPO, as defined. The Series A Unit holders were entitled to a liquidation preference in an amount equal to \$2.00 per unit in the event of a liquidation, dissolution or winding up of the Company, or in the event the Company was merged with, or acquired by, another entity. Once the Series A Unit liquidation preference was paid, any remaining assets were to be distributed first to the holders of Series 1 Units for an amount up to \$50.0 million, second, to the holders of Series 2 common units (Series 2 Units), for a per unit amount equaling the amount distributed to each Series 1 Unit holder, and any remaining assets would have been distributed pro rata to the eligible common units (regardless of series).

#### *May 2014 conversion to C corporation*

Upon conversion of the Company into a C corporation in May 2014, each outstanding Series A Unit converted into one share of Series A convertible preferred stock (Series A Stock).

#### *May 2014 Series B financing*

In May 2014, the Company issued 45,186,334 shares of Series B Stock for \$72.4 million, net of transaction costs. In conjunction with the issuance of Series B Stock, certain Series A Stock terms were amended. The Series A Stock and Series B Stock automatically convert into common stock on a one-for-one basis at a qualified IPO, as defined, or upon approval by at least 87.5% of the Series B Stock holders, subject to certain customary antidilution adjustments contained in the Company's certificate of incorporation. The Series A Stock and Series B Stock holders are entitled to receive, upon the liquidation of the Company, proceeds in proportion to their liquidation preference. Such liquidation preference is equal to the greater of (i) their respective original issue price plus any accrued but unpaid dividends and (ii) the amount per share as would have been payable had all Series A Stock and Series B Stock been converted into common stock immediately prior to such liquidation. Subsequent to the liquidation preference payments to the holders of Series A Stock and Series B Stock, the remaining assets of the Company would be distributed to the holders of common stock, Series A Stock and Series B Stock, on an as-converted-to-common stock basis, provided that the holders of Series A Stock or Series B Stock, as applicable, would participate in such distribution until such holders receive in the aggregate 2.5 times their respective original issue price. The Series A Stock and Series B Stock are entitled to receive cumulative dividends at 8% per annum, which shall accrue from day to day beginning six months following the date on which the first share of Series B Stock was issued, and shall be payable upon conversion, an event of liquidation or a qualified IPO, in each case, in shares of Series A Stock and Series B Stock, as applicable.

In May 2014, the board of directors (Board) was increased to nine members. Holders of the Series A Stock, voting as a class, are entitled to elect two members of the Board. Holders of the Series B Stock, voting as a class, are entitled to elect two members of the Board. Holders of the common stock, voting as a class, are entitled to elect two members of the Board. The holders of common stock and any other class or series of voting stock, including Series A Stock and Series B Stock, voting as a class, are entitled to elect the balance of the total number of directors.

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## **Spark Therapeutics, LLC**

### **Notes to financial statements**

#### **December 31, 2013**

##### ***(b) Common***

Pursuant to the Company's LLC agreement, the Company authorized 35,000,000 common units. The Board designated Series 1 Units, Series 2 Units and Series 3 common units (Series 3 Units). Capital distributions were to be made to and among the holders, in the following order of priority: Series A Units, Series 1 Units, Series 2 Units and Series 3 Units.

In October 2013, the Company issued an aggregate of 25,000,000 Series 1 Units at \$2.00 per unit. CHOP was issued 24,718,146 Series 1 Units in consideration for the transfer of certain intellectual property rights and the assignment of certain contracts to the Company in connection with the license and technology agreements (Note 7). UIRF was issued 281,854 Series 1 Units in consideration for entering into a license agreement with the Company (Note 5).

In the fourth quarter of 2013, 5,100,000 Series 2 Units were issued to the Company's founders. In the fourth quarter of 2013, 770,000 Series 3 Units were issued to certain employees, directors and consultants of the Company. The Series 2 Units and Series 3 Units vesting terms vary, but primarily, units vest 25% on the first anniversary of the vesting commencement date and then quarterly over three years, with accelerated vesting in the event of a change in control, as defined. Any unvested units are forfeited in the event that the individual ceases to provide services to the Company. The Series 2 Units and Series 3 Units had a grant date fair value of \$4.5 million, which is being recognized as compensation expense over the vesting period of the units. The Company recorded compensation expense of \$0.6 million in 2013. At December 31, 2013, there was \$3.8 million of unrecognized compensation expense related to these units. As of December 31, 2013, 500,000 units were vested and the 5,370,000 unvested units are subject to vesting over a weighted average period of 2.9 years. The Company did not repurchase any units in 2013. The weighted average grant date fair value for units issued in 2013, vested in 2013 and unvested as of December 31, 2013, was \$0.76, \$0.84, and \$0.75, respectively.

Upon conversion of the Company into a C corporation in May 2014, each outstanding Series 1 Unit converted into 0.2 shares of common stock, each outstanding Series 2 Unit converted into 0.2 share of common stock and each outstanding Series 3 Unit converted into 0.03883773 shares of common stock.

In May 2014, the Board increased the number of authorized shares of common stock to 95,700,000 shares.

##### ***(c) 2014 stock incentive plan***

In May 2014, the Company established the 2014 Stock Incentive Plan (the Plan), which allows for the granting of incentive stock options, nonstatutory stock options, stock appreciation rights, restricted stock awards and other stock awards to purchase an aggregate of 356,800 shares of the Company's common stock to employees, officers, directors, consultants and advisors. In connection with the Series B financing in May 2014, the Plan was amended to increase the aggregate number of shares issuable pursuant to the Plan to 2,543,299 shares.

#### **(7) Related-party transactions**

At December 31, 2013, CHOP held a majority of the common units and all of the Series A Units outstanding, and is considered a significant equity holder. CHOP committed up to \$50.0 million in funding to the Company in October 2013. CHOP invested \$10.0 million in the Series A financing in October 2013 and approximately \$22.5 million in the Series B financing in May 2014.

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## Spark Therapeutics, LLC

### Notes to financial statements

#### December 31, 2013

In October 2013, the Company entered into technology and license agreements with CHOP for certain commercialization licenses to be provided to the Company in order to develop services, methods and marketable products for commercialization. The license agreement requires the Company to reimburse CHOP for the patent costs related to the underlying licensed rights incurred after the effective date. In 2013, the Company recorded \$0.1 million of general and administrative expenses related to the reimbursement of such patent costs in the accompanying statement of operations. The Company will reimburse CHOP for patent expenses incurred prior to the first commercial sale of a licensed product. In addition, the Company is obligated to make certain payments to CHOP upon the occurrence of certain development milestones. The Company must pay a low-single-digit royalty based on net sales of licensed products by product and country. In connection with the technology and license agreements, the Company issued an aggregate of 24,718,146 Series 1 Units to CHOP. The fair value of the Units of \$49.4 million has been recorded as acquired in-process research and development expense in 2013.

In 2013, the Company entered into a number of services agreements with CHOP. The Master Research Services Agreement provides for certain research, development and manufacturing services to be provided to the Company by CHOP. A separate Services Agreement provides for clinical, technical and administrative services to be provided by CHOP to the Company. In 2013, the Company recorded \$3.8 million as research and development expense and \$31,643 as general and administrative expense related to these agreements. As part of these agreements, CHOP administered the payment of expenditures during 2013 and 2014. At December 31, 2013, the Company recorded \$4.9 million as a receivable from related party on the balance sheet for amounts due from CHOP for the remaining balance of the \$10.0 million Series A investment.

