Spark Therapeutics, Inc.
Form 10-K
March 14, 2016
Table of Contents

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, DC 20549

FORM 10-K

(Mark One)
x ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934

For the fiscal year ended December 31, 2015

OR

o TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934

For the transition period from to

Commission File Number: 001-36819

Spark Therapeutics, Inc.
(Exact Name of Registrant as Specified in Its Charter)

Delaware (State or Other Jurisdiction of Incorporation or Organization)	46-2654405 (IRS Employer Identification No.)
3737 Market Street Suite 1300 Philadelphia, PA (Address of Principal Executive Offices)	19104 (Zip Code)

(888) 772-7560
(Registrant's Telephone Number, Including Area Code)

Indicate by check mark whether the registrant: (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes x No ¨
Indicate by check mark whether the registrant has submitted electronically and posted on its corporate Web site, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T during

the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files). Yes x No ¨

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. (Check one):

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

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

As of June 30, 2015, the last day of the registrant's most recently completed fiscal quarter, the aggregate market value of the Common Stock held by non-affiliates of the registrant was approximately $779 million, based upon the closing price of the registrant's common stock on June 30, 2015.

Table of Contents

As of March 4, 2016 there were 27,109,724 shares of the registrant's Common Stock, par value $0.001 per share, outstanding.

DOCUMENTS INCORPORATED BY REFERENCE

The registrant intends to file a definitive proxy statement pursuant to Regulation 14A in connection with its 2016 Annual Meeting of Stockholders. Portions of such proxy statement are incorporated by reference into Part III of this Annual Report on Form 10-K.

Table of Contents

TABLE OF CONTENTS

Table of Contents

REFERENCES TO SPARK

In this Annual Report on Form 10-K, 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 the Children's Hospital of Philadelphia, or CHOP, or the University of Iowa Research Foundation, or UIRF;
- 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 the University of Pennsylvania, 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.

Table of Contents

Forward-looking statements

This Annual Report on Form 10-K contains forward-looking statements that involve substantial risks and uncertainties. All statements, other than statements of historical facts, contained in this Annual Report on Form 10-K, 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. The words “may,” “will,” “should,” “expects,” “plans,” “anticipates,” “could,” “intends,” “target,” “projects,” “contemplates,” “believes,” “estimates,” “predicts,” “continue” 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 Annual Report on Form 10-K include, among other things, statements about:

- the timing, scope or likelihood of regulatory filings and approvals, including the timing of our BLA submission for, and final FDA approval of, SPK-RPE65;
- the timing, progress and results of clinical trials for SPK-CHM, SPK-FIX 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;
- our estimates regarding the potential market opportunity for our 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, medical affairs, 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 processes;
- 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 our use of our capital resources;
- 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 Emerging Growth Company under the Jumpstart Our Business Startups Act of 2012, or JOBS Act.

We may not actually achieve the plans, intentions or expectations disclosed in our forward-looking statements, and you should not place undue reliance on our forward-looking statements. Actual results or events could differ materially from the plans, intentions and expectations disclosed in the forward-looking statements we make. We have included important factors in the cautionary statements included in this Annual Report on Form 10-K, 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 we may make.

You should read this Annual Report on Form 10-K and the documents that we have filed as exhibits to this Annual Report on Form 10-K 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 applicable law.

Table of Contents

PART I.

Item 1. 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. 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 recently reported statistically significant results in a pivotal Phase 3 clinical trial of our first product candidate targeting rare genetic blinding conditions, which has received both breakthrough therapy and orphan product designation. Based on these positive results, we intend to submit a Biologics License Application, or BLA, for this product candidate with the U.S. Food and Drug Administration, or FDA, in the second half of 2016 as the first step in executing our global regulatory and commercialization strategy.

We also have built a pipeline of product candidates targeting multiple rare blinding conditions, hematologic disorders and neurodegenerative diseases. Our pipeline includes: a product candidate targeting another rare genetic blinding condition currently in a Phase 1/2 clinical trial; product candidates for the treatment of hemophilia with a hemophilia B product candidate currently in a Phase 1/2 clinical trial in collaboration with Pfizer Inc., or Pfizer, and a preclinical product candidate for hemophilia A to which we retain global commercialization rights; a product candidate for the treatment of TPP1 deficiency, a form of Batten disease, for which we are currently conducting Investigational New Drug application, or IND, enabling studies; and other ophthalmic, hematologic and neurodegenerative disease programs.

Our most advanced product candidate, SPK-RPE65 (voretigene neparvovec), is intended to treat genetic blinding conditions called inherited retinal diseases, 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, notably night blindness, or nyctolopia, that make independent activities of daily living challenging and ultimately lead to blindness. 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, as well as France, Germany, Italy, Spain and the United Kingdom, which are referred to as the five major European markets. We have received orphan product designation for SPK-RPE65 for the treatment of RPE65-mediated IRDs in both the United States and the European Union.

In October 2015, we announced positive top-line results from our pivotal Phase 3 clinical trial of SPK-RPE65, the first randomized controlled Phase 3 trial of a gene therapy for genetic disease. The trial of 31 subjects met with statistical significance its primary endpoint, the bilateral mobility test change score ($p = 0.001$), as well as the first two of three secondary endpoints, specifically full-field light sensitivity threshold testing, or FST ($p < 0.001$), and the assigned first eye mobility test change score ($p = 0.001$). Statistical significance was not achieved for the third secondary endpoint, visual acuity ($p = 0.17$).

The trial demonstrated a statistically significant restoration of vision in subjects that were progressing toward complete blindness. On average, subjects that received SPK-RPE65 demonstrated an improvement in their mobility test change score of 1.9 lux, or light, levels. Of the subjects in the intervention group, 65% achieved the maximum improvement measurable on the mobility test. Similarly, on average, intervention group subjects achieved a greater than 100-fold improvement in light sensitivity as measured by FST. Further, subjects receiving SPK-RPE65 achieved a mean improvement in visual acuity of approximately two lines (9.0 letters averaged across both eyes) on the logarithm of the minimum angle of resolution, or logMAR, scale, a standard measure of visual acuity, compared with a slight improvement (1.6 letters) among control subjects.

To date, we have not observed any product candidate-related serious adverse events nor any deleterious immune responses in the Phase 3 trial or in earlier Phase 1 trials. Based on these positive results, we intend to submit a BLA for SPK-RPE65 with FDA in the second half of 2016 as the first step in executing our global regulatory and

commercialization strategy.

SPK-RPE65 also continues to demonstrate long-lasting benefit. Specifically, a cohort of eight subjects that participated in our second Phase 1 clinical trial that received the same dose and volume as used in the Phase 3 clinical trial and that would have met the eligibility criteria for the Phase 3 trial, continue to experience durable benefit as measured by mobility testing and FST over three years from time of administration, with observation ongoing.

We possess global rights to SPK-RPE65. If approved, we intend to commercialize SPK-RPE65 globally, initially in the United States, the European Union and Latin America. We plan to employ small, targeted commercial and medical affairs groups to build and promote access to the product through centers that specialize in treating IRDs in the United States, the

Table of Contents

European Union and other major markets, including in Latin America and Asia. We believe that this approach is more patient-centered and will provide the foundation for future commercial and medical affairs operations, particularly for additional gene therapy product candidates for IRDs. The five primary areas of our pre-launch efforts include patient identification, ensuring market access, developing a high-quality delivery and distribution model, building a patient-centric organization and educating stakeholders.

We are pursuing other 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 functional vision. CHM ultimately results in blindness. We have completed enrollment of subjects in the second cohort of our dose escalating Phase 1/2 trial for SPK-CHM. To date, SPK-CHM has been well tolerated and we have not observed any product candidate-related serious adverse events in this trial. We have received orphan product designation for SPK-CHM for the treatment of CHM in both the United States and the European Union.

The RPE65 and CHM genes are two of more than 220 genes that have been identified to cause IRDs. In March 2016, we acquired Genable Technologies Ltd., or Genable, and will continue the development of RhoNova, Genable's lead gene therapy product candidate addressing rhodopsin-linked autosomal dominant retinitis pigmentosa, or RHO-adRP, an IRD that we believe affects approximately12,000 people in the United States and the five major European markets. In December 2015, we in-licensed technology with which we have initiated preclinical development of SPK-LHON, addressing Leber hereditary optic neuropathy, or LHON, an IRD that we believe affects approximately three in 100,000 people. We are actively evaluating additional IRDs to further expand our ophthalmic gene therapy portfolio.

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 received a $20.0 million upfront payment, earned a $15.0 million milestone payment in December 2015 and are eligible to receive up to an additional $245.0 million in aggregate milestone payments, as well as royalties calculated as a low-teen percentage of net product sales. Pfizer and we initiated a Phase 1/2 clinical trial of our lead SPK-FIX product candidate in 2015.

In our SPK-FVIII program for the treatment of hemophilia A, we recently nominated a lead product candidate that has demonstrated production of therapeutic levels of Factor VIII in multiple preclinical models at doses that have been safely delivered to humans in hemophilia B studies. We retain global commercialization rights to the SPK-FVIII program.

We are developing a lead neurodegenerative disease product candidate in our SPK-TPP1 program that has demonstrated compelling preclinical proof-of-concept data for the treatment of a form of Batten disease, a fatal neurological disorder involving mutations of the TPP1 gene, also known as the CLN2 gene, that begins in early childhood. TPP1 deficiency results in motor and mental decline, seizures and visual deficits appearing between ages two to four and is fatal by ages ten to twelve in a majority of cases. We believe there are approximately 750 to 1,000 patients with TPP1 deficiency in the United States and the five major European markets with approximately 75 to 100 new cases annually. In a well-established preclinical model of TPP1 deficiency, administration of our lead SPK-TPP1 product candidate to the ependymal cells of the brain ventricular system resulted in delayed onset of clinical symptoms and disease progression, protection from cognitive decline and extension of lifespan relative to untreated controls. Notably, the study produced effective distribution of the TPP1 enzyme throughout the central nervous system, as evidenced by immunohistochemistry and enzyme activity assay. We initiated IND-enabling studies for our lead SPK-TPP1 product candidate in 2015.

We also are conducting preclinical studies on a product candidate for the treatment of Huntington's disease, a hereditary genetic disorder that we believe affects over 60,000 patients in the United States and the five major European markets.

Gene therapies historically made by CHOP 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. We

have a supply agreement with CHOP to make clinical and, if requested by us, commercial material. We have our own state-of-the-art current Good Manufacturing Practices, or cGMP, facility to manufacture clinical and commercial grade adeno-associated virus, or AAV, vectors.

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 AAV and lentiviral vectors. Our vectors are disarmed viruses that carry genetic material into target cells.

Table of Contents

Inherited retinal diseases

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

SPK-RPE65 is our most advanced product candidate. Patients with RPE65 mutations suffer from a variety of symptoms ranging from night blindness, or nyctolopia, 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 caused by RPE65 mutations.

In October 2015, we announced positive top-line results from our pivotal Phase 3 clinical trial of SPK-RPE65, the first randomized controlled Phase 3 trial of a gene therapy for genetic disease. The trial of 31 subjects met with statistical significance its primary endpoint, the bilateral mobility test change score ($p = 0.001$), as well as the first two of three secondary endpoints, specifically full-field light sensitivity threshold testing, or FST, ($p < 0.001$) and the assigned first eye mobility test change score ($p = 0.001$). Statistical significance was not achieved for the third secondary endpoint, visual acuity ($p = 0.17$), however, subjects receiving SPK-RPE65 achieved a mean improvement of approximately two lines (9.0 letters averaged across both eyes) on the logMAR scale, a standard measure of visual acuity, compared with a slight improvement (1.6 letters) among control subjects.

To date, we have not observed any product candidate-related serious adverse events nor any deleterious immune responses in the Phase 3 trial or in earlier Phase 1 trials. Based on these positive results, we intend to submit a BLA for SPK-RPE65 with FDA in the second half of 2016 as the first step in executing our global regulatory and commercialization strategy.

SPK-RPE65 also continues to demonstrate long-lasting benefits. Specifically, a cohort of eight subjects that participated in our second Phase 1 clinical trial that received the same dose and volume as used in the Phase 3 clinical trial and that would have met the eligibility criteria for the Phase 3 trial, continue to experience durable benefit over three years from time of administration as measured by mobility testing and FST, with observation ongoing.

We have received orphan product designation in both the United States and the European Union for SPK-RPE65 for the treatment of both Leber congenital amaurosis, or LCA, due to RPE65 mutations, which is referred to as LCA2, and retinitis pigmentosa, or RP, due to RPE65 mutations, which is referred to as RP20. LCA2 and RP20 historically are the most frequent clinical diagnoses of RPE65-mediated IRDs. We 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 and the five major European markets. We believe SPK-RPE65 could benefit patients who retain enough viable retinal cells to experience improved functional vision.

We possess global rights to SPK-RPE65. If approved, we intend to commercialize SPK-RPE65 globally, initially in the United States, the European Union and Latin America. We plan to employ small, targeted commercial and medical affairs groups to build and promote access to the product through centers that specialize in treating IRDs in the United States, the European Union and other major markets, including in Latin America and Asia. We believe that this approach is more patient-centered and will provide the foundation for future commercial and medical affairs operations, particularly for additional gene therapy product candidates for IRDs. The five primary areas of our pre-launch efforts include patient identification, ensuring market access, developing a high quality delivery and distribution model, building a patient-centric organization and educating stakeholders.

SPK-CHM for choroideremia

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 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. CHM ultimately results in 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 completed enrollment of subjects in the second cohort of the Phase 1/2 clinical trial of SPK-CHM. To date,

Table of Contents

SPK-CHM has been well tolerated and we have not observed any product candidate-related serious adverse events in this trial. We have received orphan product designation for SPK-CHM for the treatment of CHM in both the United States and the European Union.

Other IRD programs

The RPE65 and CHM genes are two of more than 220 genes that have been identified to cause IRDs. Gene therapy has the potential to address the underlying cause of IRDs by overcoming the effects of a malfunctioning gene. In March 2016, we acquired Genable and will continue the development of RhoNova, Genable's lead gene therapy product candidate addressing rhodopsin-linked autosomal dominant retinitis pigmentosa, or RHO-adRP, an IRD that we believe affects approximately 12,000 people in the United States and the five major European markets. In December 2015, we in-licensed technology, with which we have initiated preclinical development of SPK-LHON, addressing Leber hereditary optic neuropathy, or LHON, an IRD that we believe affects approximately three in 100,000 people. We are actively evaluating additional IRDs to further expand our ophthalmic gene therapy portfolio.

Hematologic disorders

SPK-FIX program for the treatment of hemophilia B

Our gene therapy platform enables us to develop gene therapies that target tissues other than the eye. Our pipeline 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 2014 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 FIX 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. Pfizer and we initiated a Phase 1/2 trial of our lead SPK-FIX product candidate in 2015. Under the terms of the agreement, we received a $20.0 million upfront payment in 2014, earned a $15.0 million milestone payment in December 2015 and are eligible to receive up to an additional $245.0 million in aggregate milestone payments, as well as royalties calculated as a low-teen percentage of net product sales.

SPK-FVIII program for the treatment of hemophilia A

In our SPK-FVIII program for the treatment of hemophilia A, we recently nominated a lead product candidate that has demonstrated production of therapeutic levels of Factor VIII in multiple preclinical models at doses that have been safely delivered to humans in hemophilia B studies. Hemophilia A is the most common form of hemophilia with approximately 140,000 patients worldwide. The only therapies currently available for moderate to severe hemophilia A are intravenously administered FVIII protein or its derivatives. We retain global commercial rights to the SPK-FVIII program.

Neurodegenerative diseases

SPK-TPP1 program for the treatment of a form of Batten disease

We are developing a lead product candidate for the treatment of a form of Batten disease in our SPK-TPP1 program. TPP1 deficiency causes severe childhood neurodegenerative disorders that result in motor and mental decline, seizures and visual deficits appearing between ages two to four, and is fatal by ages ten to twelve in a majority of cases. This autosomal recessive disease is caused by mutations in the TPP1 gene, leading to a deficiency of the soluble lysosomal enzyme tripeptidyl peptidase 1, or TPP1. TPP1 deficiency also is known as CLN2 disease. We believe there are approximately 750 to 1,000 patients with TPP1 deficiency in the United States and the five major European markets

with approximately 75 to 100 new cases annually.

In a well-established preclinical model of TPP1 deficiency, administration of the lead product candidate in our SPK-TPP1 program to ependymal cells of the brain ventricular system resulted in delayed onset of clinical symptoms and disease progression, protection from cognitive decline and extension of life span relative to untreated controls subjects. Notably, the novel delivery approach used in the study produced effective distribution of the TPP1 enzyme throughout the central nervous

Table of Contents

system, as evidenced by immunohistochemistry and enzyme activity assay. We initiated IND-enabling studies for the lead product candidate in our SPK-TPP1 program in 2015.

