Table of Contents

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, DC 20549

FORM 10-Q

(Mark One)

☒ **QUARTERLY REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

For the quarterly period ended September 30, 2017

OR

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

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

Large accelerated filer	☒	Accelerated filer	☐
Non-accelerated filer	☐ (Do not check if a smaller reporting company)	Smaller reporting company	☐
		Emerging growth company	☐

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

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

As of October 31, 2017 there were 37,005,446 shares of the registrant's Common Stock, par value $0.001 per share, outstanding.

Table of Contents

TABLE OF CONTENTS

FORWARD-LOOKING STATEMENTS

This Quarterly Report on Form 10-Q contains forward-looking statements that involve substantial risks and uncertainties. All statements, other than statements of historical facts, contained in this Quarterly Report on Form 10-Q, 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," "potential" or "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 Quarterly Report on Form 10-Q include, among other things, statements about:

- the timing, scope or likelihood of regulatory filings and approvals, including the timing of U.S. Food and Drug Administration, or FDA, and European Medicines Agency, or EMA, approval, if any, for our biologics license application, or BLA, and for our marketing authorization application, or MAA, of LUXTURNA™ (voretigene neparvovec);
- our plans to develop and commercialize our product candidates including our timing and expectations to commercialize LUXTURNA, if approved;
- the timing, progress and results of clinical trials for *SPK-7001*, *SPK-9001, SPK-8011* 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 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; and
- the impact of government laws and regulations.

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 Quarterly Report on Form 10-Q, 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 Quarterly Report on Form 10-Q and the documents that we have filed as exhibits to this Quarterly Report on Form 10-Q 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.

PART I. FINANCIAL INFORMATION

Item 1. Financial Statements

Spark Therapeutics, Inc.
Consolidated balance sheets
(unaudited)

	December 31, 2016	September 30, 2017
Assets		
Current assets:		
Cash and cash equivalents	$ 58,923,097	$ 146,434,119
Marketable securities	237,242,655	332,265,302
Other receivables	16,780,917	6,000,121
Prepaid expenses and other current assets	1,647,008	4,443,407
Total current assets	314,593,677	489,142,949
Marketable securities	21,900,129	96,199,671
Property and equipment, net	19,794,306	25,364,940
Acquired-in-process research and development	15,490,000	—
Goodwill	1,160,104	1,236,817
Other assets	924,579	723,806
Total assets	$ 373,862,795	$ 612,668,183
Liabilities and Stockholders' Equity		
Current liabilities:		
Accounts payable	$ 9,928,737	$ 9,561,865
Accrued expenses	13,826,920	15,677,442
Current portion of long-term debt	302,013	309,455
Current portion of deferred rent	771,196	1,043,375
Current portion of deferred revenue	5,168,674	4,377,284
Total current liabilities	29,997,540	30,969,421
Long-term debt	1,224,003	990,973
Long-term deferred rent	7,498,419	10,302,813
Long-term deferred revenue	3,865,885	—
Deferred tax liability	1,000,235	—
Total liabilities	43,586,082	42,263,207
Stockholders' equity:		
Preferred stock, $0.001 par value. Authorized, 5,000,000 shares; no shares issued or outstanding	—	—
Common stock, $0.001 par value. Authorized, 150,000,000 shares; 30,873,430 shares issued and 30,864,224 shares outstanding as of December 31, 2016; 36,946,198 shares issued and 36,926,603 shares outstanding as of September 30, 2017	30,874	36,947
Additional paid-in capital	583,973,682	1,015,363,029
Accumulated other comprehensive (loss) income	(794,296)	232,444
Treasury stock, at cost, 9,206 shares as of December 31, 2016 and 19,595 shares as of September 30, 2017	(552,636)	(1,185,509)
Accumulated deficit	(252,380,911)	(444,041,935)
Total stockholders' equity	330,276,713	570,404,976
Total liabilities and stockholders' equity	$ 373,862,795	$ 612,668,183

See accompanying notes to the unaudited consolidated financial statements.