In December 2013, the Company entered into a consulting agreement with an individual who became the President and Chief Scientific Officer in September 2014. As compensation for her services, the individual received 2,000,000 restricted Series 2 Units. Pursuant to the individual's employment agreement, this restricted stock vests as follows: 25% of the grant vested on March 13, 2014, with the remainder vesting in equal quarterly installments over the subsequent three-year period.

#### **(8) Subsequent event**

In April 2014, the Company began discussions with a pharmaceutical company concerning a potential manufacturing technology collaboration. The Company received a one-time, nonrefundable payment of \$1.0 million to engage in due diligence. The payment is creditable against an early milestone payment that may be negotiated as part of such potential agreement.

Table of Contents**Spark Therapeutics, Inc.****Balance sheets**

(Unaudited)

	<b>December 31, 2013</b>	<b>September 30, 2014</b>	<b>Pro forma September 30, 2014</b>
<b>Assets</b>			
Current assets:			
Cash and cash equivalents	\$	\$ 67,272,601	\$ 67,272,601
Receivable from related party	4,861,285		
Other receivables		3,287,826	3,287,826
Prepaid expenses and deferred financing costs		1,499,249	1,499,249
<b>Total current assets</b>	<b>4,861,285</b>	<b>72,059,676</b>	<b>72,059,676</b>
Property and equipment, net		8,445,967	8,445,967
Other assets		408,211	408,211
<b>Total assets</b>	<b>\$ 4,861,285</b>	<b>\$ 80,913,854</b>	<b>\$ 80,913,854</b>
<b>Liabilities and Stockholders Equity</b>			
Current liabilities:			
Accounts payable	\$	\$ 6,519,399	\$ 6,519,399
Accrued expenses	1,492,497	1,863,745	1,863,745
Deferred revenue		1,395,723	1,395,723
<b>Total current liabilities</b>	<b>1,492,497</b>	<b>9,778,867</b>	<b>9,778,867</b>
Deferred rent		8,410,462	8,410,462
<b>Total liabilities</b>	<b>1,492,497</b>	<b>18,189,329</b>	<b>18,189,329</b>
Commitments and contingencies (Note 5)			
Stockholders equity:			
Series A convertible preferred units, no par value. Authorized, 5,000,000 units; issued and outstanding, 5,000,000 units at December 31, 2013	10,000,000		
Common units, no par value. Authorized, 35,000,000 units; issued and outstanding, 30,870,000 units at December 31, 2013	50,646,585		
Series A convertible preferred stock, \$0.001 par value. Authorized, 5,000,000 shares; issued and outstanding, 5,000,000 shares at September 30, 2014		10,000,000	
Series B convertible preferred stock, \$0.001 par value. Authorized, 45,186,334 shares; issued and outstanding, 45,186,334 shares at September 30, 2014		72,437,203	
Common stock, \$0.001 par value. Authorized, 95,700,000 shares; issued and outstanding, 6,090,317 shares at September 30, 2014 and 16,127,572 shares issued and outstanding at September 30, 2014 pro forma		6,090	16,128

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Additional paid-in capital		52,868,193	135,295,358
Accumulated deficit	(57,277,797)	(72,586,961)	(72,586,961)
Total stockholders' equity	3,368,788	62,724,525	62,724,525
Total liabilities and stockholders' equity	\$ 4,861,285	\$ 80,913,854	\$ 80,913,854

*See accompanying notes to financial statements*

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Table of Contents**Spark Therapeutics, Inc.****Statements of operations**

(Unaudited)

	<b>Period from March 13, 2013  (inception) to September 30, 2013</b>	<b>Nine months ended September 30, 2014</b>
Revenues	\$	\$ 20,000
Operating expenses:		
Research and development	2,967,905	10,169,362
General and administrative	661,572	5,161,909
Total operating expenses	3,629,477	15,331,271
Loss from operations	(3,629,477)	(15,311,271)
Interest income		2,107
Net loss	\$ (3,629,477)	\$ (15,309,164)
Basic and diluted net loss per common share		\$ (2.87)
Weighted average basic and diluted common shares outstanding		5,334,610
Unaudited pro forma net loss		\$ (15,309,164)
Unaudited pro forma basic and diluted net loss per common share		\$ (1.44)
Unaudited pro forma weighted average basic and diluted common shares outstanding		10,638,070

*See accompanying notes to financial statements*

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**Spark Therapeutics, Inc.**

**Statement of stockholders' equity**

**Nine months ended September 30, 2014**

(Unaudited)

Series A convertible preferred units		Common units		Series A convertible preferred stock		Series B convertible preferred stock		Common stock		Additional paid-in capital	Accumulated Deficit
Units	Amount	Units	Amount	Shares	Amount	Shares	Amount	Shares	Amount		
5,000,000	\$ 10,000,000	30,870,000	\$ 50,646,585		\$		\$		\$	\$	\$ (57,277,797)
		1,040,667									
(5,000,000)	(10,000,000)	(31,910,667)	(50,646,585)	5,000,000	10,000,000			6,090,317	6,090	50,640,495	
						45,186,334	72,437,203				
										2,227,698	(15,309,164)
\$		\$		5,000,000	\$ 10,000,000	45,186,334	\$ 72,437,203	6,090,317	\$ 6,090	\$ 52,868,193	\$ (72,586,961)

*See accompanying notes to financial statements*

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Table of Contents**Spark Therapeutics, Inc.****Statements of cash flows**

(Unaudited)

	Period from March 13, 2013 (inception) to September 30, 2013	Nine months ended September 30, 2014
Cash flows from operating activities:		
Net loss	\$ (3,629,477)	\$ (15,309,164)
Adjustments to reconcile net loss to net cash used in operating activities:		
Noncash rent expense		409,087
Depreciation expense		15,849
Stock-based compensation expense		2,227,698
Changes in operating assets and liabilities:		
Prepaid expenses and other assets		(582,606)
Accounts payable and accrued expenses	3,629,477	2,331,976
Deferred rent		4,722,914
Deferred revenue		1,395,723
Net cash used in operating activities		(4,788,523)
Cash flows from investing activities:		
Purchases of property and equipment		(4,963,836)
Net cash used in investing activities		(4,963,836)
Cash flows from financing activities:		
Proceeds from issuance of Series A convertible preferred units		4,861,285
Proceeds from issuance of Series B convertible preferred stock, net		72,437,203
Financing costs		(273,528)
Net cash provided by financing activities		77,024,960
Net increase in cash and cash equivalents		67,272,601
Cash and cash equivalents, beginning of period		
Cash and cash equivalents, end of period	\$	\$ 67,272,601
<b>Supplemental disclosure of cash flow information:</b>		
Deferred financing costs included in accounts payable and accrued expenses	\$	\$ 1,060,691
Property and equipment purchases included in accounts payable	\$	\$ 3,497,980

*See accompanying notes to financial statements*



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**Table of Contents**

## **Spark Therapeutics, Inc.**

### **Notes to unaudited interim financial statements**

#### **(1) Background**

Spark Therapeutics, Inc. was formed on March 13, 2013 in the state of Delaware as AAVenue Therapeutics, LLC and amended its Certificate of Formation in October 2013 to change its name from AAVenue Therapeutics, LLC to Spark Therapeutics LLC. In May 2014, the Company converted from a limited liability company (LLC) to a C corporation, Spark Therapeutics, Inc. (the Company). The Company is a gene therapy company, seeking to transform the lives of patients suffering from debilitating genetic diseases by developing one-time, life-altering treatments. The Company's product candidates have the potential to provide long-lasting effects, dramatically and positively changing the lives of patients with conditions where no, or only palliative, therapies exist. The Company operates in one segment and has its principal offices in Philadelphia, Pennsylvania.