Other neurodegenerative diseases

We also are conducting preclinical studies on a product candidate for the treatment of Huntington's disease, a hereditary genetic disorder that we believe affects over 60,000 patients in the United States and the five major European markets.

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 UIRF and in-licensed additional intellectual property from Penn. We continue to collaborate with CHOP on gene therapy programs that are in preclinical stage of development.
- In May 2014, we completed a $72.7 million private placement of shares of Series B convertible preferred stock, or our 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.
- In February 2015, we completed our initial public offering of 8,050,000 shares of common stock at a public offering price of $23.00 per share, raising gross proceeds of $185.2 million before underwriting discounts and commissions and offering expenses.
- In October 2015, we announced positive top-line Phase 3 clinical trial data for our lead product candidate, SPK-RPE65, targeting rare blinding conditions, which demonstrated statistically significant restoration in functional vision in subjects that were progressing toward complete blindness.
- In November 2015, we announced the opening of a satellite office in Waltham, Massachusetts and also signed a sublease for 14,000 square feet of office space to expand our operations at our corporate headquarters in Philadelphia, Pennsylvania.
- In December 2015, we closed a public offering of 3,398,500 shares of common stock at an offering price of $47.00 per share. The offering consisted of 2,266,995 shares offered by us and 1,131,505 shares offered by CHOP, resulting in gross proceeds of $106.5 million to us and $53.2 million to CHOP before underwriting commissions and offering expenses.
- In December, 2015, we amended our license agreement with The Trustees of the University of Pennsylvania, or Penn, converting our co-exclusive license to certain patent rights owned by Penn, Cornell University and the University of Florida relating to a method of treating and retarding the development of blindness, including in particular LCA, to an exclusive license in the field of use related to the treatment of retinal disorders or diseases caused by a mutation or mutations in the RPE65 gene.
- On March 7, 2016, we acquired Genable, a private gene therapy innovator with which we have collaborated since 2014 in the development of Genable's therapeutic program targeting one of the most prevalent forms of IRD. With the acquisition, we acquire RhoNova, a potential treatment targeting RHO-adRP, an IRD that routinely leads to visual impairment and, in the most severe cases, to blindness.

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, that recently met with high statistical significance its primary endpoint and the first two of three secondary endpoints in a pivotal Phase 3 clinical trial targeting RPE65-mediated IRDs, for which there are no approved pharmacologic treatments, and that is designed to have dramatic, long-lasting effects;

10

Table of Contents

- A second IRD product candidate, SPK-CHM, for which we have completed enrollment of subjects in the second cohort of a Phase 1/2 clinical trial;

- Several other IRD programs in preclinical development;

- Programs targeting hematologic disorders, including SPK-FIX, for which we initiated a Phase 1/2 clinical trial in 2015 and that we are developing for the treatment of hemophilia B in collaboration with Pfizer, as well as SPK-FVIII for the treatment of hemophilia A, to which we retain global commercialization rights;

- Neurodegenerative disease programs, including SPK-TPP1, in preclinical development for a form of Batten disease and a preclinical program targeting Huntington's disease;

- A corporate collaboration with Pfizer for the development and global commercialization of SPK-FIX product candidates;

- 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;

- 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 and a foundation for commercial-scale manufacturing; 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:

- Obtain marketing approval for SPK-RPE65. We intend to submit a BLA for SPK-RPE65 with FDA in the second half of 2016 as the first step in executing our global regulatory and commercialization strategy. 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 RPE65-mediated IRDs.

-

Establish global commercial capabilities. 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. If approved, we intend to commercialize SPK-RPE65 globally, initially in the United States, the European Union and Latin America. We believe the value proposition for patients, families and payors would be significant, given the potentially transformative and long-lasting benefits demonstrated to date, delivered through a single administration. We plan to employ small, targeted commercial and medical affairs groups to build and promote access to the product through centers that specialize in treating IRDs in the United States, the European Union and other major markets, including in Latin America and Asia. We believe that this approach is more patient-centered and will provide the foundation for future commercial and medical affairs operations, particularly for additional gene therapy product candidates for IRDs.

Table of Contents

- Establish a franchise of gene therapies for IRDs. The RPE65 and CHM genes are two 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. 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 recently initiated Phase 1/2 clinical trial of our lead SPK-FIX product candidate for the treatment of hemophilia B, we recently nominated a lead product candidate in our SPK-FVIII program for the treatment of hemophilia A. We retain all development and commercial rights to our SPK-FVIII program and 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 multiple programs targeting neurodegenerative diseases, including SPK-TPP1 for TPP1 deficiency, a form of Batten disease, in preclinical development. We initiated an IND-enabling preclinical study of the lead product candidate in our SPK-TPP1 program in 2015. We also have a program targeting Huntington's disease.

Our product candidates

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

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, notably night blindness, or nyctalopia. 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

Table of Contents

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 LCA or RP among over 20 other clinical classifications.

One of the inclusion criteria in our clinical trials was that subjects be given a clinical diagnosis of LCA due to RPE65 mutations, as confirmed by genetic testing. This type of LCA is referred to as 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, the diagnosis of IRDs has begun to shift from clinical classification to a diagnosis based on the specific underlying causal gene. In our Phase 3 and Phase 1 clinical trials, we enrolled a genetically heterogeneous population, with 34 of 41 subjects having unique RPE65 gene mutations, and based upon a review of the literature, 26 of these mutations have been associated with clinical diagnoses other than LCA. Further, in our ongoing natural history study of patients with

Table of Contents

confirmed RPE65 gene mutations, we observed that the practice of clinical diagnosis is not standardized in this population, having encountered over 20 different clinical diagnoses given at just the first two of seven centers we are utilizing in this retrospective chart review study across the United States, Europe and Latin America.

With the broad availability of genetic testing, the corresponding shift from clinical to genetic diagnosis, the genetic heterogeneity of the subjects tested to date and the fact that SPK-RPE65 delivers a normal, functional copy of the RPE65 gene regardless of the type or location of the underlying mutations, we believe SPK-RPE65 should have broad application to all IRDs caused by autosomal recessive RPE65 gene mutations. As such, we are developing a regulatory strategy and are seeking approval for a label that would include both a description of the core clinical manifestation of RPE65-mediated disease along with a genetic characterization of the patients that should receive the product candidate. One such possible clinical manifestation is nyctalopia, or night blindness, which is not only a hallmark of RPE65-mediated disease, but was assessed by multiple endpoints in our trials and was specifically noted in our breakthrough therapy designation.

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 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 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, five vitreoretinal surgeons performed injections at two sites, CHOP and the University of Iowa.

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 used in our pivotal Phase 3 clinical trial. Our

pivotal Phase 3 clinical trial was an open label, multi-center, randomized trial of 31 subjects diagnosed with LCA due to RPE65 gene mutations.

Evaluating treatment outcomes

Currently, there is no approved pharmacologic treatment for any RPE65-mediated IRDs and, consequently, there are no precedent endpoints that have been used in a successful pivotal trial to assess the therapeutic benefits of a pharmaceutical

Table of Contents

product under development for RPE65-mediated IRDs. 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 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 patients' 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.

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:

Table of Contents

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 successfully 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, or light, 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;
- 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 by two masked 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 then 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.

Table of Contents

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;
- 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.

Other measurements of vision

We also collected data with respect to a variety of traditional and non-traditional visual and retinal function tests, including, but not limited to, full-field light sensitivity threshold, or FST, a test that 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, and visual acuity testing, which measures changes in central vision by assessing the ability of the subject to read a standard eye chart.

Phase 1 proof-of-concept trials

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. 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 1.5×10^{10} vector genomes, or vg, six subjects receiving 4.8×10^{10} vg and three subjects receiving 1.5×10^{11} vg. SPK-RPE65 was well tolerated, with no product candidate-related serious adverse events.

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, 1.5×10^{11} vg. 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 complication resulting from the vitrectomy. Eight subjects from the 102 trial that would have qualified for inclusion in our Phase 3 clinical trial all improved at least one light level and five of these eight improved to the minimum light level, which is the same level at which all normal-sighted subjects navigated the mobility test in the MTVS.

Subjects from these trials have been followed over a period of five to seven years. The results of our Phase 1 trials to date suggest that SPK-RPE65 enables subjects to perform activities of daily living with greater independence than prior to treatment and has long-lasting benefits.

Pivotal Phase 3 clinical trial

Trial design

The multicenter, pivotal Phase 3 trial randomized 31 subjects with confirmed RPE65 gene mutations, 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 University of Iowa. The intent to treat, or ITT, population included 21 subjects in the intervention group and 10 in the control group. There was no sham injection, since the trial included pediatric subjects. Subjects in our pivotal Phase 3 clinical trial received administration of 1.5×10^{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 participated 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 were eligible to crossover to the treatment group and all nine subjects in the modified intent to treat, or mITT, population chose to do so. 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.

Table of Contents

The primary objective of the Phase 3 trial was 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 was compared to subjects' pre-administration baseline.

Subjects were evaluated at baseline and 30 days, 90 days, 180 days and one year following administration of SPK-RPE65. The final score for statistical analysis was calculated based on the lowest lux level at which a subject receives a grade of "pass" one-year following injection as compared to baseline.

The secondary efficacy endpoints for our pivotal Phase 3 clinical trial included FST, mobility test changed score for the assigned first injected eye only and visual acuity. In connection with the trial, we also collected in-home evaluations of subjects at baseline and at the one-year time point. These in-home evaluations have been performed 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.

Phase 3 efficacy outcome measure results

In October 2015, we announced top-line results from our pivotal Phase 3 clinical trial of SPK-RPE65. The pivotal trial met its primary endpoint of mobility test change score ($p = 0.001$), demonstrating improvement of functional vision in the intervention group compared to the control group, as measured by the change in bilateral mobility testing between baseline and one year. The trial demonstrated a statistically significant restoration of vision in subjects that were progressing toward complete blindness. On average, intervention subjects ($n = 20$) demonstrated an improvement of 1.9 lux levels compared with an improvement of 0.2 specified lux levels in control subjects ($n = 9$) as measured by the change in bilateral mobility testing between baseline and one year in the mITT population. The mITT population ($n = 29$) includes all subjects that received SPK-RPE65, and only those who continued beyond the baseline study visit. Two subjects in the ITT population ($n = 31$) that were randomized but never received SPK-RPE65 were excluded from this efficacy analysis population. Thirteen of the 20 subjects receiving SPK-RPE65 were able to pass the mobility test at one lux at year one, demonstrating maximum improvement measurable on the mobility test score. None of the nine control subjects followed was able to pass the mobility test at one lux at year one.

Further, subjects who received SPK-RPE65 outperformed control subjects across the first two secondary endpoints: full-field light sensitivity threshold testing ($p < 0.001$) and the mobility test change score for the assigned first injected eye ($p = 0.001$). The third secondary endpoint, visual acuity, did not show statistically significant evidence of benefit ($p = 0.17$), however, subjects receiving SPK-RPE65 achieved a mean improvement of approximately two lines (9.0 letters averaged across both eyes) on the logMAR scale, a standard measure of visual acuity, compared with a slight improvement (1.6 letters) among control subjects. The charts below show the results from the first two secondary endpoints:

Phase 3 safety outcome measure results

There were no serious adverse events related to SPK-RPE65 or deleterious immune responses observed in the trial. Overall, adverse events related to the administration procedure were consistent with observations in earlier studies of SPK-

Table of Contents

RPE65. 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, which was consistent with the ocular adverse events seen in earlier Phase 1 clinical trials.

Durability of effect

SPK-RPE65 continues to demonstrate long-lasting effects. Specifically, a cohort of eight subjects that participated in our second Phase 1 clinical trial that received the same dose and volume as used in the Phase 3 clinical trial and that would have met the eligibility criteria for the Phase 3 trial, continue to experience durable benefit over three years from time of administration as measured by mobility testing and FST, with observation ongoing.

Commercialization

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

The five primary areas of our pre-launch efforts include:

- patient identification;
- ensuring market access;
- developing a high quality delivery and distribution model;
- building a patient-centric organization; and
- educating stakeholders.

SPK-CHM for the treatment of choroideremia

Overview

Choroideremia 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. CHM ultimately results in blindness. We estimate prevalence of CHM is between approximately one in 50,000 and one 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

Table of Contents

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 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.

Phase 1/2 clinical trial

We have completed enrollment of subjects in the second cohort of our Phase 1/2 clinical trial of SPK-CHM. To date, we have not observed any product candidate-related serious adverse events. The primary objective of the Phase 1/2 clinical trial is to evaluate the safety and tolerability of subretinal administration of SPK-CHM. Toxicity related to the administration of SPK-CHM was monitored in the eye and systemically, and the trial advanced 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

We acquired from Genable 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 approximately12,000 people in the United States and the five major European markets.

Unlike our existing product candidates, which add the functional gene to the target cells, RhoNova utilizes 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. This acquisition 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.

Other IRDs

The RPE65 and CHM genes are two of more than 220 genes that have been identified to cause IRDs. In December 2015, we in-licensed technology, with which we have initiated preclinical development of SPK-LHON, addressing Leber hereditary optic neuropathy, or LHON, an IRD that we believe affects approximately three in 100,000 people. We are actively evaluating additional IRDs to further expand our ophthalmic gene therapy portfolio.

Hematologic disorders

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

20

Table of Contents

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.

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 subsequently 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 and central nervous system, 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.

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 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

Table of Contents

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, earned a $15.0 million milestone payment in December 2015 and are eligible to receive up to an additional $245.0 million in aggregate milestone payments, as well as royalties calculated as a low-teen percentage of net product sales.

Pfizer and we initiated a Phase 1/2, open label dose-escalation clinical trial of this next-generation hemophilia B product candidate in 2015. We intend to enroll two to five subjects in each of three dose cohorts, injecting our product candidate 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.

SPK-FVIII for the treatment of Hemophilia A

In our SPK-FVIII program for the treatment of hemophilia A, we recently nominated a lead product candidate that has demonstrated production of therapeutic levels of Factor VIII in multiple preclinical models at doses that have been safely delivered to humans in hemophilia B studies. Hemophilia A is the most common form of hemophilia with approximately 140,000 patients worldwide. The only therapies currently available for moderate to severe hemophilia A are intravenously administered FVIII protein or its derivatives. We retain global commercialization rights to the SPK-FVIII program.

Neurodegenerative diseases

SPK-TPP1

SPK-TPP1 is our program for the treatment of TPP1 deficiency, a form of Batten disease that causes severe childhood neurodegenerative disorders that result in motor and mental decline, seizures and visual deficits appearing between ages two and four and is fatal by ages ten to twelve in a majority of cases. The autosomal recessive disease is caused by mutations in the TPP1 gene, leading to a deficiency of the soluble lysosomal enzyme tripeptidyl peptidase 1, or TPP1. TPP1 deficiency also is known as CLN2 disease. We believe there are approximately 750 to 1,000 patients with TPP1 deficiency in the United States and the five major European markets with approximately 100 new cases annually. We believe that neurodegenerative diseases are a significantly underserved market that we are particularly well positioned to address with our gene therapy platform.

In a well-established preclinical model of TPP1 deficiency, administration of our lead product candidate to the ependymal cells of the brain ventricular system resulted in delayed onset of clinical symptoms and disease progression, protection from cognitive decline and extension of lifespan relative to untreated controls. Notably, the study produced effective distribution of the TPP1 enzyme throughout the central nervous system, as evidenced by immunohistochemistry and an enzyme activity assay. We initiated IND-enabling studies for the lead product candidate in our SPK-TPP1 program in 2015.

Other neurodegenerative diseases

We are also conducting preclinical studies on a product candidate for the treatment of Huntington's disease, a hereditary genetic disorder that we believe affects over 60,000 patients in the United States and the five major European markets. We have multiple other neurodegenerative disease programs in various stages of 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 biosynthesis using the natural

Table of Contents

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 also are receiving Protocol Assistance and Scientific Advice from EMA. Prior to BLA approval of SPK-RPE65, 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. We also are evaluating potential development programs using lentiviral gene therapies.

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.

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,

Table of Contents

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 December 2015, our patent portfolio included approximately 230 U.S. and foreign patents and patent applications licensed from CHOP, UIRF, Penn and NIH. Our patent portfolio also includes patent applications that we have filed on our own technologies, including technologies related to our hemophilia A program. The patents and patent applications in our patent portfolio cover technology used in our own development programs, as well as technology used in our collaboration with Pfizer. 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 family relates to manufacture of our own product candidates as well as the product candidates and development programs that are the subject of our collaboration with Pfizer, 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, Hong Kong 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 pending in the United States, Australia, Brazil, Canada, China, Europe, India, Israel, Japan, Mexico, Russia, South Africa and South Korea. 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.