Spark Therapeutics, Inc.
Consolidated statements of operations and comprehensive income (loss)
(unaudited)

	Three months ended September 30,		Nine months ended September 30,	
	2016	2017	2016	2017
Revenues	$ 1,302,789	$ 1,899,575	$ 3,880,046	$ 4,657,275
Operating expenses:				
Research and development	22,384,109	39,341,386	60,257,545	104,678,902
Acquired in-process research and development	—	1,750,000	—	5,207,142
Impairment of acquired in-process research and development	—	—	—	15,696,017
General and administrative	12,049,954	26,640,443	31,600,567	74,782,867
Total operating expenses	34,434,063	67,731,829	91,858,112	200,364,928
Loss from operations	(33,131,274)	(65,832,254)	(87,978,066)	(195,707,653)
Interest income, net	568,867	1,112,745	1,162,833	2,230,306
Loss before income taxes	(32,562,407)	(64,719,509)	(86,815,233)	(193,477,347)
Income tax (expense) benefit	—	(292,402)	—	1,816,323
Net loss	$ (32,562,407)	$ (65,011,911)	$ (86,815,233)	$ (191,661,024)
Basic and diluted net loss per common share	$ (1.07)	$ (1.90)	$ (3.08)	$ (5.89)
Weighted average basic and diluted common shares outstanding	30,368,354	34,258,328	28,218,850	32,516,829
Net loss	$ (32,562,407)	$ (65,011,911)	$ (86,815,233)	$ (191,661,024)
Other comprehensive income (loss):				
Unrealized (loss) gain on available-for-sale securities, net of tax	(126,943)	(358,590)	(56,066)	984,501
Foreign exchange translation adjustment	(1,003)	(60,007)	2,250	42,239
Total comprehensive loss	$ (32,690,353)	$ (65,430,508)	$ (86,869,049)	$ (190,634,284)

See accompanying notes to the unaudited consolidated financial statements.

Spark Therapeutics, Inc.
Consolidated statement of stockholders' equity
For the nine months ended September 30, 2017
(unaudited)

	Common stock in treasury		Common stock		Additional paid-in capital	Accumulated other comprehensive (loss) income	Accumulated deficit	Total
	Shares	Amount	Shares	Amount				
Balance, December 31, 2016	9,206	$ (552,636)	30,873,430	$ 30,874	$ 583,973,682	$ (794,296)	$ (252,380,911)	$ 330,276,713
Issuance of common stock, net of issuance costs	—	—	5,296,053	5,296	379,864,789	—	—	379,870,085
Purchase of common stock in treasury	10,389	(632,873)	—	—	—	—	—	(632,873)
Purchase of common stock under ESPP	—	—	11,804	12	645,903	—	—	645,915
Exercise of stock options	—	—	768,321	768	17,043,583	—	—	17,044,351
Issuance of restricted stock	—	—	697	1	(1)	—	—	—
Restricted stock canceled	—	—	(4,107)	(4)	4	—	—	—
Unrealized gain on investments, net of tax	—	—	—	—	—	984,501	—	984,501
Unrealized gain on foreign currency translation	—	—	—	—	—	42,239	—	42,239
Stock-based compensation expense	—	—	—	—	33,835,069	—	—	33,835,069
Net loss	—	—	—	—	—	—	(191,661,024)	(191,661,024)
Balance, September 30, 2017	19,595	$(1,185,509)	36,946,198	$ 36,947	$1,015,363,029	$ 232,444	$ (444,041,935)	$ 570,404,976

See accompanying notes to the unaudited consolidated financial statements.

Spark Therapeutics, Inc.
Consolidated statements of cash flows
(unaudited)