#### **(2) Development-stage risks and liquidity**

The Company has incurred losses and negative cash flows from operations since inception and had an accumulated deficit of \$72.6 million at September 30, 2014. The Company anticipates incurring additional losses until such time, if ever, that it can generate significant sales of its product candidates in development. Substantial additional financing will be needed by the Company to fund its operations and to commercially develop its product candidates.

In May 2014, the Company issued shares of Series B convertible preferred stock (Series B Stock) for \$72.4 million, net of transaction costs (Note 6). Management believes that the proceeds received from the sale of Series B Stock, the cash received from the related-party receivable of \$4.9 million as of December 31, 2013 and the cash proceeds from a collaboration agreement (Note 3), are sufficient to fund the Company's planned operations through 2015.

The Company's future operations are highly dependent on a combination of factors, including: (i) the success of its research and development; (ii) regulatory approval and market acceptance of the Company's proposed future products; (iii) the timely and successful completion of additional financing; and (iv) the development of competitive therapies by other biotechnology and pharmaceutical companies.

#### **(3) Summary of significant accounting policies**

##### ***(a) Basis of presentation***

The accompanying unaudited interim financial statements of the Company have been prepared in accordance with U.S. generally accepted accounting principles (GAAP) for interim financial information. In the opinion of management, the accompanying financial statements include all normal and recurring adjustments (which primarily consist of accruals, estimates and assumptions that impact the financial statements) considered necessary to present fairly the Company's financial position as of September 30, 2014 and its results of operations and cash flows for the period from March 13, 2013 (inception) to September 30, 2013 and nine months ended September 30, 2014. Operating results for the nine months ended September 30, 2014 are not necessarily indicative of the results that may be expected for the year ending December 31, 2014. The interim financial statements, presented herein, do not contain the required disclosures under GAAP for annual financial statements. The accompanying unaudited interim financial statements should be read in conjunction with the annual audited financial statements and related notes as of December 31, 2013, and for the period from March 13, 2013 (inception) to December 31, 2013.

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**Spark Therapeutics, Inc.**

**Notes to unaudited interim financial statements**

***(b) Unaudited pro forma balance sheet presentation***

The unaudited pro forma balance sheet as of September 30, 2014 reflects:

The automatic conversion of all outstanding shares of Series A convertible preferred stock (Series A Stock) and Series B Stock as of September 30, 2014 into 10,037,255 shares of common stock upon the closing of the initial public offering (IPO) contemplated by the Company's prospectus.

The shares of common stock issued in the IPO and the related estimated net proceeds are excluded from such pro forma information.

***(c) Use of estimates***

The preparation of financial statements in conformity with GAAP requires management to make estimates and assumptions that affect the reported amounts of assets and liabilities and disclosure of contingent assets and liabilities at the date of the financial statements and the reported amounts of expenses during the reporting period. Actual results could differ from such estimates.

***(d) Cash and cash equivalents***

The Company considers all highly liquid investments that have maturities of three months or less when acquired to be cash equivalents. Cash equivalents as of September 30, 2014 consisted primarily of money market mutual funds.

***(e) Other receivable***

The Company has recorded a receivable for tenant improvement costs incurred which will be reimbursed to the Company by the lessor under the terms of the Company's operating lease for laboratory and office space in Philadelphia (Note 5).

***(f) Fair value of financial instruments***

Management believes that the carrying amounts of the Company's financial instruments, including cash equivalents, receivable from related party, other receivables, accounts payable and accrued expenses approximate fair value due to the short-term nature of those instruments.

***(g) Income taxes***

From inception through May 1, 2014, the Company was a Delaware LLC for federal and state tax purposes and, therefore, all items of income or loss through May 1, 2014 flowed through to the members of the LLC. Effective May 2, 2014, the Company converted from an LLC to a C corporation for federal and state income tax purposes. Accordingly, prior to the conversion to a C corporation, the Company did not record deferred tax assets or liabilities or have any net operating loss carryforwards. The Company recognizes deferred tax assets and liabilities for temporary differences between the financial reporting basis and the tax basis of its assets and liabilities and the expected benefits of net operating loss carryforwards. The impact of changes in tax rates and laws on deferred taxes, if any, is applied during the years in which temporary differences are expected to be settled and is reflected in the financial statements in the period of enactment. The measurement of deferred tax assets is reduced, if necessary, if, based on weight of the evidence, it is more likely than not that some, or all, of the deferred tax assets will not be realized. At September 30, 2014, the Company has concluded that a full valuation allowance is necessary for its deferred tax assets.





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## **Spark Therapeutics, Inc.**

### **Notes to unaudited interim financial statements**

#### ***(h) Revenue recognition***

The Company has generated revenue solely through license and collaborative agreements. The Company recognizes revenue in accordance with Financial Accounting Standards Board (FASB) Accounting Standards Codification (ASC) Topic 605-25, *Revenue Recognition for Arrangements with Multiple Elements*, which addresses the determination of whether an arrangement involving multiple deliverables contains more than one unit of accounting. A delivered item within an arrangement is considered a separate unit of accounting only if both of the following criteria are met:

the delivered item has value to the customer on a stand-alone basis; and

if the arrangement includes a general right of return relative to the delivered item, delivery or performance of the undelivered item is considered probable and substantially in control of the vendor.

Under FASB ASC Topic 605-25, if both of the criteria above are not met, then separate accounting for the individual deliverables is not appropriate. Revenue recognition for arrangements with multiple deliverables constituting a single unit of accounting is recognized generally over the greater of the term of the arrangement or the expected period of performance, either on a straight-line basis or on a modified proportional performance method.

Milestones related to research and development activities are accounted for in accordance with FASB ASC Topic 605-28, milestone method of revenue recognition. FASB ASC Topic 605-28 allows for the recognition of consideration, which is contingent on the achievement of a substantive milestone in its entirety, in the period the milestone is achieved. A milestone is considered to be substantive if all of the following criteria are met: the milestone is commensurate with either: (1) the performance required to achieve the milestone or (2) the enhancement of the value of the delivered items resulting from the performance required to achieve the milestone; the milestone relates solely to past performance; and the milestone payment is reasonable relative to all of the deliverables and payment terms within the agreement.

Amounts received prior to satisfying the revenue recognition criteria are recorded as deferred revenue on the Company's balance sheet. Amounts expected to be recognized as revenue in the next 12 months following the balance sheet date are classified as current liabilities.

To date, the Company has not generated any revenues from the commercial sales of products. Nonrefundable license fees are recognized as revenue upon delivery provided there are no undelivered elements in the arrangement.