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

In December 2015, we converted a co-exclusive in-license from Penn of certain rights to 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 to an exclusive license in the field of use related to the treatment of retinal disorders or diseases caused by a mutation or mutations in the RPE65 gene. 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.

Table of Contents

We also in-licensed from CHOP U.S. and Patent Cooperation Treaty, or 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 from Penn that relates to a certain plasmid used in the manufacture of SPK-CHM. This patent will expire in 2032 excluding any potential patent term extensions or adjustments. A continuing patent application of this patent is pending.

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.

- 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.

- A U.S. patent application relating to modified FIX expression cassettes. We expect any patents issuing from this application will expired in 2036, 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 96 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.

25

Table of Contents

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 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. In December 2015, we earned a $15.0 million milestone payment and also are eligible to receive up to an additional $245.0 million in aggregate milestone payments under the agreement, $125.0 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.

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.

Table of Contents

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 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 June 30, 2018 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 amended this agreement in March 2016 to extend the expiration date for services other than the supply of SPK-RPE65 vectors. 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.

We also entered into an additional licensing agreement with CHOP in November 2015. The licensing agreement supplements our existing license agreement with CHOP by granting us a worldwide exclusive license, with the right to sublicense, to use and practice a provisional patent application related to the production of gene therapies on substantially the same terms and conditions as the existing agreement.

University of Pennsylvania

In December 2015, we converted a co-exclusive license agreement to certain patent rights with Penn, Cornell University and the University of Florida relating 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 to an exclusive license in the field of use related to the treatment of retinial disorders or diseases caused by a mutation or mutations in the RPE65 gene. Penn can no longer grant an additional license to a third party with same scope of rights that we have received under our amended license agreement with Penn, including a right to commercialize products covered by the licensed patent rights.

Table of Contents

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. 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 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 December 2013, we entered into our a license agreement with UIRF, which we amended in January 2016 to expand the list of patent and patent applications to which we have rights. Under the license agreement, as amended, UIRF granted us an exclusive worldwide license, with the right to sublicense, to a portfolio of approximately 96 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

Table of Contents

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.

Clearside Biomedical

In April 2015, we entered into a research, license and option agreement with Clearside Biomedical, Inc., or Clearside, under which we entered into a research collaboration with Clearside and acquired an option to obtain an exclusive license to Clearside's microinjector technology to develop and commercialize gene therapy products delivered using the Clearside technology. Under the agreement, the companies will explore the feasibility of using Clearside's microinjector technology to deliver viral vectors to the choroid and the retina through the suprachoroidal space. In connection with this agreement, we made an upfront payment of $0.5 million for services to be rendered in the development of licensed products. During the year ended December 31, 2015, we recorded $0.5 million as research and development expense related to the upfront payment.

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.

We are aware of companies focused on developing gene therapies in various indications, including bluebird bio, Inc., Annapurna Therapeutics, Applied Genetic Technologies Corporation, or AGTC, Asklepios BioPharmaceutical, Inc., Audentes Therapeutics, Inc., Avalanche Biotechnologies, Inc., AveXis, Inc., Abeona Therapeutics Inc., Baxalta Incorporated, Dimension Therapeutics, Inc., GenSight Biologics SA, Horama SAS, Lysogene SAS, MeiraGTx Limited, NightstaRx Ltd., ReGenX Biosciences, LLC, uniQure N.V. and Voyager Therapeutics, Inc. 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:

- SPK-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 patients. QLT Inc. completed a Phase 1b clinical trial of a vitamin A derivative to treat RP and LCA. In the gene therapy space, certain companies and several academic institutions have conducted or plan to conduct clinical trials involving RPE65-based product candidates. To date, none of these

organizations has completed a trial involving injection of a subject’s second eye or has initiated a Phase 3 trial.

- SPK-CHM. We are aware that NightstaRx Ltd. is developing an AAV-based gene therapy for the treatment of choroideremia. NightstaRx Ltd. has obtained orphan product designation in the United States and the European Union for this product candidate for the treatment of choroideremia and is conducting a Phase 1/2 trial.

Table of Contents

- SPK-FIX. 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 Baxalta Incorporated, Dimension Therapeutics Inc. and uniQure N.V.

- SPK-FVIII. The only therapies currently available for moderate to severe hemophilia A are intravenously administered FVIII protein or its derivatives. The main competitors with product candidates under development to treat hemophilia A include Baxalta Incorporated, BioMarin Pharmaceutical Inc., Dimension Therapeutics Inc. in collaboration with Bayer HealthCare, uniQure N.V., Sangamo Biosciences, Inc., Telethon Institute for Gene Therapy in collaboration with Biogen Inc., Alnylam Incorporated, Novo Nordisk A/S and Roche Holding AG.

- SPK-TPP1. While there are currently no approved curative therapies for Batten disease, there are a number of companies and academic centers developing enzyme replacement, cell and gene therapies for TPP1 deficiency, including BioMarin Pharmaceuticals Inc., StemCells, Inc. and the Weill Medical College of Cornell University.

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.

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;

Table of Contents

- 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 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.

Table of Contents

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.

- 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.

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

Table of Contents

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.

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, 2016, the user fee for an application requiring clinical data, such as a BLA, is $2,374,200. PDUFA also imposes an annual product fee for biologics ($114,450) and an annual establishment license fee ($585,200) 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.

Table of Contents

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.

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

Table of Contents

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.

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 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,

Table of Contents

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 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 State's 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.

Table of Contents

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 a marketing authorization application, or 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.

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.

Table of Contents

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 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.

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

Table of Contents

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.

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 March 4, 2016, we had 113 full-time employees, including a total of 39 employees with M.D. or Ph.D. degrees. Of our workforce, 52 employees are engaged in research and development, 32 employees are engaged in manufacturing and 29 employees are engaged in finance, legal, commercial, human resources and general management. None of our employees are 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. We also occupy approximately 14,000 square feet of office space in Philadelphia, Pennsylvania under a sublease that expires in November 2018. In addition, we lease approximately 3,400 square feet of office space in Waltham, Massachusetts, which expires in September 2016. In

Table of Contents

February 2016, we entered into a lease for approximately 6,500 square feet of additional office space in Philadelphia for corporate and commercial purposes that expires in 2021.

Corporate Information

We were incorporated in the State of Delaware on March 13, 2013. Our principal executive offices are located at 3737 Market Street Suite 1300 Philadelphia, PA, and our telephone number is (888) 772-7560.

Our corporate website address is www.sparktx.com. Our website is an inactive textual reference and nothing on our website is incorporated by reference in this Annual report. Our Annual Report on Form 10-K, Quarterly Reports on Form 10-Q, Current Reports on Form 8-K, and amendments to reports filed pursuant to Sections 13(a) and 15(d) of the Securities Exchange Act of 1934, as amended, or the Exchange Act, are available free of charge on our website as soon as reasonably practicable after we electronically file such material with, or furnish it to, the Securities and Exchange Commission. The Securities and Exchange Commission maintains an internet site that contains our public filings with the Securities and Exchange Commission and other information regarding our company, at www.sec.gov. These reports and other information concerning our company may also be accessed at the Securities and Exchange Commission's Public Reference Room at 100 F Street, NE, Washington, DC 20549. The public may obtain information on the operation of the Public Reference Room by calling the Securities and Exchange Commission at 1-800-SEC-0330. The contents of these websites are not incorporated into this Annual Report. Further, our references to the URLs for these websites are intended to be inactive textual reference only.

Legal proceedings

We are not currently a party to any material legal proceedings.

Table of Contents

Item 1A. Risk Factors

The following risk factors and other information included in this Annual Report on Form 10-K should be carefully considered. The risks and uncertainties described below are not the only ones we face. Additional risks and uncertainties not presently known to us or that we presently deem less significant may also impair our business operations. Please see page 5 of this Annual Report on Form 10-K for a discussion of some of the forward-looking statements that are qualified by these risk factors. If any of the following risks occur, our business, financial condition, results of operations and future growth prospects could be materially and adversely affected.

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 losses were $24.3 million and $47.1 million for the year ended December 31, 2014 and 2015, respectively. As of December 31, 2015, we had an accumulated deficit of $128.7 million. We have financed our operations primarily through private placements of our preferred stock, our IPO, which closed on February 4, 2015, and a follow-on offering, which closed on December 21, 2015. We received net proceeds from the IPO and follow-on offering of $268.3 million, after deducting underwriting discounts and commissions and other offering expenses payable by us. 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:

- 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;
- continue our clinical development of our product candidates, including our Phase 1/2 clinical trials for SPK-CHM and SPK-FIX;
- initiate additional preclinical studies and clinical triails for our other product candidates;
- seek to identify additional product candidates;
- validate a commercial-scale current good manufacturing practices, or cGMP, manufacturing facility;
- further develop our gene therapy platform;
- expand our medical affairs capabilities;
- 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.

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 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 our stockholders to lose all or part of their 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:

Table of Contents

- 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
- 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.

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

We were 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 obtain marketing approvals, manufacture a commercial-scale product or conduct sales and marketing activities necessary for successful commercialization. Consequently, any predictions stockholders 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.

We may 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, we expect to

continue 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 December 31, 2015, our cash and cash equivalents were $293.5 million. Our research and development expenses increased from $16.4 million for the year ended

Table of Contents

December 31, 2014 to $46.0 million for the year ended December 31, 2015. We estimate that our cash and cash equivalents as of December 31, 2015 will enable us to fund our operating expenses and capital expenditure requirements into 2019.

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

- the costs of preparing and filing a BLA with FDA and an MMA with EMA for SPK-RPE65;
- the cost and our ability to establish commercial infrastructure and manufacturing capabilities required to support the launch of SPK-RPE65;
- whether additional clinical testing is required to secure regulatory approvals for all intended or desired indications of SPK-RPE65;
- the scope, progress, results and costs of drug discovery, recruitment, 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;
- revenue, if any, received from commercial sale of our products, including amounts reimbursed by government and third party payors 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 for a genetic disease 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, European Medicines Agency, or 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

Table of Contents

studied product candidates. Only one gene therapy product for a genetic disease, uniQure N.V.'s Glybera, 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 the 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 U.S. National Institutes of Health, or NIH, also potentially are subject to review by the NIH office of Biotechnology Activities' Recombinant DNA Advisory Committee, or 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 Investigational New Drug exemption, or 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.

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 RPE65 mutations, 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.

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 clinical trials, including our Phase 3 clinical trial for SPK-RPE65, to provide clinically meaningful results.

There are no pharmacologic therapies approved to treat IRDs 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

Table of Contents

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 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. 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 FDA or EMA will not have additional questions or comments with respect to our data analyses or any of the endpoints of our Phase 3 trial or that we will adequately address any questions or comments that they may have.

We developed a mobility test of functional vision 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 used 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. Through continuing dialogue pursuant to the breakthrough therapy designation of SPK-RPE65, we modified the designation of pupillary light reflex to be an exploratory endpoint and the analysis of the mobility test change score for an assigned first eye became a secondary endpoint, resulting in three secondary endpoints: full-field light sensitivity threshold testing, the assigned first eye mobility test change score and visual acuity.

Even though we achieved statistical significance in the pre-specified primary mobility test endpoint and the first two secondary efficacy endpoints, FDA has discretion to reserve judgment on whether the endpoints and the change scores seen in our trial sufficiently demonstrate clinical meaningfulness, including the weight FDA places on the secondary endpoint visual acuity, which was not met to a degree of statistical significance, until FDA reviews our BLA. 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 were balanced as to age, there is a risk that regulators may question whether subjects at this age could demonstrate improvement in the mobility test 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. As a result of any of the above, FDA may decide that our results are not clinically meaningful 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.

Table of Contents

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 limited safety and no clinical efficacy data for the use of SPK-CHM or SPK-FIX in humans. In addition, we have no clinical data demonstrating either the safety or efficacy of our current SPK-FVIII or SPK-TPP1 product candidates in humans. There can be no assurance that the success we achieved in the preclinical studies for any of our product candidates ultimately will result in success in our planned clinical trials. In addition, there can be no assurance that we will be able to achieve the same or similar success in our preclinical studies and clinical trials of our other product candidates.
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 prior hemophilia trials, and we may experience similar delays in any of our current or future clinical trials. In addition, the small number of patients with Batten disease and efforts by competitors to conduct clinical trials for their product candidates in the same indication may hamper our ability to enroll a sufficient number of patients in any future clinical trials of SPK-TPP1. 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.

Table of Contents

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 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 Institutional Review Board, or 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;
- 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

47

Table of Contents

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.

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 any potential 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.

Table of Contents

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.

We may be unable to obtain additional orphan drug designations or orphan drug exclusivity for any product. 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 both LCA and RP due to RPE65 mutations. SPK-CHM has 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 current or future 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 and FDA for its product candidate for the treatment of choroideremia that is in a Phase 1/2 clinical trial.

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 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

Table of Contents

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.

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

Table of Contents

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 European Union, 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, SPK-CHM and SPK-FIX 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.

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

Table of Contents

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.

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 companies focused on developing gene therapies in various indications, including bluebird bio, Inc., Annapurna Therapeutics, Applied Genetic Technologies Corporation, Asklepios BioPharmaceutical Inc., Audentes Therapeutics, Inc., Avalanche Biotechnologies, Inc., AveXis, Inc., Abeona Therapeutics Inc., Baxalta Incorporated, Dimension Therapeutics, Inc., GenSight Biologics S.A., Horama SAS, Lysogene SAS, MeiraGTx Limited, NightstaRx Ltd., REGENEXBIO Inc., uniQure N.V. and Voyager Therapeutics, Inc., 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 programs, the main competitors include:

- SPK-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. completed a Phase 1b clinical trial of a vitamin A derivative to treat RP and LCA. In the gene therapy space, certain companies and several academic institutions have conducted or plan to conduct clinical trials involving RPE65-based product candidates. To date, none of these organizations has completed a trial involving injection of a subject's second eye or has initiated a Phase 3 trial.
- SPK-CHM. We are aware that NightstaRx Ltd. is developing an AAV-based gene therapy for the treatment of choroideremia. NightstaRx Ltd. has been granted orphan product designation by the European Commission and FDA for this product candidate for the treatment of choroideremia and is conducting a Phase 1/2 trial.
- SPK-FIX. 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 Baxalta Incorporated, Dimension Therapeutics, Inc. and uniQure N.V.
- SPK-FVIII. The only therapies currently available for moderate to severe hemophilia A are intravenously administered FVIII protein or its derivatives. The main competitors with product candidates under development to treat hemophilia A include Baxalta Incorporated, BioMarin Pharmaceutical Inc., Dimension Therapeutics Inc. in collaboration with Bayer HealthCare, uniQure N.V., Sangamo Biosciences, Inc., Telethon Institute for Gene Therapy in collaboration with Biogen Inc., Alnylam Incorporated, Novo Nordisk A/S and Roche Holding AG.
- SPK-TPP1. While there are currently no approved curative therapies for Batten disease, there are a number of companies and academic centers developing enzyme replacement, cell and gene therapies for TPP1 deficiency, including BioMarin Pharmaceuticals Inc., StemCells, Inc. and the Weill Medical College of Cornell University.

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.

Table of Contents

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 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 licensing and collaboration agreements with third parties, including our collaboration agreement with Pfizer for the development and commercialization of SPK-FIX 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, into which we entered 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.

We may potentially enter into additional collaborations with third parties in the future. Our relationships with collaborators, including Pfizer, 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;

- we may not achieve any milestones, or receive any milestone payments, under our collaborations, including milestones and/or payments that we expect to achieve or receive;
- 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;

Table of Contents

- 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;
- 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
- 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 "Risk Factors" section 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

Table of Contents

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.

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 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 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 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

Table of Contents

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.

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.

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. We currently have a manufacturing agreement with CHOP, which we recently amended this agreement to provide for continued production of our current and future early stage clinical trials for our other product candidates. Under certain circumstances, CHOP is entitled to terminate its 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.

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 fail 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.

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.

Table of Contents

Because we currently rely on CHOP and other third parties to manufacture certain 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.

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

Table of Contents

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 that specialize in treating IRDs, 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.

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

Table of Contents

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.

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 used. 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 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;

Table of Contents

- 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 for a genetic disease to date in the United States and only one gene therapy product for a genetic disease 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 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.

60

Table of Contents

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 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 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.

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

Table of Contents

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 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:

Table of Contents

- 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); 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, presently governed by the provisions of the Data Protection Directive will be replaced with the General Data Protection Regulation, or GDPR, which is currently going through the adoption process. The GDPR will impose several requirements relating to the consent of the individuals to whom the personal data relates, the information provided to the individuals, the security and confidentiality of the personal data, data breach notification and using third party processors in connection with the processing of the personal data. The GDPR will also

Table of Contents

impose 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 GDPR and the applicable national data protection laws of the European Union Member States may result in fines and other administrative penalties. The GDPR will introduce substantial fines for breaches of the data protection rules. It is expected to be formally adopted in 2016 and to become enforceable in 2018. Once it is enforceable, the GDPR may increase our responsibility and liability in relation to personal data that we process. To comply with the new data protection rules imposed by the GDPR we may be required to put in place additional mechanisms ensuring compliance. 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, 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.

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

Table of Contents

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.

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 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.

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.

Table of Contents

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.

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 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, as well as license agreements with Clearside, 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.

Table of Contents

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;
- 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.

Table of Contents

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 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 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.

Table of Contents

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 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, our SPK-RPE65, SPK-CHM, SPK-FIX, SPK-FVIII, and SPK-TPP1 programs. 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 product candidates in our SPK-RPE65, SPK-CHM, SPK-FIX, SPK-FVIII, and SPK-TPP1 programs or any 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

Table of Contents

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 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 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

Table of Contents

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." On December 6, 2014, a memorandum entitled "2014 Interim Guidance on Subject Matter Eligibility" was published. On July 30, 2015, an update pertaining to patent subject matter eligibility was published by the USPTO. 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 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.

There can be no assurance 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

Table of Contents

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 allowed trademark applications with the USPTO for the mark "SPARK" and the Spark logo, however, a valid statement of use must be filed for such applications to issue as registered trademarks. Whether allowed or 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 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 ownership of our common stock

Our executive officers, directors and principal stockholders maintain the ability to exert substantial control over matters submitted to stockholders for approval.

As of March 4, 2016, our executive officers, directors and principal stockholders, in the aggregate, beneficially own shares representing approximately 38.4% of our outstanding capital stock. As a result, if these stockholders were to act together, they would be able to exert substantial control over 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

Table of Contents

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.

A significant number of our total outstanding shares may be sold into the market in the near future, which could cause the market price of our common stock to drop significantly, 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. 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. All lock-up agreements entered into in connection with our following-on offering expire on March 14, 2016. Our outstanding shares of common stock may be freely sold in the public market at any time to the extent permitted by Rules 144 and 701 under the Securities Act of 1933, as amended, or the Securities Act, or to the extent such shares have already been registered under the Securities Act and are held by non-affiliates of ours. Moreover, as of March 4, 2016, holders of a substantial number of shares of our common stock 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. In January 2015, we filed a registration statement registering all shares of common stock that we may issue under our equity compensation plans. As of March 4, 2016, we had outstanding options to purchase an aggregate of 4,001,578 shares of our common stock, of which options to purchase 738,539 were vested. These shares can be freely sold in the public market upon issuance, subject to volume limitations and black-out periods applicable to affiliates.

In addition, certain of our employees, executive officers, directors and affiliated stockholders, including Sofinnova Venture Partners VIII, L.P., have entered or may enter into Rule 10b5-1 plans providing for sales of shares of our common stock from time to time. Under a Rule 10b5-1 plan, a broker executes trades pursuant to parameters established by the employee, director or officer when entering into the plan, without further direction from the employee, officer, director or affiliated stockholder. A Rule 10b5-1 plan may be amended or terminated in some circumstances. Our employees, executive officers, directors and affiliated stockholders also may buy or sell additional shares outside of a Rule 10b5-1 plan when they are not in possession of material, nonpublic information.

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 relies, in part, on the research and reports that industry or financial analysts publish about us or our business. If no additional analysts commence coverage of us, the trading price of our stock could decrease. In addition, although we have obtained 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 or fail to regularly publish reports on us, 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 our stockholders.

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, our stockholders may not be able to sell their shares of common stock at or above the price they paid for their shares. 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;

Table of Contents

- 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.

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 be sustained.

Our shares of common stock began trading on the NASDAQ Global Select Market on January 30, 2015. Given the limited trading history of our common stock, there is a risk that an active trading market for our shares may not continue to develop or be sustained. If an active market for our common stock does not continue to develop or is not sustained, it may be difficult for our stockholders to sell shares without depressing the market price for the shares, or at all.

We have broad discretion in the use of our cash and cash equivalents and may not use them effectively.

Our management has broad discretion in the application of our cash and cash equivalents and could spend these funds 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 in a manner that does not produce income or that loses value.

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) December 31, 2020; (iii) the date on which we have issued more than $1 billion in nonconvertible debt during the previous three years; or (iv) the date on which we are deemed to be a large accelerated filer under the rules of the 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.

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 Annual Report on Form 10-K. 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.

Table of Contents

We incur increased costs as a result of operating as a public company, and our management is now required to devote substantial time to new compliance initiatives.

As a public company we incur, and particularly after we are no longer an EGC, we will incur further, 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 devote a substantial amount of time to these compliance initiatives. Moreover, these rules and regulations have increased our legal and financial compliance costs and will make some activities more time-consuming and costly.

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 may discourage, delay or prevent a merger, acquisition or other change in control of us that stockholders may consider favorable, including transactions in which stockholders might otherwise receive a premium for their 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 stockholders' sole source of gain.

Table of Contents

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 stockholders' sole source of gain for the foreseeable future.

Item 1B. Unresolved Staff Comments.

None.

Item 2. Properties

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. We also occupy approximately 14,000 square feet of office space in Philadelphia, Pennsylvania under a sublease that expires in November 2018. In addition, we occupy approximately 3,400 square feet of office space in Waltham, Massachusetts under a lease that expires in September 2016. In February 2016, we entered into a lease for approximately 6,500 square feet of additional office space in Philadelphia for corporate and commercial purposes that expires in 2021.

Item 3. Legal Proceedings

We are not currently subject to any material legal proceedings.

Item 4. Mine Safety Disclosures.

Not applicable.

Table of Contents

PART II.

Item 5. Market for Registrant's Common Equity, Related Stockholder Matters and Issuer's Purchase of Equity Securities

Our common stock has been publicly traded on NASDAQ Global Market under the symbol "ONCE" since January 30, 2015. Prior to that time, there was no public market for our common stock. The following table shows the high and low sale prices per share of our common stock as reported on the Nasdaq Global Select Market for the periods indicated:

	High	Low
2015		
First Quarter (beginning January 30, 2015)	$79.50	$40.16
Second Quarter	78.48	47.01
Third Quarter	71.75	36.96
Fourth Quarter	61.91	39.62
2016		
First Quarter (through March 4, 2016)	$44.71	$21.20

On March 4, 2016, the last reported sale price for our common stock on the Nasdaq Global Select Market was $34.53 per share.

Holders

As of March 4, 2016, there were approximately 19 holders of record of our common stock. This number does not include beneficial owners whose shares are held by nominees in the street name.

Dividends

We have not declared or paid any cash dividends on our common 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.

Information about our equity compensation plans

Information required by Item 5 of Form 10-K regarding our equity compensation plans is incorporated herein by reference to Item 12 of Part III of this Annual Report on Form 10-K.

Recent Sales of Unregistered Securities

We did not sell any shares of our common stock or our preferred stock, or grant any stock options or restricted stock awards, during the year ended December 31, 2015 that were not registered under the Securities Act of 1933, as amended, or the Securities Act, and that have not otherwise been described in a Quarterly Report on Form 10-Q.

Purchase of equity securities

We did not purchase any of our registered equity securities during the period covered by this Annual Report on Form 10-K.

Use of proceeds from registered securities

On February 4, 2015, we closed our initial public offering of 8,050,000 shares of our common stock, including 1,050,000 shares of our common stock pursuant to the exercise by the underwriters of an option to purchase additional shares, at a public offering price of $23.00 per share for an aggregate offering of approximately $185.2 million. The offer and sale of all of the shares in the offering were registered under the Securities Act pursuant to registration statement on Form S-1 (File No. 333-201318), which was declared effective by the SEC on January 29, 2015, and registration statement on Form S-1 MEF (File No. 333-201764) filed pursuant to Rule 462(b) of the Securities Act. J.P. Morgan Securities LLC and Credit Suisse

77

Table of Contents

Securities (USA) LLC acted as joint book-running managers for the offering and as representatives of the underwriters. Cowen and Company, LLC acted as lead manager and Sanford C. Bernstein & Co., LLC acted as co-manager. The offering commenced on January 29, 2015 and did not terminate until the sale of all of the shares offered.

We received aggregate net proceeds from the offering of $168.9 million, after deducting underwriting discounts and commissions and other estimated offering expenses payable by us. None of the underwriting discounts and commissions or other offering expenses were incurred or paid to directors or officers of ours or their associates or to persons owning 10% or more of our common stock or to any affiliates of ours.

There has been no material change in our planned use of the net proceeds from the offering as described in our final prospectus filed with the SEC pursuant to Rule 424(b) under the Securities Act. As of December 31, 2015, the entire amount of the net proceeds is included as cash and cash equivalents.

Table of Contents

Item 6. Selected Financial Data

The following selected financial data should be read together with our financial statements and the related notes appearing elsewhere in this Annual Report on Form 10-K and the "Management's Discussion and Analysis of Financial Condition and Results of Operations" section of this Annual Report on Form 10-K. We have derived the statements of operations data for the period from March 13, 2013 (inception) to December 31, 2013 and for the years ended December 31, 2014 and 2015 and the balance sheet data at December 31, 2014 and 2015, from our audited financial statements included elsewhere in this Annual Report on Form 10-K. 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	Year ended December 31, 2014	Year ended December 31, 2015
	(in thousands, except per unit/share data)		
Statement of operations data:			
Revenues	$—	$634	$22,064
Operating expenses:			
Research and development	4,897	16,351	46,030
Acquired in-process research and development	50,000	750	—
General and administrative	2,381	7,863	23,352
Total operating expenses	57,278	24,964	69,382
Loss from operations	(57,278)	(24,330)	(47,318)
Interest income	—	5	192
Net loss	(57,278)	(24,325)	(47,126)
Preferred stock dividends	—	(707)	(635)
Net loss applicable to common stockholders	$(57,278)	$(25,032)	$(47,761)
Basic and diluted net loss per common unit/share (1)	$(8.44)	(2) $(4.64)	$(2.10)
Weighted average basic and diluted common units/shares outstanding (1)	6,788,396	(2) 5,397,599	22,710,105

(1) See Note 3(j) to our audited financial statements 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

(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.

	December 31, 2014	2015
	(in thousands)	
Balance sheet data:		
Cash and cash equivalents	$74,567	$293,531
Working capital	$61,509	$289,492
Total assets	$90,446	$329,773
Total preferred stock (3)	$82,437	$—
Total stockholders' equity	$55,206	$290,538

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

Table of Contents

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

The following discussion and analysis of our financial condition and results of operations should be read together with our financial statements and related notes appearing in this Annual Report on Form 10-K. Some of the information contained in this discussion and analysis or set forth elsewhere in this Annual Report on Form 10-K, including information with respect to our plans and strategy for our business includes forward-looking statements that involve risks and uncertainties. As a result of many factors, including those factors set forth under Item 1A "Risk Factors" and under "Forward-Looking Statements" of this Annual Report on Form 10-K, 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 "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. 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 recently reported statistically significant results in a pivotal Phase 3 clinical trial of our first product candidate targeting rare genetic blinding conditions, which has received both breakthrough therapy and orphan product designation. Based on these positive results, we intend to submit a Biologics License Application, or BLA, for this product candidate with the U.S. Food and Drug Administration, or FDA, in the second half of 2016 as the first step in executing our global regulatory and commercialization strategy.

We also have built a pipeline of product candidates targeting multiple rare blinding conditions, hematologic disorders and neurodegenerative diseases. Our pipeline includes: a product candidate targeting another rare genetic blinding condition currently in a Phase 1/2 clinical trial; product candidates for the treatment of hemophilia with a hemophilia B product candidate currently in a Phase 1/2 clinical trial in collaboration with Pfizer Inc., or Pfizer, and a preclinical product candidate for hemophilia A; a product candidate for the treatment of TPP1 deficiency, a form of Batten disease, for which we commenced Investigational New Drug application, or IND, enabling studies in 2015; and other ophthalmic, hematologic and neurodegenerative disease programs.

Our most advanced product candidate, SPK-RPE65 (voretigene neparvovec), is intended to treat genetic blinding conditions called inherited retinal diseases, 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, notably night blindness, or nyctolopia, that make independent activities of daily living challenging and ultimately lead to blindness. 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.

We are pursuing other 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. CHM ultimately results in blindness. We have completed enrollment of subjects in the second cohort of our dose escalating Phase 1/2 trial for SPK-CHM. To date, SPK-CHM has been well tolerated and we have not observed any product candidate-related serious adverse events in this trial. We have received orphan product designation for SPK-CHM for the treatment of CHM in both the United States and the European Union.

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 received a $20.0 million upfront payment in 2014, earned a $15 million milestone payment in December 2015 and are eligible to receive up to an additional $245.0 million in aggregate milestone payments, as well as royalties calculated as a low-teen percentage of net product sales. Pfizer and we initiated a Phase 1/2 clinical trial of

our lead SPK-FIX product candidate in 2015.

In our SPK-FVIII program for the treatment of hemophilia A, we recently nominated a lead product candidate that has demonstrated production of therapeutic levels of Factor VIII in multiple preclinical models at doses that have been safely delivered to humans in hemophilia B studies. We retain global commercialization rights to the SPK-FVIII program.

We are developing a lead neurodegenerative disease product candidate in our SPK-TPP1 program that has demonstrated compelling preclinical proof-of-concept data for the treatment of TPP1 deficiency, a form of Batten disease, a fatal neurological

Table of Contents

disorder involving mutations of the TPP1 gene, also known as the CLN2 gene, that begins in early childhood. We initiated IND-enabling studies for our lead SPK-TPP1 product candidate in 2015.

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 they deliver a functional gene that allows production of a normal protein.

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 The Children's Hospital of Philadelphia, or CHOP, and 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.

We have never been profitable and have incurred net losses since inception. We have an accumulated deficit of $128.7 million as of December 31, 2015. 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. For the years ended December 31, 2014 and 2015, we incurred $16.4 million and $46.0 million of research and development expenses, respectively, and $7.9 million and $23.4 million of general and administrative expenses, respectively.

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 December 31, 2015, we have received aggregate net proceeds from sales of our equity securities, after deducting underwriting discounts and commissions and other offering expenses payable by us, of $350.7 million. On February 4, 2015, we closed our initial public offering, or IPO, whereby we sold 8,050,000 shares of common stock, inclusive of 1,050,000 shares of common stock sold by us pursuant to the full exercise of an overallotment option granted to the underwriters in connection with the offering, at a price to the public of $23.00 per share. Our shares began trading on January 30, 2015. The aggregate net proceeds received by us from the IPO were $168.9 million, net of underwriting discounts and commissions and offering expenses payable by us. Upon the closing of the IPO, all outstanding shares of convertible preferred stock, including accrued dividends, converted into 10,200,500 shares of common stock.

On December 28, 2015, we closed a follow-on offering whereby we sold 2,266,995 shares of common stock at a price to the public of $47.00 per share. The aggregate net proceeds received by us from the follow-on offering were $99.4 million, net of underwriting discounts and commissions and offering expenses payable by us.

Financial operations overview

Revenue

To date, we have not generated any revenues from product sales. Our revenues have been derived from collaboration agreements.

In March 2014, we entered into a development and manufacturing agreement with Genable Technologies Ltd, 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 RP, or RHO-adRP. RHO-adRP is an IRD that is a genetic subtype of RP that results in severe vision loss and often blindness. Under the agreement, 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 years ended December 31, 2014 and 2015, we recognized $20,000 and $0.9 million, respectively, of revenue from Genable. In March 2016, we acquired Genable, See Note 13 in our Notes to Financial Statements for more information.

Table of Contents

In April 2014, we entered into discussions with a pharmaceutical company concerning a potential manufacturing technology agreement. We received a one-time, nonrefundable payment of $1.0 million for engaging in due diligence. We concluded discussions on a potential arrangement with the pharmaceutical company in the first quarter of 2015 and, as a result, we recognized the nonrefundable payment of $1.0 million as revenue in the year ended December 31, 2015.

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. In December 2015, we earned a $15.0 million milestone payment. During the years ended December 31, 2014 and 2015, we recognized $0.6 million and $20.2 million, respectively, of revenue, as of December 31, 2015, there was $5.2 million and $9.0 million of current and long-term deferred revenue, respectively, included on our balance sheet related to this 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 internal and external costs incurred for the development of our product candidates, which include:

- employee-related expenses, including salaries, benefits, travel and other compensation expenses, including stock-based compensation;
- 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 for the portion of our facilities related to research and development.