In March 2014, the Company entered into a collaboration agreement with Genable Technologies Limited (Genable) in which the Company will be the exclusive manufacturer and provide development advice and expertise in the ongoing development of Genable's lead therapeutic product. Under a license agreement, the Company also granted certain rights to manufacturing patent applications. The Company is eligible to earn development milestone payments and mid-single-digit royalties on future product sales. During the nine months ended September 30, 2014, the Company received \$20,000 for the license and recognized \$20,000 of revenue. The Company also received \$0.4 million during the nine months ended September 30, 2014 representing a payment for manufacturing and supply services the Company is rendering pursuant to the terms of the agreement. As the final product being manufactured is subject to final testing, the Company will recognize manufacturing revenues when product is released. Accordingly, as of September 30, 2014, the Company recorded \$0.4 million of current deferred revenue related to the Genable collaboration.

Table of Contents**Spark Therapeutics, Inc.****Notes to unaudited interim financial statements**

In April 2014, the Company began discussions with a pharmaceutical company concerning a potential manufacturing technology collaboration. The Company received a one-time, nonrefundable payment of \$1.0 million to engage in due diligence. The payment is creditable against an early milestone payment that may be negotiated as part of such potential agreement. As of September 30, 2014, there is \$1.0 million of current deferred revenue for this payment.

*(i) Net loss per common share*

Basic and diluted net loss per common share is determined by dividing net loss by the weighted average number of common shares outstanding during the period. For all periods presented, the outstanding shares of Series A Stock, Series B Stock, unvested restricted shares and common stock options have been excluded from the calculation because their effect would be anti-dilutive. Therefore, the weighted average shares outstanding used to calculate both basic and diluted loss per share are the same.

The following potentially dilutive securities have been excluded from the computations of diluted weighted average shares outstanding as of September 30, 2014 as they would be anti-dilutive:

	<b>September 30, 2014</b>
Convertible preferred stock	50,186,334
Unvested restricted common shares	537,341
Options issued and outstanding	1,732,995

Amounts in the table above reflect the common stock equivalents of the noted instruments.

The unaudited pro forma net loss per common share is computed using the weighted average number of common shares outstanding and assumes the conversion of all outstanding shares of the Company's Series A Stock and Series B Stock into an aggregate of 10,037,255 shares of common stock upon the closing of the Company's contemplated IPO, as if they had occurred at the later of the beginning of the period or date of issuance. The Company believes the unaudited pro forma net loss per common share provides material information to investors, as the conversion of the Company's preferred stock to common stock will occur upon the closing of an IPO, and the disclosure of pro forma net loss per common share provides an indication of net loss per common share that is comparable to the net loss per common share that will be reported by the Company as a public company following the closing of an IPO.

The following table summarizes the calculation of unaudited pro forma basic and diluted net loss per common share:

	<b>Nine months ended September 30, 2014</b>
<b>Numerator:</b>	
Pro forma net loss	\$ (15,309,164)
<b>Denominator:</b>	
Weighted average common shares outstanding	5,334,610

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Conversion of convertible preferred stock	5,303,460
Shares used in computing unaudited pro forma weighted average basic and diluted common shares outstanding	10,638,070
Unaudited pro forma basic and diluted net loss per common share	\$ (1.44)

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Table of Contents**Spark Therapeutics, Inc.****Notes to unaudited interim financial statements***(j) Deferred rent*

Rent expense, including rent holidays and scheduled rent increases, is recorded on a straight-line basis over the term of the lease commencing on the date the Company takes possession of the leased property, which was May 1, 2014 for the Company's new corporate headquarters. Tenant improvement allowances from the lessor are included in the accompanying balance sheet as deferred rent and are amortized as a reduction of rent expense over the term of the lease from the possession date. Deferred rent as of September 30, 2014 represents the net excess of rent expense over the actual cash paid for rent and the tenant improvement allowances received/receivable.

*(k) Recapitalization*

On January 16, 2015, the Company effected a reverse stock split of the Company's common stock at a ratio of one share for every five shares previously held. All common stock share and common stock per share data included in these financial statements reflect the reverse stock split. The unit and per unit data included in these financial statements do not reflect the reverse stock split as the reverse split was not applicable to the units.

**(4) Accrued expenses**

Accrued expenses consist of the following:

	<b>December 31, 2013</b>	<b>September 30, 2014</b>
Compensation and benefits	\$ 138,761	\$ 714,483
Consulting and professional fees	518,485	512,003
Research and development	799,585	600,390
Other	35,666	36,869
	<b>\$ 1,492,497</b>	<b>\$ 1,863,745</b>

**(5) Commitments and contingencies***(a) Lease*

In March 2014, the Company entered into an operating lease for laboratory and office space in Philadelphia, PA, through October 2025. Rent expense under this lease was \$0.4 million for the nine months ended September 30, 2014. Future minimum lease payments under this lease are as follows:

Year ending December 31: 2014	\$
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2015	600,000
2016	1,600,000
2017	1,600,000
2018	1,600,000
2019 and thereafter	12,200,000
Total	\$ 17,600,000

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## **Spark Therapeutics, Inc.**

### **Notes to unaudited interim financial statements**

#### ***(b) License agreements***

See Note 8 for a discussion of The Children's Hospital of Philadelphia (CHOP) license agreement.

In October 2013, the Company entered into a patent license agreement with The Trustees of the University of Pennsylvania (Penn) for certain intellectual property licenses to be provided by Penn to the Company in the fields of research, development, manufacture and commercialization. The license agreement requires the Company to reimburse Penn for the patent costs related to the underlying licensed rights. For the nine months ended September 30, 2014, the Company recorded \$0 of general and administrative expenses related to the reimbursement of such patent costs in the accompanying statement of operations. The Company is obligated to make payments to Penn upon the occurrence of first commercial sale for certain licensed products in both the United States and Europe. The Company must pay a low-single-digit royalty based on net sales of licensed products by territory, which royalties will be reduced if the Company is required to license patents or intellectual property from third parties.

In December 2014, the Company entered into a license agreement with Penn for certain intellectual property licenses. The Company issued 200,000 shares of restricted common stock in connection with the agreement and is obligated to make milestone payments upon the achievement of certain regulatory milestones up to \$5.5 million in the aggregate. Additionally, the Company is obligated to pay Penn single-digit-royalties based on its net sales of licensed products by territory.

In October 2013, the Company entered into a license agreement with the University of Iowa Research Foundation (UIRF) for certain intellectual property licenses. The license agreement requires the Company to reimburse UIRF for the patent costs related to the underlying licensed rights. For the nine months ended September 30, 2014, the Company recorded \$0.2 million of general and administrative expenses related to the reimbursement of such patent costs in the accompanying statement of operations. The Company is obligated to make payments to UIRF upon the occurrence of various development and commercialization milestones. The Company must pay a low-single-digit royalty to UIRF based on net sales of licensed products by territory. In connection with the license agreement, the Company issued 281,854 Series 1 common units (Series 1 Units) to UIRF. The fair value of the units of \$0.6 million has been recorded as acquired in-process research and development expense in the fourth quarter of 2013.

#### **(6) Stockholders' equity**

The Company's certificate of incorporation and bylaws contain the rights, preferences and privileges of the Company's stockholders and their respective shares.

##### ***(a) Convertible preferred***

###### *October 2013 Series A financing*

In October 2013, the Company entered into an agreement with CHOP to sell 5,000,000 Series A Units at \$2.00 per unit for proceeds of \$10.0 million. As discussed in Note 8, the Company recorded a receivable from CHOP for the Series A Units, as CHOP managed the Company's expenditures during 2013. The remaining proceeds from the sale of the Series A Units of \$4,861,285 are reflected on the accompanying balance sheet as of December 31, 2013 as receivable from related party. The receivable was collected by the Company in 2014.

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## Spark Therapeutics, Inc.

### Notes to unaudited interim financial statements

Each Series A Unit was convertible into one Series 1 Unit (subject to certain antidilution adjustments) at any time at the option of the holder. The Series A Units were mandatorily convertible into common stock in the event of an IPO, as defined. The Series A Unit holders were entitled to a liquidation preference in an amount equal to \$2.00 per unit in the event of a liquidation, dissolution or winding up of the Company, or in the event the Company was merged with, or acquired by, another entity. Once the Series A Unit liquidation preference was paid, any remaining assets were to be distributed first to the holders of Series 1 Units for an amount up to \$50.0 million, second, to the holders of Series 2 common units (Series 2 Units), for a per unit amount equaling the amount distributed to each Series 1 Unit holder, and any remaining assets would have been distributed pro rata to the eligible common units (regardless of series).

#### *May 2014 conversion to C corporation*

Upon conversion of the Company into a C corporation in May 2014, each outstanding Series A Unit converted into one share of Series A Stock.

#### *May 2014 Series B financing*

In May 2014, the Company issued 45,186,334 shares of Series B Stock for \$72.4 million, net of transaction costs. In conjunction with the issuance of Series B Stock, certain Series A Stock terms were amended. Every five shares of Series A Stock and Series B Stock automatically convert into one share of common stock at a qualified IPO, as defined, or upon approval by at least 87.5% of the Series B Stock holders, subject to certain customary antidilution adjustments contained in the Company's certificate of incorporation. The Series A Stock and Series B Stock holders are entitled to receive, upon the liquidation of the Company, proceeds in proportion to their liquidation preference. Such liquidation preference is equal to the greater of (i) their respective original issue price plus any accrued but unpaid dividends and (ii) the amount per share as would have been payable had all Series A Stock and Series B Stock been converted into common stock immediately prior to such liquidation. Subsequent to the liquidation preference payments to the holders of Series A Stock and Series B Stock, the remaining assets of the Company would be distributed to the holders of common stock, Series A Stock and Series B Stock, on an as-converted-to-common-stock basis, provided that the holders of Series A Stock or Series B Stock, as applicable, would participate in such distribution until such holders receive in the aggregate 2.5 times their respective original issue price. The Series A Stock and Series B Stock are entitled to receive cumulative dividends at 8% per annum, which shall accrue from day to day beginning six months following the date on which the first share of Series B Stock was issued and shall be payable upon conversion, an event of liquidation or a qualified IPO, in each case, in shares of Series A Stock and Series B Stock, as applicable.

In May 2014, the board of directors (Board) was increased to nine members. Holders of the Series A Stock, voting as a class, are entitled to elect two members of the Board. Holders of the Series B Stock, voting as a class, are entitled to elect two members of the Board. Holders of common stock, voting as a class, are entitled to elect two members of the Board. The holders of common stock and any other class or series of voting stock, including Series A Stock and Series B Stock, voting as a class, are entitled to elect the balance of the total number of directors.

Table of Contents**Spark Therapeutics, Inc.****Notes to unaudited interim financial statements***(b) Common*

The Company has authorized 95,700,000 common shares. Through May 1, 2014, the Board designated Series 1 Units, Series 2 Units and Series 3 common units (Series 3 Units). Capital distributions were to be made to and among the holders, in the following order of priority: Series A Units, Series 1 Units, Series 2 Units and Series 3 Units.

Upon conversion of the Company into a C corporation in May 2014, each outstanding Series 1 Unit converted into 0.2 shares of common stock, each outstanding Series 2 Unit converted into 0.2 shares of common stock and each outstanding Series 3 Unit converted into 0.03883773 shares of common stock. The vesting terms of the previously issued equity remained consistent.

During the nine months ended September 30, 2014, 170,000 Series 2 Units were issued to a Company founder and 1,040,667 Series 3 Units were issued to various employees, directors and consultants of the Company. The Series 2 Units and Series 3 Units vesting terms vary, but primarily, shares vest 25% on the first anniversary of the vesting commencement date and then quarterly over three years, with accelerated vesting in the event of a change in control, as defined. Any unvested shares are forfeited in the event that the individual ceases to provide services to the Company.

The Series 2 Units and Series 3 Units had a grant date fair value of \$0.4 million, which is being recognized as compensation expense over the vesting period of the shares. The Company recorded compensation expense of \$1.8 million during the nine months ended September 30, 2014. At September 30, 2014, there was \$1.8 million of unrecognized compensation expense related to common shares which is expected to be recognized over a weighted-average period of 2.8 years. The following table summarizes restricted stock activity:

	Number of units/shares	Weighted- average grant date fair value
Nonvested units at December 31, 2013	5,370,000	\$ 0.75
Units granted	1,210,667	0.32
Units vested	(2,286,377)	0.83
Units forfeited	(170,000)	0.84
Conversion to C corporation and effect of reverse stock split	(3,586,949)	
Nonvested shares at September 30, 2014	537,341	3.82

**(7) 2014 stock incentive plan**

In May 2014, the Company established the 2014 Stock Incentive Plan (the Plan), which allows for the granting of incentive stock options, nonstatutory stock options, stock appreciation rights, restricted stock awards and other stock awards to purchase an aggregate of 356,800 shares of the Company's common stock to employees, officers, directors, consultants and advisors. In connection with the Series B financing in May 2014, the Plan was amended to increase the aggregate number of shares issuable pursuant to the Plan to 2,543,299 shares. As of September 30, 2014, 741,003 shares were available for future grants under the Plan.

The Company measures employee stock-based awards at grant-date fair value and records employee compensation expense on a straight-line basis over the vesting period of the award.





Table of Contents**Spark Therapeutics, Inc.****Notes to unaudited interim financial statements**

Determining the appropriate fair value of stock-based awards requires the input of subjective assumptions, including the fair value of the Company's common stock and for stock options, the expected life of the option and expected stock price volatility. The Company uses the Black-Scholes option pricing model to value its stock option awards. The assumptions used in calculating the fair value of stock-based awards represent management's best estimates and involve inherent uncertainties and the application of management's judgment. As a result, if factors change and management uses different assumptions, stock-based compensation expense could be materially different for future awards.

The expected life of stock options was estimated using the simplified method, as the Company has no historical information to develop reasonable expectations about future exercise patterns and post-vesting employment termination behavior for its stock options grants. The simplified method is based on the average of the vesting tranches and the contractual life of each grant. For stock price volatility, the Company uses comparable public companies as a basis for its expected volatility to calculate the fair value of options grants. The risk-free interest rate is based on U.S. Treasury notes with a term approximating the expected life of the option.

Nonemployee awards are revalued until an award vests and compensation expense is recorded on a straight-line basis over the vesting period of each separated vesting tranche of the award, or the accelerated attribution method. The estimation of the number of stock awards that will ultimately vest requires judgment, and to the extent actual results or updated estimates differ from the Company's current estimates, such amounts will be recorded as an adjustment in the period in which estimates are revised.

The following table summarizes stock option activity:

	Number of shares	Weighted- average exercise price	Aggregate intrinsic value
Outstanding at December 31, 2013			
Granted	1,732,995	\$ 3.45	
Outstanding at September 30, 2014	1,732,995	\$ 3.45	\$
Vested at September 30, 2014 and expected to vest	1,732,995	\$ 3.45	\$
Exercisable at September 30, 2014	8,058	\$ 3.45	\$

The weighted average remaining contractual term of options outstanding as of September 30, 2014 is 9.8 years.