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.

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 non-IND studies required to support the SPK-RPE65 program, including a natural history study;
- expanding our medical affairs group;
- certain pre-launch activities for SPK-RPE65;
- proposed regulatory submissions for SPK-RPE65;
- the 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, TPP1 deficiency and other liver and neurodegenerative diseases; and
- continued acquisition and manufacture of clinical trial materials in support of our clinical trials.

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;

82

Table of Contents

- 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" in this Annual Report on Form 10-K.

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 product candidates. We also anticipate continued increases in 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 December 31, 2014 and 2015, 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, revenues 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 Annual Report on Form 10-K, 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 primarily from our Pfizer agreement. 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

Table of Contents

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.

Non-refundable license fees are recognized as revenue when we have a contractual right to receive such payments, 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 under collaboration agreements 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 based on estimates of the services received and efforts expended 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 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

We issue stock-based awards to employees and non-employees, generally in the form of stock options. We account for our stock-based awards in accordance with FASB ASC Topic 718, Compensation-Stock Compensation, or ASC 718. ASC 718 requires all stock-based payments to employees, including grants of employee stock options and modifications to existing stock options, to be recognized in the statements of operations based on their fair values. We account for stock-based awards to non-employees in accordance with FASB ASC Topic 505-50, Equity-Based Payments to Non-Employees, which requires the fair value of the award to be remeasured at fair value as the award vests.

Our stock-based awards are subject to either service or performance-based vesting conditions. Compensation expense related to awards to employees and directors with service-based vesting conditions is recognized on a straight-line basis based on the grant date fair value over the associated service period of the award, which generally is the vesting term. Compensation expense related to awards to non-employees with service-based vesting conditions is recognized on the then-current fair value at each financial reporting date prior to the measurement date over the associated service period of the award, which generally is the vesting term, using the accelerated attribution method. Compensation expense related to awards to non-employees with performance-based vesting conditions is recognized based on the then-current fair value at each financial reporting date prior to the measurement date over the requisite service period using the accelerated attribution method to the extent achievement of the performance condition is probable.

Described below is the methodology we have utilized in measuring stock-based compensation expense. Following the consummation of our IPO, stock option values have been determined based on the quoted market price for our common stock.

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

Table of Contents

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

As a privately held company prior to January 2015 with a limited operating history, we used 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 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 the 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 was no public market for our common stock prior to January 2015, the estimated fair value of our common stock had 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 have elected to not take advantage of the extended transition period afforded by the JOBS Act for the implementation of new or revised accounting standards and, as a result, will comply with new or revised accounting standards on the relevant dates on which adoption of such standards is required for non-EGCs.

Subject to certain conditions, as an EGC, we intend to rely on certain exemptions under the JOBS Act, including without limitation (i) from the requirement to provide 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) from 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) December 31, 2020; (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.

85

Table of Contents

Results of operations

Comparison of the period from March 13, 2013 (inception) to December 31, 2013 and the year ended December 31, 2014

	Period from March 13, 2013 (inception) to December 31, 2013	Year ended December 31, 2014
	(in thousands)	
Revenues	$—	$634
Operating expenses:		
Research and development	4,897	16,351
Acquired in-process research and development	50,000	750
General and administrative	2,381	7,863
Total operating expenses	57,278	24,964
Loss from operations	(57,278)	(24,330)
Interest income	—	5
Net loss	$(57,278)	$(24,325)

Revenues

We did not recognize any revenue in 2013. In the year ended December 31, 2014, we recognized $0.6 million of revenue, primarily associated with our Pfizer agreement.

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 year ended December 31, 2014 were $16.4 million. The $11.5 million increase was due to a $7.4 million increase in internal research and development expenses, due primarily to significantly increased headcount, and a $4.0 million increase in external research and development expenses, primarily for clinical trials for SPK-RPE65 and SPK-CHM and a predecessor product candidate under our SPK-FIX program, as well as preclinical studies for our SPK-CHM and SPK-FIX programs and research and development of other product candidates.

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 year ended December 31, 2014:

	Period from March 13, 2013 (inception) to December 31, 2013	Year ended December 31, 2014
	(in thousands)	
External research and development expenses:		
SPK-RPE65	$4,038	$4,404
SPK-CHM	230	915
SPK-FIX	255	2,263
Other product candidates	115	1,090
Total external research and development expenses	4,638	8,672
Total internal research and development expenses	259	7,679
Total research and development expenses	$4,897	$16,351

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 internal research and development expenses in the table above.

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 equity securities, which have since converted into 5.0 million

Table of Contents

shares of our common stock, issued to CHOP and UIRF in consideration for our acquisition and in-license of certain rights and property. Our acquired in-process research and development expense for the year ended December 31, 2014 was $0.8 million. This amount represents the fair value of the vested shares of common stock issued to Penn which are subject to certain milestone-based vesting conditions, in consideration for our acquisition of certain rights and property. We recognized these amounts 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 year ended December 31, 2014 were $7.9 million. General and administrative expenses consist primarily of salaries and related costs, including stock-based compensation, legal and patent costs and other professional fees. The $5.5 million increase primarily was due to increased headcount in 2014.

Comparison of the years ended December 31, 2014 and 2015

	Year ended December 31,	
	2014	2015
	(in thousands)	
Revenues	$634	$22,064
Operating expenses:		
Research and development	16,351	46,030
Acquired in-process research and development	750	—
General and administrative	7,863	23,352
Total operating expenses	24,964	69,382
Loss from operations	(24,330)	(47,318)
Interest income	5	192
Net loss	$(24,325)	$(47,126)

Revenues

In the year ended December 31, 2014 we recognized $0.6 million of revenue primarily associated with our Pfizer agreement. In the year ended December 31, 2015, we recognized $22.1 million in revenue, of which $20.2 million was associated with our Pfizer agreement, and included a $15.0 million milestone payment. The other revenue we recognized was $1.0 million of a non-refundable payment after we concluded discussions on a potential agreement with a pharmaceutical company and $0.9 million in revenue associated with our Genable agreement.

Research and development expenses

Our research and development expenses for the year ended December 31, 2014 were $16.4 million and for the year ended December 31, 2015 were $46.0 million. The $29.6 million increase was due to a $24.3 million increase in internal research and development expenses, due primarily to significantly increased headcount, and an increase of $5.3 million in external research and development expenses, primarily from an increase of $2.1 million in expenses related to clinical trials for SPK-RPE65, SPK-CHM and SPK-FIX, and an increase of $3.2 million for other product candidates to support our advancing and expanding pipeline.

Table of Contents

The following table summarizes our research and development expenses by product candidate or program for the years ended December 31, 2014 and 2015:

	Year ended December 31,	
	2014	2015
	(in thousands)	
External research and development expenses:		
SPK-RPE65	$4,404	$5,096
SPK-CHM	915	2,162
SPK-FIX	2,263	2,513
Other product candidates	1,090	4,286
Total external research and development expenses	8,672	14,057
Total internal research and development expenses	7,679	31,973
Total research and development expenses	$16,351	$46,030

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 internal research and development expenses in the table above.

Acquired in-process research and development expense

Our acquired in-process research and development expense for the year ended December 31, 2014 was $0.8 million. This amount represents the fair value of the vested shares of common stock issued to Penn which are subject to certain milestone-based vesting conditions, in consideration for our acquisition 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. Our acquired in-process research and development expense for the year ended December 31, 2015 was zero.

General and administrative expenses

Our general and administrative expenses for the year ended December 31, 2014 were $7.9 million and for the year ended December 31, 2015 were $23.4 million. General and administrative expenses consist primarily of salaries and related costs, including stock-based compensation, legal and patent costs and other professional fees. The $15.5 million increase primarily was due to increased legal, insurance, professional fees and other operating costs as a result of becoming a public company and increased headcount, including stock-based compensation.

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:

	Period from March 13, 2013 (inception) to December 31, 2013	Year ended December 31, 2014	2015
	(in thousands)		
Net cash provided by (used in):			
Operating activities	$(5,139)	$10,386	$(47,478)
Investing activities	—	(11,697)	(4,522)
Financing activities	5,139	75,878	270,964
Net increase in cash and cash equivalents	$—	$74,567	$218,964

Net cash (used in) provided by operating activities

The net cash used in operating activities was $5.1 million from inception through December 31, 2013, and consisted 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 provided by operating activities was $10.4 million for the year ended December 31, 2014, and consisted of a net loss of $24.3 million adjusted for non-cash items, including the acquired-in-process research and development of $0.8 million, depreciation expense of $0.2 million, stock-based compensation expense of $3.0 million, non-cash rent expense of

Table of Contents

$0.6 million and a net increase in operating assets and liabilities of $30.2 million. The significant items in the change in operating assets and liabilities include an increase in deferred rent of $7.9 million related to our tenant improvement allowance, an increase in deferred revenue of $20.8 million, of which $19.4 million is related to our Pfizer agreement, $0.4 million is related to our Genable agreement and $1.0 million is related to 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 $0.8 million increase in prepaid expenses and other assets.

The net cash used in operating activities was $47.5 million for the year ended December 31, 2015, and consisted of a net loss of $47.1 million adjusted for non-cash items, including depreciation expense of $1.7 million, stock-based compensation expense of $13.6 million, non-cash rent expense of $0.2 million and a net increase in operating assets and liabilities of $15.8 million. The significant items in the change in operating assets and liabilities include a decrease in deferred revenue of $6.6 million, of which $5.2 million is related to our Pfizer agreement, $1.0 million is related to the non-refundable payment received for engaging in due diligence with a potential manufacturing technology partner and $0.4 million is related to our Genable agreement, and an increase of $6.7 million in accounts payable and accrued expenses and an increase of $17.5 million in prepaid expenses and other assets primarily due to the $15.0 million milestone receivable earned from Pfizer in December 2015.

Net cash used in investing activities

Net cash used in investing activities for the year ended December 31, 2014 was $11.7 million consisting of costs related to the purchase of property and equipment.

Net cash used in investing activities for the year ended December 31, 2015 was $4.5 million, consisting of costs related to the purchase of property and equipment.

Net cash provided by financing activities

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 year ended December 31, 2014 was $75.9 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 $1.4 million relating to our IPO in February 2015.

Net cash provided by financing activities for the year ended December 31, 2015 was $271.0 million, consisting of $270.4 million of proceeds from the issuance of common stock in our IPO that closed in February 2015 and our follow-on offering that closed in December 2015, net of expenses paid and $1.1 million from the exercise of stock options during the year. This was partially offset by our repurchase of stock for tax withholding obligations on restricted stock that vested during 2015.

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.

The expected use of our cash and cash equivalents of $293.5 million as of December 31, 2015 represents our intentions based upon our current plans and business conditions, which could change in the future as our plans and business conditions evolve. The amounts and timing of our actual expenditures may vary significantly depending on numerous factors, including the progress of our development programs, the status of, and results from, clinical trials, the potential need to conduct additional clinical trials to obtain approval of our product candidates for all intended indications, as well as any technology acquisitions or additional collaborations into which we may enter with third parties for our product candidates and any unforeseen cash needs. As a result, our management retains broad discretion over the allocation of our existing cash and cash equivalents.

Based on our planned use of our cash and cash equivalents, 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, substantially 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 2019. 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.

Table of Contents

Contractual obligations

The following table summarizes our contractual obligations as of December 31, 2015:

	Payments due by period (in thousands)				
	Total	Less than 1 year	1-3 years	3-5 years	More than 5 years
Operating leases(1)	$18,118	$1,998	$3,903	$3,425	$8,792
Total(2)	$18,118	$1,998	$3,903	$3,425	$8,792

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

(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 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.

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 applicable Securities and Exchange Commission rules.

Recent Accounting Pronouncements

In November 2015, the FASB issued ASU 2015-17, “Balance Sheet Classification of Deferred Taxes”, which requires that deferred tax assets and liabilities be classified as noncurrent in a classified statement of financial position. This update is effective for financial statements issued for fiscal years beginning after December 15, 2016, and interim periods within those fiscal years, and may be applied either prospectively to all deferred tax assets and liabilities or retrospectively to all periods presented. We elected to early-adopt this update on a retrospective basis. The adoption of this update had no effect on the our results of operations.

In February 2016, the FASB issued ASU 2016-02, “Leases.” ASU 2016-02 requires that lease arrangements longer than 12 months result in an entity recognizing an asset and liability. The updated guidance is effective for interim and annual periods beginning after December 15, 2018, and early adoption is permitted. We have not evaluated the impact of the updated guidance on our financial statements.

Item 7A. Quantitative and Qualitative Disclosures about Market Risk

We are exposed to market risk related to changes in interest rates. As of December 31, 2015, we had cash and cash equivalents of $293.5 million, consisting of investments in cash and money market accounts. We have policies requiring us to invest in the securities of high-quality issuers, limit our exposure to any individual issuer and ensure adequate liquidity. Our primary exposure to market risk is interest rate sensitivity, which is affected by changes in the general level of U.S. interest rates, particularly because our investments are in short-term securities. Due to the short-term duration of our investment portfolio and the low risk profile of our investments, an immediate 100 basis point change in interest rates would not have a material effect on the fair market value of our portfolio.

Item 8. Financial Statements and Supplementary Data

Our financial statements, together with the report of our independent registered public accounting firm, appear on pages F-1 through F-20 of this Annual Report of Form 10-K.

Item 9. Changes in and Disagreements with Accountants on Accouting and Financial Disclosure

None.

Item 9A. Controls and Procedures

Evaluation of disclosure controls and procedures

Our management, with the participation of our Chief Executive Officer and Chief Financial Officer, evaluated the effectiveness of our disclosure controls and procedures as of December 31, 2015. The term "disclosure controls and procedures," as defined in Rules 13a-15(e) and 15d-15(e) under the Exchange Act, means controls and other procedures of a company that are designed to ensure that information required to be disclosed by a company in the reports that it files or submits under the Exchange Act is recorded, processed, summarized and reported, within the time periods specified in the Securities and Exchange Commission's rules and forms. Disclosure controls and procedures include, without limitation, controls and procedures designed to ensure that information required to be disclosed by a company in the reports that it files or submits under the Exchange Act is accumulated and communicated to the company's management, including its principal executive and principal financial officers, as appropriate to allow timely decisions regarding required disclosure. Management recognizes that any controls and procedures, no matter how well designed and operated, can provide only reasonable assurance of achieving their objectives and management necessarily applies its judgment in evaluating the cost-benefit relationship of possible controls and procedures. Based on the evaluation of our disclosure controls and procedures as of December 31, 2015, our Chief Executive Officer and Chief Financial Officer concluded that, as of such date, our disclosure controls and procedures were effective at the reasonable assurance level.

Table of Contents

Management's annual report on internal control over financial reporting

Management is responsible for establishing and maintaining adequate internal control over financial reporting as defined in Rules 13a-15(f) and 15d-15(f) under the Exchange Act. Our internal control over financial reporting is a process designed to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with general accepted accounting principles. Because of its inherent limitations, internal control over financial reporting may not prevent or detect misstatements. Projections of any evaluation of effectiveness to future periods are subject to the risk that controls may become inadequate because of changes in conditions, or that the degree of compliance with the policies or procedures may deteriorate.

This Annual Report on Form 10-K does not include an attestation report of our independent registered public accounting firm due to a transition period established by rules of the SEC for "emerging growth companies".

Changes in internal control over financial reporting

No change in our internal control over financial reporting (as defined in Rules 13a-15(f) and 15d-15(f) under the Exchange Act) occurred during the fiscal quarter ended December 31, 2015 that has materially affected, or is reasonably likely to materially affect, our internal control over financial reporting.

Item 9B. Other Information

On March 10, 2016 we entered into a first amendment to our master research services agreement with CHOP. Pursuant to such amendment, the termination date for services to be provided by CHOP for services other than those relating to the supply of RPE65 vectors was extended from July 1, 2015 to June 30, 2018. See Part I, “Item 1. Business-Collaboration and license agreements-In-license agreements-The Children’s Hospital of Philadelphia” of this Annual Report on Form 10-K.

PART III

Item 10. Directors, Executive Officers and Corporate Goverance.

The information required by this Item is incorporated by reference from the information that will be contained in our Proxy Statement for our 2016 Annual Meeting of Stockholders, which we intend to file with the SEC within 120 days of the end of the fiscal year to which this Annual Report on Form 10-K relates pursuant to General Instruction G(3) of Form 10-K.

Item 11. Executive Compensation

The information required by this Item is incorporated by reference from the information that will be contained in Proxy Statement for our 2016 Annual Meeting of Stockholders, which we intend to file with the SEC within 120 days of the end of the fiscal year to which this Annual Report on Form 10-K relates pursuant to General Instruction G(3) of Form 10-K.