During the nine months ended September 30, 2014, the Company recorded compensation expense of \$0.4 million for stock options. At September 30, 2014, there was \$4.6 million of unrecognized compensation expense, which is expected to be recognized over a weighted average period of 3.6 years.

The weighted average fair value of the options granted in 2014 was estimated at \$2.85 per share on the date of grant using the Black-Scholes option-pricing model with the following weighted-average assumptions:

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Expected volatility	110.4%
Risk-free interest rate	1.9%
Expected term (in years)	6.03
Expected dividend yield	0.0%

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## **Spark Therapeutics, Inc.**

### **Notes to unaudited interim financial statements**

#### **(8) Related-party transactions**

In October 2013, the Company entered into technology and license agreements with CHOP for certain commercialization licenses to be provided to the Company in order to develop services, methods and marketable products for commercialization. The license agreement requires the Company to reimburse CHOP for the patent costs related to the underlying licensed rights incurred after the effective date. For the nine months ended September 30, 2014, the Company recorded \$0.1 million of general and administrative expenses related to the reimbursement of such patent costs in the accompanying statement of operations.

In 2013, the Company entered into a number of services agreements with CHOP. The Master Research Services Agreement provides for certain research, development, and manufacturing services to be provided to the Company by CHOP. A separate Services Agreement provides for clinical, technical, and administrative services to be provided by CHOP to the Company. For the period from March 13, 2013 (inception) to September 30, 2013, the Company recorded \$2.5 million as research and development expense related to these agreements. For the nine months ended September 30, 2014, the Company recorded \$4.5 million as research and development expense and \$47,578 as general and administrative expense related to these agreements. As part of these agreements, CHOP managed payment of Company expenditures during 2013 and early 2014.

In December 2013, the Company entered into a consulting agreement with an individual who became the President and Chief Scientific Officer in September 2014. As compensation for her services, the individual received 2,000,000 restricted Series 2 Units. Pursuant to the individual's employment agreement, this restricted stock vests as follows: 25% of the grant vested on March 13, 2014, with the remainder vesting in equal quarterly installments over the subsequent three-year period.

#### **(9) Collaboration agreement**

In December 2014, the Company entered into a global collaboration agreement with Pfizer for the development and commercialization of SPK-FIX product candidates for the treatment of hemophilia B. Under the agreement, the Company granted Pfizer an exclusive worldwide license to any FIX gene therapy that it develops, manufactures or commercializes prior to December 31, 2024.

Under the terms of the agreement, the Company will be primarily responsible for conducting all research and development activities through completion of Phase 1/2 clinical trials of hemophilia B product candidates. Pfizer and the Company will share development costs incurred under an agreed product development plan for each product candidate with the Company's share of development costs under the agreement limited to \$10.6 million. Following the completion of Phase 1/2 clinical trials, Pfizer will be primarily responsible for development, manufacture, regulatory approval and commercialization, including all costs associated therewith.

Under the terms of the agreement, the Company is entitled to a \$20.0 million upfront payment. The Company also is eligible to receive up to \$260.0 million in aggregate milestone payments, \$140.0 million of which relate to potential development, regulatory and commercial milestones for the first product candidate to achieve each milestone and \$120.0 million of which relate to potential regulatory milestones for additional product candidates. In addition, the Company is entitled to receive royalties calculated as a low-teen percentage of net sales of licensed products. The royalties may be subject to certain reductions, including for a specified portion of royalty payments that Pfizer may become required to pay under any third-party license agreements, subject to a minimum royalty. Under the agreement, the Company remains solely responsible for the payment of license payments payable by the Company under specified license agreements.

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**Spark Therapeutics, Inc.**

**Notes to unaudited interim financial statements**

The agreement will expire on a country-by-country basis upon the latest of: (i) the expiration of the last-to-expire valid claim, as defined in the agreement, in licensed patent rights covering a licensed product, (ii) the expiration of the last-to-expire regulatory exclusivity granted with respect to a licensed product or (iii) 15 years after the first commercial sale of the last licensed product to be launched, in each case, in the applicable country. Pfizer may terminate the agreement on a licensed product-by-licensed product and country-by-country basis, or in its entirety, for any or no reason subject to notice requirements.

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Until \_\_\_\_\_, 2015 (25 days after the commencement of this offering), all dealers that buy, sell or trade shares of our common stock, whether or not participating in this offering, may be required to deliver a prospectus. This delivery requirement is in addition to the obligation of dealers to deliver a prospectus when acting as underwriters and with respect to their unsold allotments or subscriptions.

Table of Contents**Part II****Information not required in prospectus****Item 13. Other expenses of issuance and distribution.**

The following table indicates the expenses to be incurred in connection with the offering described in this registration statement, other than underwriting discounts and commissions, all of which will be paid by us. All amounts are estimated except the Securities and Exchange Commission registration fee, the Financial Industry Regulatory Authority, Inc. ( FINRA ) filing fee and the NASDAQ Global Select Market listing fee.

	<b>Amount</b>
Securities and Exchange Commission registration fee	\$ 18,241
FINRA filing fee	24,047
NASDAQ Global Select Market listing fee	125,000
Accountants' fees and expenses	700,000
Legal fees and expenses	1,500,000
Blue sky fees and expenses	5,000
Transfer agent's fees and expenses	10,000
Printing and engraving expenses	350,000
Miscellaneous	267,712
Total expenses	\$ 3,000,000

**Item 14. Indemnification of directors and officers.**

Section 102 of the General Corporation Law of the State of Delaware permits a corporation to eliminate the personal liability of directors of a corporation to the corporation or its stockholders for monetary damages for a breach of fiduciary duty as a director, except where the director breached his duty of loyalty, failed to act in good faith, engaged in intentional misconduct or knowingly violated a law, authorized the payment of a dividend or approved a stock repurchase in violation of Delaware corporate law or obtained an improper personal benefit. Our restated certificate of incorporation, which will become effective upon the closing of this offering, provides that no director of the Registrant shall be personally liable to it or its stockholders for monetary damages for any breach of fiduciary duty as a director, notwithstanding any provision of law imposing such liability, except to the extent that the General Corporation Law of the State of Delaware prohibits the elimination or limitation of liability of directors for breaches of fiduciary duty.

Section 145 of the General Corporation Law of the State of Delaware provides that a corporation has the power to indemnify a director, officer, employee, or agent of the corporation, or a person serving at the request of the corporation for another corporation, partnership, joint venture, trust or other enterprise in related capacities against expenses (including attorneys' fees), judgments, fines and amounts paid in settlement actually and reasonably incurred by the person in connection with an action, suit or proceeding to which he was or is a party or is threatened to be made a party to any threatened, ending or completed action, suit or proceeding by reason of such position, if such person acted in good faith and in a manner he reasonably believed to be in or not opposed to the best interests of the corporation, and, in any criminal action or proceeding, had no reasonable cause to believe his conduct was unlawful, except that, in the case of actions brought by or in the right of the corporation, no indemnification shall be made with respect to any claim, issue or matter as to which such person shall have been adjudged to be liable to the corporation unless and only to the extent that the Court of Chancery or other adjudicating court determines that, despite the adjudication of liability but in view of

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all of the circumstances of the case, such person is fairly and reasonably entitled to indemnity for such expenses which the Court of Chancery or such other court shall deem proper.

Our restated certificate of incorporation, which will become effective upon the closing of this offering, provides that we will indemnify each person who was or is a party or threatened to be made a party to any threatened, pending or completed action, suit or proceeding (other than an action by or in the right of us) by reason of the fact that he or she is or was, or has agreed to become, a director or officer, or is or was serving, or has agreed to serve, at our request as a director, officer, partner, employee or trustee of, or in a similar capacity with, another corporation, partnership, joint venture, trust or other enterprise (all such persons being referred to as an Indemnitee ), or by reason of any action alleged to have been taken or omitted in such capacity, against all expenses (including attorneys' fees), judgments, fines and amounts paid in settlement actually and reasonably incurred in connection with such action, suit or proceeding and any appeal therefrom, if such Indemnitee acted in good faith and in a manner he or she reasonably believed to be in, or not opposed to, our best interests, and, with respect to any criminal action or proceeding, he or she had no reasonable cause to believe his or her conduct was unlawful. Our restated certificate of incorporation provides that we will indemnify any Indemnitee who was or is a party to an action or suit by or in the right of us to procure a judgment in our favor by reason of the fact that the Indemnitee is or was, or has agreed to become, a director or officer, or is or was serving, or has agreed to serve, at our request as a director, officer, partner, employee or trustee of, or in a similar capacity with, another corporation, partnership, joint venture, trust or other enterprise, or by reason of any action alleged to have been taken or omitted in such capacity, against all expenses (including attorneys' fees) and, to the extent permitted by law, amounts paid in settlement actually and reasonably incurred in connection with such action, suit or proceeding, and any appeal therefrom, if the Indemnitee acted in good faith and in a manner he or she reasonably believed to be in, or not opposed to, our best interests, except that no indemnification shall be made with respect to any claim, issue or matter as to which such person shall have been adjudged to be liable to us, unless a court determines that, despite such adjudication but in view of all of the circumstances, he or she is entitled to indemnification of such expenses. Notwithstanding the foregoing, to the extent that any Indemnitee has been successful, on the merits or otherwise, he or she will be indemnified by us against all expenses (including attorneys' fees) actually and reasonably incurred in connection therewith. Expenses must be advanced to an Indemnitee under certain circumstances.

We intend to enter into indemnification agreements with each of our directors and executive officers. These indemnification agreements may require us, among other things, to indemnify our directors and executive officers for some expenses, including attorneys' fees, judgments, fines and settlement amounts incurred by a director or executive officer in any action or proceeding arising out of his or her service as one of our directors or executive officers, or any of our subsidiaries or any other company or enterprise to which the person provides services at our request.

We maintain a general liability insurance policy that covers certain liabilities of directors and executive officers of our corporation arising out of claims based on acts or omissions in their capacities as directors or officers.

In any underwriting agreement we enter into in connection with the sale of common stock being registered hereby, the underwriters will agree to indemnify, under certain conditions, us, our directors, our officers and persons who control us within the meaning of the Securities Act of 1933, as amended (the Securities Act ), against certain liabilities.

## **Item 15. Recent sales of unregistered securities.**

Set forth below is information regarding shares of capital stock issued by us since inception. Also included is the consideration received by us for such shares and information relating to the section of the Securities Act, or rule of the Securities and Exchange Commission, under which exemption from registration was claimed.



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***(a) Conversion to corporation***

On May 2, 2014, Spark Therapeutics, LLC, a Delaware limited liability company converted into Spark Therapeutics, Inc. (the corporate conversion). As a result, 31,910,667 common membership units of Spark Therapeutics, LLC were converted into 6,090,317 shares of common stock of Spark Therapeutics, Inc. and 5,000,000 series A preferred units were converted into 5,000,000 shares of series A preferred stock. The corporate conversion was effected in accordance with the terms of the Amended and Restated Limited Liability Company Agreement of Spark Therapeutics, LLC and did not constitute a sale for purposes of the Securities Act.

***(b) Issuance of preferred stock***

In October 2013, Spark Therapeutics LLC issued and sold equity interests since converted into an aggregate of 5,000,000 shares of series A preferred stock to CHOP for an aggregate purchase price of \$10.0 million.

In May 2014, we issued and sold an aggregate of 45,186,334 shares of our series B preferred stock at a price per shares of \$1.61 per share for an aggregate purchase price of \$72.75 million.

No underwriters were involved in the foregoing sales of securities. The securities described in this section (b) of Item 15 were issued to investors in reliance upon the exemption from the registration requirements of the Securities Act, as set forth in Section 4(a)(2) under the Securities Act and Regulation D promulgated thereunder relative to transactions by an issuer not involving any public offering, to the extent an exemption from such registration was required. All purchasers of shares of preferred stock described above represented to us in connection with their purchase that they were accredited investors and were acquiring the shares for their own account for investment purposes only and not with a view to, or for sale in connection with, any distribution thereof and that they could bear the risks of the investment and could hold the securities for an indefinite period of time. The purchasers received written disclosures that the securities had not been registered under the Securities Act and that any resale must be made pursuant to a registration statement or an available exemption from such registration.

***(c) Issuance of common stock***

In December 2014, we issued 200,000 shares of common stock to Penn as consideration for entering into a license agreement.

In October 2013, Spark Therapeutics LLC issued equity interests since converted into 4,943,629 and 56,370 shares of our common stock to CHOP and UIRF, respectively, as consideration for assets we determined to have a fair market value of \$50.0 million.

No underwriters were involved in the foregoing sales of securities. The securities described above were issued to investors in reliance upon the exemption from the registration requirements of the Securities Act, as set forth in Section 4(a)(2) under the Securities Act and Regulation D promulgated thereunder relative to transactions by an issuer not involving any public offering, to the extent an exemption from such registration was required.

Since our inception on March 13, 2013, we have issued to certain employees and non-employees equity representing an aggregate of 1,090,318 shares of restricted common stock as of January 15, 2015. The issuances of common stock to certain employees described above were issued pursuant to written compensatory plans or arrangements with our employees in reliance on the exemption from the registration requirements of the Securities Act provided by Rule 701 promulgated under the Securities Act, or pursuant to Section 4(a)(2) under the Securities Act, relative to transactions by an issuer not involving any public offering, to the extent an exemption from such registration was required. All recipients either received adequate information about us or had access, through employment relationships, to such information.

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### ***(d) Stock option grants***

Since our inception on March 13, 2013, we have issued to certain employees, directors and consultants options to purchase an aggregate of 2,357,505 shares of common stock as of January 15, 2015, of which, no options to purchase shares of common stock had been exercised, 93,008 options to purchase shares had been forfeited or cancelled and options to purchase 2,264,497 shares of common stock remained outstanding at a weighted average exercise price of \$4.52 per share.

The stock options and the shares of common stock issued upon the exercise of such options as described in this section (d) of Item 15 were issued pursuant to written compensatory plans or arrangements with our employees, directors and consultants, in reliance on the exemption from the registration requirements of the Securities Act provided by either Section 4(a)(2) of the Securities Act or Rule 701 promulgated under the Securities Act, or pursuant to Section 4(a)(2) under the Securities Act, relative to transactions by an issuer not involving any public offering, to the extent an exemption from such registration was required. All recipients either received adequate information about us or had access, through employment or other relationships, to such information.