Item 12. Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters

The information required by this Item is incorporated by reference from the information that will be contained in our Proxy Statement for our 2016 Annual Meeting of Stockholders, which we intend to file with the SEC within 120 days of the end of the fiscal year to which this Annual Report on Form 10-K relates pursuant to General Instruction G(3) of Form 10-K.

Item 13. Certain Relationships and Related Transactions, and Director Independence

The information required by this Item is incorporated by reference from the information that will be contained in our Proxy Statement for our 2016 Annual Meeting of Stockholders, which we intend to file with the SEC within 120 days of the end of the fiscal year to which this Annual Report on Form 10-K relates pursuant to General Instruction G(3) of Form 10-K.

Item 14. Principal Accounting Fees and Services

The information required by this Item is incorporated by reference from the information that will be contained in our Proxy Statement for our 2016 Annual Meeting of Stockholders, which we intend to file with the SEC within 120 days of the end of the fiscal year to which this Annual Report on Form 10-K relates pursuant to General Instruction G(3) of Form 10-K.

Table of Contents

PART IV

Item 15. Exhibits, Financial Statement Schedules

The financial statements listed in the Index to the Financial Statements beginning on F-1 are filed as part of this Annual Report on Form 10-K.

No financial statement schedules have been filed as part of this Annual Report on Form 10-K because they are not applicable, not required or because the information is otherwise included in our financial statements or notes thereto.

The exhibits filed as part of this Annual Report on Form 10-K are set forth on the Exhibit Index immediately following our financial statements. The Exhibit Index is incorporated herein by reference.

Table of Contents

Spark Therapeutics, Inc.
Index to financial statements

Table of Contents

Report of Independent Registered Public Accounting Firm
The Board of Directors and Stockholders
Spark Therapeutics, Inc.:

We have audited the accompanying balance sheets of Spark Therapeutics, Inc. (formerly Spark Therapeutics, LLC) (the Company) as of December 31, 2014 and 2015, and the related statements of operations, members'/stockholders' equity and cash flows for the period from March 13, 2013 (inception) through December 31, 2013 and the years ended December 31, 2014 and December 31, 2015. 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 audits.

We conducted our audits 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 audits provide 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, 2014 and 2015, and the results of its operations and its cash flows for the period from March 13, 2013 (inception) through December 31, 2013 and the years ended December 31, 2014 and December 31, 2015, in conformity with U.S. generally accepted accounting principles.

/s/ KPMG LLP

Philadelphia, Pennsylvania
March 14, 2016

Table of Contents

Spark Therapeutics, Inc.
Balance sheets

	December 31, 2014	December 31, 2015
Assets		
Current assets:		
Cash and cash equivalents	$74,566,963	$293,530,590
Other receivables	244,393	16,944,568
Prepaid expenses and other current assets	2,551,912	1,132,626
Total current assets	77,363,268	311,607,784
Property and equipment, net	12,674,372	16,999,445
Other assets	408,211	1,165,285
Total assets	$90,445,851	$329,772,514
Liabilities and Stockholders' Equity		
Current liabilities:		
Accounts payable	$2,676,697	$9,687,594
Accrued expenses	3,163,154	6,529,263
Current portion of deferred rent	—	715,959
Current portion of deferred revenue	10,014,377	5,182,835
Total current liabilities	15,854,228	22,115,651
Long-term deferred rent	8,618,489	8,084,509
Long-term deferred revenue	10,767,414	9,034,559
Total liabilities	35,240,131	39,234,719
Stockholders' equity:		
Preferred stock, $0.001 par value. Authorized, 5,000,000 shares; no shares issued or outstanding at December 31, 2014 and 2015, respectively	—	—
Series A convertible preferred stock, $0.001 par value. Authorized, issued and outstanding, 5,000,000 shares at December 31, 2014; no shares authorized, issued or outstanding as of December 31, 2015	10,000,000	—
Series B convertible preferred stock, $0.001 par value. Authorized, issued and outstanding, 45,186,334 shares at December 31, 2014; no shares authorized, issued or outstanding, at December 31, 2015	72,437,203	—
Common stock, $0.001 par value. Authorized, 150,000,000 shares; issued and outstanding, 6,290,317 shares at December 31, 2014; 27,082,493 shares issued and 27,073,287 outstanding at December 31, 2015	6,290	27,083
Additional paid-in capital	54,364,833	419,791,732
Treasury stock, at cost 9,206 shares at December 31, 2015	—	(552,636)
Accumulated deficit	(81,602,606)	(128,728,384)
Total stockholders' equity	55,205,720	290,537,795
Total liabilities and stockholders' equity	$90,445,851	$329,772,514

See accompanying notes to financial statements.

F-4

Spark Therapeutics, Inc.
Statements of operations

	Period from March 13, 2013 (inception) to December 31, 2013	For the Year Ended December 31,	
		2014	2015
Revenues	$—	$633,932	$22,063,674
Operating expenses:			
Research and development	4,897,152	16,351,005	46,029,314
Acquired in-process research and development	50,000,000	750,000	—
General and administrative	2,380,645	7,863,256	23,352,171
Total operating expenses	57,277,797	24,964,261	69,381,485
Loss from operations	(57,277,797)	(24,330,329)	(47,317,811)
Interest income	—	5,520	192,033
Net loss	(57,277,797)	(24,324,809)	(47,125,778)
Preferred stock dividends	—	(707,342)	(634,794)
Net loss applicable to common stockholders	$(57,277,797)	$(25,032,151)	$(47,760,572)
Basic and diluted net loss per common share	$(8.44)	$(4.64)	$(2.10)
Weighted average basic and diluted common shares outstanding	6,788,396	5,397,599	22,710,105

See accompanying notes to the financial statements.

Spark Therapeutics, Inc.
Statement of members'/stockholders' equity
Period from March 31, 2013 (inception) to December 31, 2013 and for the year ended December 31,2014

	Series A convertible preferred		Common		Series A convertible preferred stock		Series B convertible preferred stock		Common Stock	
	Units	Amount	Units	Amount	Shares	Amount	Shares	Amount	Shares	Amo
Issuance of common units in connection with license and technology agreements	—	$—	25,000,000	$50,000,000	—	$—	—	$—	—	$—
Issuance of Series A convertible preferred units	5,000,000	10,000,000	—	—	—	—	—	—	—	—
Issuance of restricted common units	—	—	5,870,000	—	—	—	—	—	—	—
Common membership units compensation expense	—	—	—	646,585	—	—	—	—	—	—
Net loss										
Balance, December 31, 2013	5,000,000	10,000,000	30,870,000	50,646,585	—	—	—	—	—	—
Issuance of restricted units, net of forfeitures	—	—	1,040,667	—	—	—	—	—	—	—
Conversion from LLC to C corporation	(5,000,000)	(10,000,000)	(31,910,667)	(50,646,585)	5,000,000	10,000,000	—	—	6,090,317	6,090
Issuance of Series B convertible preferred stock, net of transaction cost of $312,795	—	—	—	—	—	—	45,186,334	72,437,203	—	—
Issuance of common stock in connection with license agreement	—	—	—	—	—				200,000	200
	—	—	—	—	—	—	—	—	—	—

Stock-based compensation expense									
Net loss	—	—	—	—	—				
Balance, December 31, 2014	—	$—	$—	5,000,000	$10,000,000	45,186,334	$72,437,203	6,290,317	$6,2

See accompanying notes to financial statements.

Spark Therapeutics, Inc.
Statement of members'/stockholders' equity

For the year ended December 31, 2015

	Series A convertible preferred stock		Series B convertible preferred stock		Common stock in treasury		Common stock		Additional paid-in
	Shares	Amount	Shares	Amount	Shares	Amount	Shares	Amount	capital
Balance, December 31, 2014	5,000,000	$10,000,000	45,186,334	$72,437,203			6,290,317	$6,290	$54,364,833
Conversion of Series A preferred stock and dividends to common stock upon initial public offering	(5,000,000)	(10,000,000)	—	—	—	—	1,016,219	1,016	9,998,984
Conversion of Series B preferred stock and dividends to common stock upon initial public offering	—	—	(45,186,334)	(72,437,203)	—	—	9,183,831	9,184	72,428,019
Issuance of common stock, net of issuance costs	—	—	—	—	—	—	10,316,995	10,317	268,311,626
Issuance of common stock for services	—	—	—	—	—	—	3,556	4	193,905
Issuance of restricted stock	—	—	—	—	—	—	49,750	50	(50)
Purchase of common stock in treasury	—	—	—	—	9,206	(552,636)	—	—	—
Exercise of stock options	—	—	—	—	—	—	221,825	222	1,115,821
Stock-based compensation expense	—	—	—	—	—	—	—	—	13,378,594
Net loss	—	—	—	—	—	—	—	—	—

Balance, December 31, 2015	—	$—	—	$—	9,206	(552,636)	27,082,493	$27,083	$419,791,732

See accompanying notes to financial statements.

Spark Therapeutics, Inc.
Statements of cash flows

	Period from March 13, 2013 (inception) to December 31, 2013	For the Year ended December 31, 2014	2015
Cash flows from operating activities:			
Net loss	$(57,277,797)	$(24,324,809)	$(47,125,778)
Adjustments to reconcile net loss to net cash (used in) provided by operating activities:			
Noncash rent expense	—	617,114	181,979
Depreciation and amortization expense	—	169,790	1,732,983
Acquired in-process research and development	50,000,000	750,000	—
Stock-based compensation expense	646,585	2,974,538	13,572,503
Changes in operating assets and liabilities:			
Prepaid expenses and other assets	—	(670,309)	(1,627,602)
Other receivables	—	(144,393)	(16,700,175)
Accounts payable and accrued expenses	1,492,497	2,331,282	9,052,260
Deferred rent	—	7,901,375	—
Deferred revenue	—	20,781,791	(6,564,397)
Net cash (used in) provided by operating activities	(5,138,715)	10,386,379	(47,478,227)
Cash flows from investing activities:			
Purchases of property and equipment	—	(11,696,962)	(4,521,769)
Net cash used in investing activities	—	(11,696,962)	(4,521,769)
Cash flows from financing activities:			
Proceeds from issuance of Series A convertible preferred units	5,138,715	4,861,285	—
Proceeds from issuance of Series B convertible preferred stock, net	—	72,437,203	—
Financing costs	—	(1,420,942)	—
Repurchase of common stock	—	—	(552,636)
Proceeds from exercise of options	—	—	1,116,043
Proceeds from public offerings of common stock, net	—	—	270,400,216
Net cash provided by financing activities	5,138,715	75,877,546	270,963,623
Net increase in cash and cash equivalents	—	74,566,963	218,963,627
Cash and cash equivalents, beginning of period	—	—	74,566,963
Cash and cash equivalents, end of period	$—	$74,566,963	$293,530,590
Supplemental disclosure of cash flow information:			
Deferred financing costs included in accounts payable and accrued expenses	$—	$868,872	$657,331
Property and equipment purchases included in accounts payable and accrued expenses	$—	$1,147,200	$2,683,487

See accompanying notes to financial statements.

Spark Therapeutics, Inc.
Notes to 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 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 operates in one segment and has its principal offices in Philadelphia, Pennsylvania.

(a) Initial Public Offering (IPO)

On February 4, 2015, the Company closed its IPO, having sold 8,050,000 shares of common stock at an IPO price of $23.00 per share, for aggregate gross proceeds of $185.2 million. The Company received net proceeds from the IPO of $168.9 million, after deducting underwriting discounts and commissions and other offering expenses. As part of the IPO, all of the outstanding shares of preferred stock, including shares of preferred stock issued as accrued dividends, were converted into an aggregate of 10,200,050 shares of common stock.

On December 28, 2015, the Company completed its follow-on public offering, having sold 2,266,995 shares of common stock at a offering price of $47.00 per shares, for aggregate gross proceeds of $106.5 million. The Company received net proceeds from the public offering of $99.4 million, after deducting underwriting discounts and commissions and other offering expenses.

(2) Development-stage risks

The Company has incurred losses and negative cash flows from operations since inception and had an accumulated deficit of $128.7 million at December 31, 2015. The Company anticipates incurring additional losses until such time, if ever, that it can generate significant sales of its product candidates in development. Additional financing may be needed by the Company to fund its operations and to commercially develop its product candidates.

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, or 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 revenues and 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 cash equivalents, other receivables and accounts payable and accrued expenses approximate fair value due to the short-term nature of those instruments.

(c) 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 December 31, 2014 and 2015 consisted primarily of money market funds.

(d) Property and equipment

Property and equipment consists of computer and laboratory equipment, software, office equipment, furniture and leasehold improvements and is recorded at cost. Maintenance and repairs that do not improve or extend the lives of

the respective assets are expensed to operations as incurred. Upon disposal, retirement or sale, the related cost and accumulated depreciation are

removed from the accounts and any resulting gain or loss is included in the results of operations. Property and equipment are depreciated on a straight-line basis over their estimated useful lives. The Company uses a life of three years for computer equipment and software, five years for laboratory and office equipment and seven years for furniture. Leasehold improvements are amortized over the shorter of the lease term or the estimated useful life of the asset.

The Company reviews long-lived assets, such as property and equipment, for impairment when events or changes in circumstances indicate the carrying value of the assets may not be recoverable. Recoverability is measured by comparison of the book values of the assets to estimated undiscounted future cash flows that the assets are expected to generate. If the carrying amount of an asset exceeds its estimated future cash flows, then an impairment charge is recognized for the amount by which the carrying value of the asset exceeds the fair value of the asset. No impairment charges have been recorded since inception.

(e) 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 employee 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. When the Company is reimbursed by a collaboration partner for work performed, the costs incurred are recorded as research and development expenses and the related reimbursement is recorded as a reduction to research and development expenses.

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.

(f) 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 December 31, 2015, the Company has concluded that a full valuation allowance is necessary for its deferred tax assets.

(g) 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.

Nonrefundable license fees are recognized as revenue upon delivery provided there are no undelivered elements in the arrangement. For licenses with no stand-alone value, revenues are recognized on a straight-line basis over the related performance period.

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 sale of products.

(h) Stock-based compensation and fair value of stock

The Company accounts for its stock-based compensation awards in accordance with FASB ASC Topic 718, Compensation-Stock Compensation ("ASC 718"). ASC 718 requires all stock-based payments to employees, including grants of employee stock options and restricted stock units and modifications to existing stock options, to be recognized in the statements of operations based on their fair values. The Company uses the Black-Scholes option pricing model to determine the fair value of options granted.

The Company's stock-based awards are subject to either service or performance-based vesting conditions. Compensation expense related to awards to employees and directors with service-based vesting conditions is recognized on a straight-line basis based on the grant date fair value over the associated service period of the award, which is generally the vesting term. Compensation expense related to awards to non-employees with service-based vesting conditions is recognized based on the then-current fair value at each financial reporting date prior to the measurement date over the associated service period of the award, which is generally the vesting term, using the accelerated attribution method. Compensation expense related to awards to employees with performance-based vesting conditions is recognized based on the grant date fair value over the requisite service period using the accelerated attribution method to the extent achievement of the performance condition is probable.

The Company expenses restricted stock unit awards to employees based on the fair value of the award on a straight-line basis over the associated service period of the award. Awards of restricted stock units to non-employees are adjusted through share-based compensation expense at each reporting period end to reflect the current fair value of such awards and expensed over the vesting period.

The Company estimates the fair value of its option awards to employees and directors using the Black-Scholes option pricing model, which requires the input of and subjective assumptions, including (i) the expected stock price volatility, (ii) the calculation of the expected term of the award, (iii) the risk-free interest rate, and (iv) expected dividends. Due to the lack of company specific historical and implied volatility data of its common stock, the Company has based its estimate of expected volatility on the historical volatility of a group of similar companies that are publicly traded. When selecting these public companies on which it has based its expected stock price volatility, the Company selected companies with comparable characteristics to it, including enterprise value, risk profiles, position within the industry, and with historical share price information sufficient to meet the expected term of the stock-based awards. The Company computes historical volatility data using the daily closing prices for the selected companies' shares during the equivalent period of the calculated expected term of the stock-based awards. The Company will continue to apply this process until a sufficient amount of historical information regarding the volatility of its own stock price becomes

available. The Company has estimated the expected term of its employee stock options using the “simplified” method, whereby, the expected term equals the arithmetic average of the vesting term and the original contractual term of the option due to its lack of sufficient historical data. The risk-free interest rates for periods within the expected term of the option are based on the U.S. Treasury securities with a maturity date commensurate with the expected term of the associated award. The Company has never paid, and does not expect to pay dividends in the foreseeable future.