All of the foregoing securities are deemed restricted securities for purposes of the Securities Act. All certificates representing the issued shares of capital stock described in this Item 15 included appropriate legends setting forth that the securities have not been registered and the applicable restrictions on transfer.

## **Item 16. Exhibits and financial statement schedules.**

(a) The exhibits to the registration statement are listed in the Exhibit Index attached hereto and incorporated by reference herein.

(b) Financial Statement Schedules.

## **Item 17. Undertakings.**

(a) The undersigned registrant hereby undertakes to provide to the underwriter, at the closing specified in the underwriting agreement, certificates in such denominations and registered in such names as required by the underwriter to permit prompt delivery to each purchaser.

(b) Insofar as indemnification for liabilities arising under the Securities Act may be permitted to directors, officers and controlling persons of the registrant pursuant to the foregoing provisions, or otherwise, the registrant has been advised that in the opinion of the Securities and Exchange Commission such indemnification is against public policy as expressed in the Securities Act and is, therefore, unenforceable. In the event that a claim for indemnification against such liabilities (other than the payment by the registrant of expenses incurred or paid by a director, officer or controlling person of the registrant in the successful defense of any action, suit or proceeding) is asserted by such director, officer or controlling person in connection with the securities being registered, the registrant will, unless in the opinion of its counsel the matter has been settled by controlling precedent, submit to a court of appropriate jurisdiction the question whether such indemnification by it is against public policy as expressed in the Securities Act and will be governed by the final adjudication of such issue.

(c) The undersigned hereby undertakes that:

(1) For purposes of determining any liability under the Securities Act, the information omitted from the form of prospectus filed as part of this registration statement in reliance upon Rule 430A and

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contained in a form of prospectus filed by the registrant pursuant to Rule 424(b)(1) or (4) or 497(h) under the Securities Act shall be deemed to be part of this registration statement as of the time it was declared effective.

- (2) For the purpose of determining any liability under the Securities Act, each post-effective amendment that contains a form of prospectus shall be deemed to be a new registration statement relating to the securities offered therein, and the offering of such securities at that time shall be deemed to be the initial bona fide offering thereof.

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## Signatures

Pursuant to the requirements of the Securities Act, the registrant has duly caused this registration statement to be signed on its behalf by the undersigned, thereunto duly authorized, in the City of Philadelphia, Commonwealth of Pennsylvania, on this 28<sup>th</sup> day of January, 2015.

Spark Therapeutics, Inc.

By: /s/ Jeffrey D. Marrazzo  
Jeffrey D. Marrazzo  
Chief Executive Officer

**Table of Contents****Signatures**

Pursuant to the requirements of the Securities Act of 1933, this Registration Statement has been signed by the following persons in the capacities held on the dates indicated.

<b>Signature</b>	<b>Title</b>	<b>Date</b>
/s/ Jeffrey D. Marrazzo	Director and Chief Executive Officer	January 28, 2015
Jeffrey D. Marrazzo	(Principal Executive Officer)	
/s/ Stephen W. Webster	Chief Financial Officer	January 28, 2015
Stephen W. Webster	(Principal Financial and Accounting Officer)	
*	Director	January 28, 2015
Katherine A. High, M.D.		
*	Director	January 28, 2015
Steven M. Altschuler, M.D.		
*	Director	January 28, 2015
A. Lorris Betz, M.D., Ph.D.		
*	Director	January 28, 2015
Lars Ekman, M.D., Ph.D.		
*	Director	January 28, 2015
Anand Mehra, M.D.		
*	Director	January 28, 2015
Vincent Milano		
*	Director	January 28, 2015
Elliott Sigal, M.D., Ph.D.		

\* By: /s/ Jeffrey D. Marrazzo  
Jeffrey D. Marrazzo  
Attorney-in-Fact

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<b>Exhibit number</b>	<b>Description of exhibit</b>
1.1*	Underwriting Agreement
3.1*	Certificate of Incorporation of the Registrant, as amended
3.2*	Amended and Restated Bylaws of the Registrant
3.3*	Form of Restated Certificate of Incorporation of the Registrant (to be effective upon the closing of this offering)
3.4*	Form of Amended and Restated Bylaws of the Registrant (to be effective upon the closing of this offering)
4.1*	Specimen Stock Certificate evidencing the shares of common stock
4.2*	Investors' Rights Agreement dated as of May 23, 2014
5.1	Opinion of Wilmer Cutler Pickering Hale and Dorr LLP
10.1*	2014 Stock Incentive Plan
10.2*	Form of Incentive Stock Option Agreement under 2014 Stock Incentive Plan
10.3*	Form of Nonstatutory Stock Option Agreement under 2014 Stock Incentive Plan
10.4*	Form of Restricted Stock Agreement under 2014 Stock Incentive Plan
10.5*	2015 Stock Incentive Plan
10.6*	Form of Incentive Stock Option Agreement under 2015 Stock Incentive Plan
10.7*	Form of Nonstatutory Stock Option Agreement under 2015 Stock Incentive Plan
10.8*	2015 Employee Stock Purchase Plan
10.9*	License Agreement dated October 14, 2013 between the Registrant and The Children's Hospital of Philadelphia, as amended.
10.10*	Technology Assignment Agreement dated October 14, 2013 between the Registrant and The Children's Hospital of Philadelphia.
10.11*	Master Research Services Agreement dated October 14, 2013 between the Registrant and The Children's Hospital of Philadelphia.
10.12*	Services Agreement dated December 26, 2013 between the Registrant and The Children's Hospital of Philadelphia.
10.13*	License Agreement dated October 14, 2013 between the Registrant and the University of Iowa Research Foundation, as amended.
10.14*	Patent License Agreement dated October 14, 2013 between the Registrant and The Trustees of the University of Pennsylvania
10.15*	License Agreement dated March 18, 2014 between the Registrant and Genable Technologies Limited.
10.16*	Manufacturing Agreement dated March 18, 2014 between the Registrant and Genable Technologies Limited.
10.17*	Development Consultancy Agreement dated March 18, 2014 between the Registrant and Genable Technologies Limited.
10.18*	Patent License Agreement dated December 2, 2014 between the Registrant and the Trustees of the University of Pennsylvania.

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<b>Exhibit number</b>	<b>Description of exhibit</b>
10.19*	License Agreement dated December 6, 2014 between the Registrant and Pfizer Inc.
10.20*	Lease Agreement, dated as of March 31, 2014, between the Registrant and Wexford-UCSC 3737, LLC
10.21*	Employment Agreement between the Registrant and Jeffrey D. Marrazzo
10.22*	Common Share Membership Agreement between the Registrant and Katherine A. High
10.23*	Employment Agreement between the Registrant and Katherine A. High
10.24*	Employment Agreement between the Registrant and Rogério Vivaldi
10.25*	Employment Agreement between the Registrant and Stephen W. Webster
10.26*	Form of Indemnification Agreement between the Registrant and each of the executive officers and directors
23.1	Consent of KPMG LLP
23.2	Consent of Wilmer Cutler Pickering Hale and Dorr LLP (included in Exhibit 5.1)
24.1*	Power of Attorney (included on signature page)
24.2*	Power of Attorney for A. Lorris Betz

\* Previously filed.

Confidential treatment requested as to portions of the exhibit. Confidential materials omitted and filed separately with the Securities and Exchange Commission.