Spark Therapeutics, Inc.
Notes to financial statements

The Company also is required to estimate forfeitures at the time of grant, and revise those estimates in subsequent periods if actual forfeitures differ from its estimates. The Company uses historical data to estimate pre-vesting option forfeitures and records stock-based compensation expense only for those awards that are expected to vest. To the extent that actual forfeitures differ from the Company's estimates, the differences are recorded as a cumulative adjustment in the period the estimates were revised. Stock-based compensation expense recognized in the financial statements is based on awards that are ultimately expected to vest.
Consistent with the guidance in FASB ASC Topic 505-50, Equity-Based Payments to Non-Employees, the fair value of each non-employee stock option and restricted stock award is estimated at the date of grant using the Black-Scholes option pricing model with assumptions generally consistent with those used for employee stock options, with the exception of expected term, which is over the contractual life.

(i) 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.

(j) 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 convertible preferred 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 units/shares outstanding as of December 31, 2014 and 2015 as they would be anti-dilutive:

	Period from March 13, 2013 (inception) to December 31,	December 31,	
	2013	2014	2015
Convertible preferred units	5,000,000	—	—
Unvested restricted common units	5,370,000	—	—
Convertible preferred shares	—	10,037,255	—
Unvested restricted common shares	—	578,994	373,655
Options issued and outstanding	—	2,264,497	3,071,372

Amounts in the table above reflect the common stock equivalents of the noted instruments.

(k) 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 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 December 31, 2015 represents the net excess of rent expense over the actual cash paid for rent and the tenant improvement allowances received.

(l) Recent Accounting Pronouncements

In November 2015, the FASB issued ASU 2015-17, "Balance Sheet Classification of Deferred Taxes", which requires that deferred tax assets and liabilities be classified as noncurrent in a classified statement of financial position. This

update is effective for financial statements issued for fiscal years beginning after December 15, 2016, and interim periods within those fiscal years, and may be applied either prospectively to all deferred tax assets and liabilities or retrospectively to all periods

Spark Therapeutics, Inc.
Notes to financial statements

presented. The Company elected to early-adopt this update on a retrospective basis. The adoption of this update had no effect on the Company's results of operations.

In February 2016, the FASB issued ASU 2016-02, “Leases.” ASU 2016-02 requires that lease arrangements longer than 12 months result in an entity recognizing an asset and liability. The updated guidance is effective for interim and annual periods beginning after December 15, 2018, and early adoption is permitted. The Company has not evaluated the impact of the updated guidance on the Company's financial statements.

(4) Fair value of financial instruments

The Company follows FASB accounting guidance on fair value measurements for financial assets and liabilities measured on a recurring basis. The guidance requires fair value measurements to maximize the use of “observable inputs.” The three-level hierarchy of inputs to measure fair value are as follows:

- Level 1: Unadjusted quoted prices in active markets that are accessible at the measurement date for identical, unrestricted assets or liabilities
- Level 2: Significant other observable inputs other than Level 1 prices such as quoted prices in markets that are not active, or inputs that are observable, either directly or indirectly, for substantially the full term of the asset or liability
- Level 3: Prices or valuation techniques that require inputs that are both significant to the fair value measurement and unobservable (i.e., supported by little or no market activity)

The Company has classified assets and liabilities measured at fair value on a recurring basis as follows:

	Fair value measurements at reporting date using		
	Quoted prices in active markets for identical assets (Level 1)	Significant other observable inputs (Level 2)	Significant unobservable inputs (Level 3)
At December 31, 2014:			
Assets:			
Money market funds (included in cash and cash equivalents)	$74,025,841	—	—
At December 31, 2015:			
Assets:			
Money market funds (included in cash and cash equivalents)	$293,530,590	—	—

(5) Property and equipment, net

Property and equipment consist of the following:

	December 31,	
	2014	2015
Laboratory equipment	$2,961,494	$4,415,121
Computer and software	52,710	158,280
Furniture and fixtures	290,818	470,151
Office equipment	59,635	72,308
Leasehold improvements	5,113,269	11,274,721
Construction in progress	4,366,236	2,511,636
Property and equipment, gross	12,844,162	18,902,217
Less accumulated depreciation and amortization	(169,790)	(1,902,772)
Property and equipment, net	$12,674,372	$16,999,445

Spark Therapeutics, Inc.
Notes to financial statements

Depreciation and amortization expense was $0.2 million and $1.7 million for the years ended December 31, 2014 and 2015, respectively.

(6) Accrued expenses

Accrued expenses consist of the following:

	December 31,	
	2014	2015
Compensation and benefits	$1,385,013	$4,880,239
Consulting and professional fees	1,327,942	432,346
Research and development	247,448	978,156
Other	202,751	238,522
	$3,163,154	$6,529,263

(7) 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. The Company has authorized 150,000,000 shares of common stock and 5,000,000 shares of preferred stock.

(a) Convertible preferred

October 2013 Series A financing

In October 2013, the Company entered into an agreement with The Children's Hospital of Philadelphia (CHOP) to sell 5,000,000 Series A Units at $2.00 per unit for proceeds of $10.0 million. 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.

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 convertible preferred stock (Series B Stock) for $72.4 million, net of transaction costs. In conjunction with the issuance of Series B Stock, certain Series A convertible preferred stock (Series A Stock) terms were amended. Every five shares of Series A Stock and Series B Stock were to 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 were entitled to receive cumulative dividends at 8% per annum, which accrued from day to day beginning November 23, 2014 and were 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. As of February 4, 2015, dividends of $1.3 million had accumulated, and in connection with the IPO, were declared and converted along with all outstanding shares of Series A Stock and Series B Stock into an aggregate of 10,200,050 shares of common stock.

(b) Common

Through May 1, 2014, the Board designated Series 1 Units, Series 2 Units and Series 3 common units (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 (post-split) of common stock, each outstanding Series 2 Unit converted into 0.2 shares (post-split) of common stock and each outstanding Series 3 Unit converted into 0.03883773 shares (post-split) of common stock. In 2013 and 2014, the Company issued Series 2 Units and Series 3 Units to various employees, directors and consultants of the Company with specified vesting provisions. In connection with the conversion to a C corporation, the units converted to common stock. The vesting terms of the common stock 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. Upon conversion, the vesting terms of the previously issued equity remained consistent.

During 2013, the Company recorded compensation expense of $0.1 million and $0.6 million in general and administrative expense and research and development expense, respectively, related to the restricted units. For the year ended December 31, 2014, the Company recorded compensation expense of $1.2 million and $1.0 million in general and administrative expense and research and development expense, respectively, related to the restricted shares. For the year ended December 31, 2015, the

Spark Therapeutics, Inc.
Notes to financial statements

Company recorded compensation expense of $0.1 million and $1.8 million in general and administrative expense and research and development expense, respectively, related to the restricted shares.

In December 2014, 200,000 restricted shares of common stock were issued to The Trustees of the University of Pennsylvania (Penn) in connection with a license agreement (Note 9). The shares are subject to certain milestone-based vesting conditions and had a grant date fair value of $1.5 million. The Company recorded in-process research and development expense of $0.8 million during the year ended December 31, 2014. No milestone vesting conditions were achieved in 2015.

At December 31, 2015, there was $1.8 million of unrecognized compensation expense related to the restricted common shares which is expected to be recognized over a weighted-average period of 1.4 years.

The following table summarizes restricted stock activity for the instruments discussed above:

	Number of units/shares	Weighted-average grant date fair value
Nonvested shares at December 31, 2013	5,370,000	$0.75
Units granted	1,210,667	$0.32
Units vested	(526,667)	$0.81
Units forfeited	(170,000)	$0.84
Conversion to C Corporation and effect of reverse stock split	(5,294,713)	$—
Shares granted	200,000	$7.50
Shares vested	(210,293)	$5.61
Nonvested shares at December 31, 2014	578,994	$4.46
Shares vested	(230,439)	$3.87
Nonvested shares at December 31, 2015	348,555	$4.83

(8) Stock incentive plans

In May 2014, the Company established the 2014 Stock Incentive Plan (the 2014 Plan), which allows for the granting of incentive stock options, nonstatutory stock options, stock appreciation rights, restricted stock awards and other stock awards of the Company’s common stock to employees, officers, directors, consultants and advisors. In January 2015, upon the IPO, the 2014 plan was terminated and the 209,500 shares available for future grants under the 2014 Plan were rolled into the 2015 Stock Incentive Plan (the 2015 Plan).

In January 2015, the Company established the 2015 Plan, which became effective immediately prior to the closing of the IPO. 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 to employees, officers, directors, consultants and advisors. Under the 2015 Plan, the number of shares of common stock reserved for issuance is 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 common stock then available for issuance under the 2014 Plan and the number of shares of common stock subject to outstanding awards under the 2014 Plan that expire, terminate or are otherwise surrendered, cancelled, forfeited or repurchased by the Company 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 common stock, 4% of the number of shares of common stock outstanding on the first day of such fiscal year and an amount determined by the board of directors. As of December 31, 2015, 970,275 shares were available for future grants under the 2015 Plan.

In January 2015, the Company established the 2015 employee stock purchase plan (the 2015 ESPP), which became effective immediately prior to the closing of the IPO. The 2015 ESPP initially will provide participating employees with the opportunity to purchase an aggregate of 220,000 shares of common stock. The number of shares of 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 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 common stock; (2) 1% of the total number of shares of common stock outstanding on the first day of the applicable fiscal year; and (3) an amount determined by the board of directors. No shares were issued under the 2015 ESPP as of December 31, 2015.

Spark Therapeutics, Inc.
Notes to financial statements

The following table summarizes stock option activity:

	Number of shares	Weighted-average exercise price	Aggregate intrinsic value(a)
Outstanding at December 31, 2013	—	$—	
Granted	2,357,505	$4.48	
Forfeited	(93,008)	$3.45	
Outstanding at December 31, 2014	2,264,497	$4.52	
Granted	1,031,700	$59.80	
Exercised	(221,825)	$5.03	
Forfeited	(3,000)	$75.57	
Outstanding at December 31, 2015	3,071,372	$22.99	
Vested at December 31, 2015	599,814	$4.31	$24,590,030
Vested at December 31, 2015 and expected to vest	3,027,793	$22.44	$86,791,237

(a) The aggregate intrinsic value is calculated as the difference between the exercise price of the underlying options and the estimated fair value of the common stock.

The weighted average remaining contractual term of options outstanding as of December 31, 2015 is 8.8 years. The weighted average remaining contractual term of options exercisable as of December 31, 2015 is 8.6 years.

During the year ended December 31, 2014, the Company recorded compensation expense of $0.3 million and $0.5 million in research and development expense and general and administrative expense, respectively, related to stock options. During the year ended December 31, 2015, the Company recorded compensation expense of $3.9 million and $5.9 million in research and development expense and general and administrative expense, respectively, related to stock options.

At December 31, 2015, there was $36.9 million of unrecognized compensation expense related to stock options, which is expected to be recognized over a weighted average period of 3.1 years.

The weighted average grant date fair value of the options granted in 2014 and 2015 was $3.25 and $40.51 per share, respectively, using the Black-Scholes option-pricing model with the following weighted-average assumptions:

	Years Ended December 31,	
	2014	2015
Expected volatility	87.6%	76.8%
Risk-free interest rate	1.90%	1.67%
Expected term (in years)	6.02	6.10
Expected dividend yield	0.0%	0.0%

The following table summarizes restricted common stock activity:

	Number of shares	Weighted-average grant date fair value
Nonvested shares at December 31, 2014	—	—
Shares granted	49,750	$60.03
Shares vested	(24,650)	$60.03
Nonvested shares at December 31, 2015	25,100	$60.03

Spark Therapeutics, Inc.
Notes to financial statements

The Company issued a restricted stock grant to certain employees totaling 49,750 shares in November 2015. The vesting provisions of this grant are based on the acheivement of certain Company milestones. During the year ended December 31, 2015, the Company recorded compensation expense of $1.1 million and $0.6 million in research and development expense and general and administrative expense, respectively, related to restricted common stock.

At December 31, 2015, there was $1.3 million of unrecognized compensation expense related to the performance-based restricted common stock.

(9) Commitments and contingencies

(a) Leases

In March 2014, the Company entered into an operating lease for laboratory and office space at its corporate headquarters in Philadelphia, PA, through October 2025. Under this lease, the Company received $8.0 million of tenant improvement allowances during 2014. As of December 31, 2015, $8.1 million is recorded as long-term deferred rent and $0.7 million is recorded as current deferred rent on the accompanying balance sheet. In November 2015, the Company entered into a sublease agreement for approximately 14,000 square feet of additional office space at its corporate headquarters. The sublease will terminate on November 30, 2018. The Company made a $1.2 million upfront payment in connection with the sublease and as of December 31, 2015 the $0.4 million is recorded as prepaid expenses and other current assets and $0.8 million is recorded as other assets on the accompanying balance sheet. In addition, the Company leased approximately 3,400 square feet of office space in Waltham, Massachusetts under a lease that expires in September 2016.

Rent expense under these leases was $0.6 million and $1.0 million for the years ended December 31, 2014 and 2015, respectively.

Future minimum lease payments under these leases are as follows:

Year Ending December 31,	
2016	$1,997,647
2017	1,941,450
2018	1,961,168
2019	1,691,486
2020	1,733,774
2021 and thereafter	8,792,077
Total	$18,117,602

b) License agreements

See Note 10 for a discussion of the CHOP license agreement.

In October 2013, the Company entered into a patent license agreement with Penn for certain intellectual property licenses to be provided by Penn to the Company in the fields of research, development, manufacture and commercialization. On December 31, 2015, the Company amended and restated the patent license agreement with Penn. The license agreement requires the Company to reimburse Penn for the patent costs related to the underlying licensed rights. For the period from March 13, 2013 to December 31, 2013, and for the year ended December 31, 2014 and 2015, the Company recorded $94,501, $17,840 and $34,873, respectively, of general and administrative expense related to the reimbursement of such patent costs in the accompanying statements 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 to Penn 200,000 shares of restricted common stock (Note 7), which are subject to performance-based vesting conditions, 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.

Spark Therapeutics, Inc.
Notes to financial statements

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 period from March 13, 2013 to December 31, 2013, and for the year ended December 31, 2014 and 2015, the Company recorded $0.3 million, $0.3 million and $0.4 million, respectively, of general and administrative expense related to the reimbursement of such patent costs in the accompanying statements 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 was recorded as acquired in-process research and development expense in the fourth quarter of 2013.

(10) Related-party transactions

As of December 31, 2014 and 2015, CHOP was considered a significant equity holder. 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 period from inception to December 31, 2013 and for the years ended December 31, 2014 and 2015, the Company recorded $0.1 million, $0.6 million and $0.7 million, respectively, of general and administrative expense related to the reimbursement of such patent costs in the accompanying statements 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 inception to December 31, 2013 and for the years ended December 31, 2014 and 2015, the Company recorded $3.8 million, $6.0 million and $5.2 million, respectively, as research and development expense and for the period from inception to December 31, 2013 and for the year ended December 31, 2014, the Company recorded $31,643 and $49,393, respectively, as general and administrative expense related to these agreements.

As of December 31, 2014, $0.1 million and $0.9 million were recorded in accrued expenses and accounts payable, respectively, as amounts due to CHOP. As of December 31, 2015, $0.2 million and $1.7 million were recorded in accrued expenses and accounts payable, respectively, as amounts due to CHOP.

(11) Collaboration and license agreements

In March 2014, the Company entered into an 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 year ended December 31, 2014, the Company received $20,000 for the license and recognized it as revenue. During the year ended December 31, 2015, the Company recognized $0.9 million revenue related to manufacturing of product pursuant to the Genable agreement. In March 2016, the Company acquired Genable (See Note 13).

In April 2014, the Company began discussions with a biopharmaceutical company concerning a potential manufacturing technology agreement. The Company received a one-time, nonrefundable payment of $1.0 million to engage in due diligence. In March 2015, the Company concluded discussions on a potential arrangement with the biopharmaceutical company and, as a result, the Company recognized the nonrefundable payment of $1.0 million as revenue during the year ended December 31, 2015.

In December 2014, the Company entered into a global collaboration agreement with Pfizer Inc. (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 Factor IX gene therapy that it develops, manufactures or commercializes prior to December 31, 2024. 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. In connection with this agreement, the Company received a $20.0 million upfront payment for the license in December 2014. As there is no stand-alone value for the license, the Company is recognizing revenue through the estimated completion date of Phase 1/2 clinical trials. In December 2015, the Company earned a $15.0 million milestone payment, which is included in other receivables on the accompanying balance sheet. During the years ended December 31, 2014 and 2015, the Company recognized $0.6 million and $20.2 million of revenue, respectively. As of December 31, 2015, there is $5.2 million and $9.0 million of current and long term deferred revenue for this payment, respectively. During the years ended December

Spark Therapeutics, Inc.
Notes to financial statements

31, 2014 and 2015, the Company recorded $0.1 million and $1.3 million, respectively, as a reduction to research and development expenses for the reimbursement of costs from Pfizer.

The Company is eligible to receive up to an additional $245.0 million in aggregate milestone payments, $125.0 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.

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.

In April 2015, the Company entered into a research, license and option agreement with Clearside Biomedical, Inc. (Clearside) under which the Company acquired exclusive rights to license Clearside's microinjector technology and the option to further develop and commercialize gene therapy products delivered using the Clearside technology. Under the agreement, the companies will explore the feasibility of using Clearside's microinjector technology to deliver viral vectors to the choroid and the retina through the suprachoroidal space. In connection with this agreement, the Company made an upfront payment of $0.5 million for services to be rendered in the development of licensed products. During the year ended December 31, 2015, the Company recorded $0.5 million as research and development expense related to the upfront payment.

(12) Income taxes

A reconciliation of income tax expense computed at the statutory federal income tax rate to income taxes as reflected in the financial statements is as follows:

	December 31,			
	2014		2015	
Federal income tax expense at statutory rate	34.0	%	34.0	%
Loss prior to C corporation conversion	(7.1	)	—	
Permanent differences	(0.6	)	(2.7	)
Tax credits	7.3		13.0	
Change in valuation allowance	(33.6	)	(44.3	)
Effective income tax rate	—	%	—	%

Deferred taxes are recognized for temporary differences between the basis of assets and liabilities for financial statement and income tax purposes. The significant components of the Company's deferred tax assets are comprised of the following:

Spark Therapeutics, Inc.
Notes to financial statements

	December 31, 2014	2015
Deferred tax assets (liabilities):		
U.S. net operating loss carryforwards	$5,133,763	$11,385,094
Tax credit carryforwards	2,623,967	11,694,170
Stock based compensation	916,695	3,363,805
Deferred rent	3,709,831	3,581,023
Deferred revenue	625,987	6,376,558
Accruals and other	378,976	2,024,542
Fixed Assets	(3,433,053)	(4,598,986)
Total net deferred tax assets	9,956,166	33,826,206
Less valuation allowance	(9,956,166)	(33,826,206)
Net deferred taxes	$—	$—

As of December 31, 2015, the Company had U.S. federal net operating loss carryforwards of 25.5 million, which may be available to offset future income tax liabilities and will expire in 2034. As of December 31, 2015, the Company also had U.S. state net operating loss carryforwards of $24.5 million which may be available to offset future income tax liabilities and will expire in 2034.

The Company has recorded a full valuation allowance against its net deferred tax assets as of December 31, 2015 and 2014, respectively, because the Company has determined that is it more likely than not that these assets will not be fully realized due to historic net operating losses incurred. The Company experienced a net change in valuation allowance of $10.0 million and $23.4 million in the years ended December 31, 2014 and 2015, respectively.

As of December 31, 2015, the Company had federal research and development and orphan drug tax credit carryforwards of $0.7 million and $11.0 million, respectively, available to reduce future tax liabilities which expire in 2034.

Under the provisions of the Internal Revenue Code, the net operating loss and tax credit carryforwards are subject to review and possible adjustment by the Internal Revenue Service and state tax authorities. Net operating loss and tax credit carryforwards may become subject to an annual limitation in the event of certain cumulative changes in the ownership interest of significant shareholders over a three-year period in excess of 50%, as defined under Sections 382 and 383 of the Internal Revenue Code, respectively, as well as similar state provisions. This could limit the amount of tax attributes that can be utilized annually to offset future taxable income or tax liabilities. The amount of the annual limitation is determined based on the value of the Company immediately prior to the ownership change. Subsequent ownership changes may further affect the limitation in future years. The Company has completed financing since its inception which may have resulted in a change in control as defined by Sections 382 and 383 of the Internal Revenue Code, or could result in a change in control in the future.

The Company will recognize interest and penalties related to uncertain tax positions in income tax expense. As of December 31, 2015, the Company had no accrued interest or penalties related to uncertain tax positions and no amounts have been recognized in the Company’s statements of operations.

For the year ended December 31, 2015, the Company generated research credits but has not conducted a study to document the qualified activities. This study may result in an adjustment to the Company’s research and development credit carryforwards; however, until a study is completed and any adjustment is known, no amounts are being presented as an uncertain tax position for these years. A full valuation allowance has been provided against the Company’s research and development credits and, if an adjustment is required, this adjustment would be offset by an adjustment to the deferred tax asset established for the research and development credit carryforwards and the valuation allowance.

(13) Subsequent Events

On March 7, 2016, the Company acquired Dublin, Ireland-based Genable, a private gene therapy company with which the Company has collaborated since 2014 in the development of Genable's therapeutic program targeting a form of inherited retinal disease (IRD). With the acquisition, the Company acquires RhoNova™, a potential treatment targeting rhodopsin-linked autosomal dominant retinitis pigmentosa (RHO-adRP), an IRD that routinely leads to visual impairment and in the most severe cases to blindness. The consideration paid to Genable shareholders consisted of $6 million in cash and 265,000 shares of the Company's common stock.

Spark Therapeutics, Inc.
Notes to financial statements

(14) Selected quarterly financial data (unaudited)

The following table contains quarterly financial information for 2014 and 2015. The Company believes that the following information reflects all normal recurring adjustments necessary for a fair presentation of the information for the periods presented. The operating results for any quarter are not necessarily indicative of results for any future period.

2014 (1)	First Quarter	Second Quarter	Third Quarter	Fourth Quarter	Total
Revenues	$20,000	$—	$—	$613,932	$633,932
Research and development	3,387,733	2,129,573	4,652,056	6,181,643	16,351,005
Acquired in-process research and development	—	—	—	750,000	750,000
General and administrative	1,016,123	2,038,909	2,106,877	2,701,347	7,863,256
Total operating expenses	4,403,856	4,168,482	6,758,933	9,632,990	24,964,261
Loss from operations	(4,383,856)	(4,168,482)	(6,758,933)	(9,019,058)	(24,330,329)
Net loss	$(4,383,856)	$(4,168,384)	$(6,756,924)	$(9,015,645)	$(24,324,809)
Basic and diluted net loss per common unit	$(0.86)	$(0.79)	$(1.22)	$(1.74)	$(4.64)

2015 (1)	First Quarter	Second Quarter	Third Quarter	Fourth Quarter	Total
Revenues	$2,274,467	$1,288,629	$1,302,789	$17,197,789	$22,063,674
Research and development	8,334,108	9,343,972	11,796,455	16,554,779	46,029,314
General and administrative	3,684,880	6,333,123	6,461,675	6,872,493	23,352,171
Total operating expenses	12,018,988	15,677,095	18,258,130	23,427,272	69,381,485
Loss from operations	(9,744,521)	(14,388,466)	(16,955,341)	(6,229,483)	(47,317,811)
Net loss	$(9,733,507)	$(14,336,842)	$(16,900,560)	$(6,154,869)	$(47,125,778)
Basic and diluted net loss per common share	$(0.58)	$(0.60)	$(0.70)	$(0.25)	$(2.10)

(1) The sum of the quarterly per share amounts may not equal per share amounts reported for the year due to rounding.

SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized.

Date: March 14, 2016

SPARK THERAPEUTICS, INC.

By: /s/ Jeffrey D. Marrazzo
Jeffrey D. Marrazzo
Chief Executive Officer
(Principal Executive Officer)

Pursuant to the requirements of the Securities and Exchange Act of 1934, this report has been signed by the following persons on behalf of the registrant in the capacities and on the dates indicated.

Signature	Title	Date
/s/ Jeffrey D. Marrazzo Jeffrey D. Marrazzo	Director and Chief Executive Officer (Principal Executive Officer)	March 14, 2016
/s/ Stephen W. Webster Stephen W. Webster	Chief Financial Officer (Principal Financial and Accounting Officer)	March 14, 2016
/s/ Katherine A. High, M.D. Katherine A. High, M.D.	Director	March 14, 2016
/s/ Steven M. Altschuler, M.D. Steven M. Altschuler, M.D.	Director	March 14, 2016
/s/ A. Lorris Betz, M.D., Ph.D. A. Lorris Betz, M.D., Ph.D.	Director	March 14, 2016
/s/ Lars Ekman, M.D., Ph.D. Lars Ekman, M.D., Ph.D.	Director	March 14, 2016
/s/ Anand Mehra, M.D. Anand Mehra, M.D.	Director	March 14, 2016
/s/ Vincent Milano Vincent Milano	Director	March 14, 2016
/s/ Elliott Sigal, M.D., Ph.D. Elliott Sigal, M.D., Ph.D.	Director	March 14, 2016
/s/ Lota Zoth, CPA Lota Zoth, CPA	Director	March 14, 2016

EXHIBIT INDEX

Exhibit Number	Description of Exhibit	Incorporated by Reference				Filed Herewith
		Form	File Number	Date of Filing	Exhibit Number	
3.1	Restated Certificate of Incorporation of the Registrant	8-K	001-36819	2/6/2015	3.1	
3.2	Amended and Restated By-Laws of the Registrant	8-K	001-36819	2/6/2015	3.2	
4.1	Specimen Stock Certificate evidencing the shares of common stock	S-1/A	333-201318	1/20/2015	4.1	
4.2	Investors' Rights Agreement dated as of May 23, 2014	S-1	333-201318	12/30/2014	4.2	
10.1+	2014 Stock Incentive Plan	S-1	333-201318	12/30/2014	10.1	
10.2+	Form of Incentive Stock Option Agreement under 2014 Stock Incentive Plan	S-1	333-201318	12/30/2014	10.2	
10.3+	Form of Nonstatutory Stock Option Agreement under 2014 Stock Incentive Plan	S-1	333-201318	12/30/2014	10.3	
10.4+	Form of Restricted Stock Agreement under 2014 Stock Incentive	S-1	333-201318	12/30/2014	10.4	
10.5+	2015 Stock Incentive Plan	S-1/A	333-201318	1/20/2015	10.5	
10.6+	Form of Incentive Stock Option Agreement under 2015 Stock Incentive Plan	S-1/A	333-201318	1/20/2015	10.6	
10.7+	Form of Nonstatutory Stock Option Agreement under 2015 Stock Incentive Plan	S-1/A	333-201318	1/20/2015	10.7	
10.8+	2015 Employee Stock Purchase Plan	S-1/A	333-201318	1/20/2015	10.8	
10.9†	License Agreement dated October 14, 2013 between the Registrant and The Children's Hospital of Philadelphia, as amended	S-1	333-201318	12/30/2014	10.8	
10.10†	Technology Assignment Agreement dated October 14, 2013 between the Registrant and The Children's Hospital of Philadelphia	S-1	333-201318	12/30/2014	10.9	
10.11†	Master Research Services Agreement dated October 14, 2013 between the Registrant and The Children's Hospital of Philadelphia	S-1	333-201318	12/30/2014	10.10	

10.12†	Services Agreement dated December 26, 2013 between the Registrant and The Children's Hospital of Philadelphia	S-1	333-201318	12/30/2014	10.11
10.13†	License Agreement dated October 14, 2013 between the Registrant and the University of Iowa Research Foundation, as amended	S-1	333-201318	12/30/2014	10.12
10.14†	Patent License Agreement dated October 14, 2013 between the Registrant and The Trustees of the University of Pennsylvania	S-1	333-201318	12/30/2014	10.13
10.15†	License Agreement dated March 18, 2014 between the Registrant and Genable Technologies Limited	S-1	333-201318	12/30/2014	10.14
10.16†	Manufacturing Agreement dated March 18, 2014 between the Registrant and Genable Technologies Limited	S-1	333-201318	12/30/2014	10.15

Exhibit Number	Description of Exhibit	Incorporated by Reference				
		Form	File Number	Date of Filing	Exhibit Number	Filed Herewith
10.17†	Development Consultancy Agreement dated March 18, 2014 between the Registrant and Genable Technologies Limited	S-1	333-201318	12/30/2014	10.16	
10.18†	License Agreement dated December 6, 2014 between the Registrant and Pfizer Inc.	S-1	333-201318	12/30/2014	10.18	
10.19	Lease Agreement, dated as of March 31, 2014, between the Registrant and Wexford-UCSC 3737, LLC	S-1	333-201318	12/30/2014	10.19	
10.20+	Employment Agreement between the Registrant and Jeffrey D. Marrazzo	S-1/A	333-201318	1/20/2015	10.21	
10.21+	Common Share Membership Agreement between the Registrant and Katherine A. High	S-1/A	333-201318	1/20/2015	10.21	
10.22+	Employment Agreement between the Registrant and Katherine A. High	S-1/A	333-201318	1/20/2015	10.23	
10.23+	Employment Agreement between the Registrant and Rogério Vivaldi	S-1/A	333-201318	1/20/2015	10.24	
10.24+	Employment Agreement between the Registrant and Stephen W. Webster	S-1/A	333-201318	1/20/2015	10.25	
10.25+	Form of Indemnification Agreement between the Registrant and each of the executive officers and directors	S-1/A	333-201318	1/20/2015	10.26	
10.26†	Amendment No. 2, dated March 23, 2015 to License Agreement dated October 14, 2013 between the Registrant and the University of Iowa Research Foundation, as amended	10-Q	001-36819	5/11/2015	10.1	
10.27†	Amendment No.1 dated August 5, 2015 to the Services Agreement dated December 26, 2013 between the Registrant and the Children's Hospital of Philadelphia	10-Q	001-36819	11/6/2015	10.1	
10.28†	Amendment No.4 dated October 8, 2015 to the License Agreement dated October 14, 2013 between the Registrant and the Children's Hospital of Philadelphia	10-Q	001-36819	11/6/2015	10.2	
10.29		8-K	001-36819	11/16/2015	99.1	

	Sublease Agreement dated November 10, 2015 between the Registrant and Penn Presbyterian Medical Center					
10.30†	License Agreement dated November 23, 2015 between the Registrant and the The Children's Hospital of Philadelphia	8-K	001-36819	11/23/2016	99.1	
10.31††	Amended and Restated Patent License Agreement dated December 31, 2015, between the Registrant and The Trustees of the University of Pennsylvania					X
10.32+	Amendment, dated January 5, 2016 to the Employment Agreement between the Registrant and Jeffrey D. Marrazzo					X
10.33††	Amendment No. 3, dated January 6, 2016 to License Agreement dated October 14, 2013 between the Registrant and the University of Iowa Research Foundation					X
10.34††	Amendment No. 1, dated March 10, 2016 to Master Research Services Agreement dated October 14, 2013 between the Registrant and The Children's Hospital of Philadelphia					X
10.35	Lease Agreement, dated as of February 1, 2016, between the Registrant and Wexford-UCSC II, LP					X

Exhibit Number	Description of Exhibit	Incorporated by Reference				Filed Herewith
		Form	File Number	Date of Filing	Exhibit Number	
10.36††	Amendment dated March 10, 2016, to the License Agreement dated November 23, 2015 between the Registrant and The Children's Hospital of Philadelphia					X
23.1	Consent of KPMG LLP					X
31.1	Certification of principal executive officer pursuant to Rule 13a-14(a)/15d-14(a) of the Securities Exchange Act of 1934, as amended					X
31.2	Certification of principal financial officer pursuant to Rule 13a-14(a)/15d-14(a) of the Securities Exchange Act of 1934, as amended					X
32.1	Certification of principal executive officer pursuant to 18 U.S.C. §1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002					X
32.2	Certification of principal financial officer pursuant to 18 U.S.C. §1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002					X
101	The following materials from the Company’s Annual Report on Form10-K Period from March 13, 2013 (inception) to December 31, 2013 and for the year ended December 31, 2015, formatted in XBRL (eXtensible Business Reporting Language): (i) Balance Sheets as of December 31, 2014 and December 31, 2015, (ii) Statements of Operations for the Period from March 13, 2013 (inception) to December 31, 2013 and for the year ended December 31, 2014 and 2015, (iii) Statement of Stockholders’ Equity as of December 31, 2014 and December 31, 2015 (iv) Statements of Cash Flows for the Period from March 13, 2013 (inception) to December 31, 2013 and for the year ended December 31, 2014 and 2015 and (v) Notes to Audited Financial Statements.					X

† Confidential treatment has been granted as to certain portions of the exhibit. Confidential materials omitted and filed separately with the Securities and Exchange Commission.

†† Confidential treatment requested as to portions of the exhibit. Confidential materials omitted and filed separately with the Securities and Exchange Commission.

+ Management contract or compensatory plan or arrangement filed in response to Item 15(a)(3) of the Instructions to the Annual Report on Form 10-K.