	Nine months ended September 30,	
	2016	**2017**
Cash flows from operating activities:		
Net loss	$ (86,815,233)	$ (191,661,024)
Adjustments to reconcile net loss to net cash used in operating activities:		
Non-cash rent expense	(542,975)	596,372
Depreciation expense	2,613,420	3,498,657
Acquired in-process research and development	—	5,207,142
Stock-based compensation expense	17,301,617	33,835,069
Impairment of acquired in-process research and development	—	15,696,017
Non-cash income tax benefit	—	(1,816,323)
Changes in operating assets and liabilities:		
Prepaid expenses and other assets	(262,144)	(2,501,042)
Other receivables	15,517,533	10,689,868
Accounts payable and accrued expenses	4,221,805	839,408
Deferred rent	—	2,480,201
Deferred revenue	(3,880,046)	(4,657,275)
Net cash used in operating activities	(51,846,023)	(127,792,930)
Cash flows from investing activities:		
Purchase of acquired in-process research and development	—	(4,820,358)
Payment for acquisition, net of cash acquired	(5,911,243)	—
Purchases of marketable securities	(273,010,018)	(374,746,940)
Proceeds from maturities of marketable securities	5,000,000	206,825,252
Purchases of property and equipment	(7,466,103)	(8,895,165)
Net cash used in investing activities	(281,387,364)	(181,637,211)
Cash flows from financing activities:		
Proceeds from exercise of stock options	1,834,196	17,044,351
Purchase of treasury stock	—	(632,873)
Proceeds from public offerings of common stock, net	126,908,733	380,007,534
Proceeds from issuance of common stock under ESPP	—	645,915
Proceeds from long-term debt	1,600,000	—
Payments on long-term debt	(24,594)	(225,588)
Net cash provided by financing activities	130,318,335	396,839,339
Effect of exchange rate changes on cash and cash equivalents	—	101,824
Net (decrease) increase in cash and cash equivalents	(202,915,052)	87,511,022
Cash and cash equivalents, beginning of period	293,530,590	58,923,097
Cash and cash equivalents, end of period	$ 90,615,538	$ 146,434,119
Supplemental disclosure of cash flow information:		
Deferred financing costs included in accounts payable and accrued expenses	$ —	$ 137,449
Property and equipment purchases included in accounts payable and accrued expenses	$ 623,117	$ 855,916

See accompanying notes to the unaudited consolidated financial statements.

Spark Therapeutics, Inc.
Notes to consolidated financial statements
(unaudited)

(1) The Company

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, it 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 potentially one-time, life-altering treatments. The Company operates in one segment and has its principal offices in Philadelphia, Pennsylvania.

(a) Follow-on public offering

On August 9, 2017, the Company completed a follow-on public offering, having sold 5,296,053 shares of common stock at an offering price of $76.00 per share, for aggregate gross proceeds of $402.5 million. The Company received net proceeds from the public offering of $379.9 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 $444.0 million as of September 30, 2017. The Company anticipates incurring additional losses until such time, if ever, that it can generate significant sales of its product candidates in development. The Company may need additional financing 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) Basis of presentation

The accompanying unaudited interim consolidated financial statements of the Company and its wholly-owned subsidiaries have been prepared in accordance with U.S. generally accepted accounting principles (GAAP) for interim financial information. In the opinion of management, the accompanying consolidated financial statements include all normal and recurring adjustments (which consist primarily of accruals, estimates and assumptions that impact the consolidated financial statements) considered necessary to present fairly the Company's financial position as of September 30, 2017, its results of operations for the three and nine months ended September 30, 2016 and 2017 and cash flows for the nine months ended September 30, 2016 and 2017. Operating results for the three and nine months ended September 30, 2017 are not necessarily indicative of the results that may be expected for the year ending December 31, 2017 or any other period. The interim consolidated financial statements presented herein do not contain the required disclosures under U.S. GAAP for annual consolidated financial statements.

The accompanying unaudited interim consolidated financial statements should be read in conjunction with the annual audited consolidated financial statements and related notes as of and for the year ended December 31, 2016 included in the Company's Annual Report on Form 10-K for the fiscal year ended December 31, 2016.

(b) Use of estimates

The preparation of financial statements in conformity with U.S. 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 consolidated financial statements and the reported amounts of revenues and expenses during the reporting period. Actual results could differ from such estimates.

(c) 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. Management believes the carrying value of debt approximates fair value as the interest rates are reflective of the rate the Company could obtain on debt with similar terms and conditions.

(d) 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) Subtopic 605-25, *Revenue Recognition: Multiple Element Arrangements*, 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 Subtopic 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 Subtopic 605-28, *Revenue Recognition: Milestone Method*. FASB ASC Subtopic 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 consolidated 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.

(e) 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, unvested restricted shares and common stock options have been excluded from the calculation because their effect would be anti-dilutive. Therefore, the weighted average shares outstanding used to calculate both basic and diluted loss per share are the same.

The following potentially dilutive securities have been excluded from the computations of diluted weighted average shares outstanding as of September 30, 2016 and 2017 as they would be anti-dilutive:

	September 30,	
	2016	**2017**
Unvested restricted common shares	296,621	781,703
Stock options issued and outstanding	4,109,025	3,771,059

(f) 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. Tenant improvement allowances from the lessor are included in the accompanying consolidated balance sheet as deferred rent and are amortized as a reduction of rent expense over the term of the lease from the possession date. Deferred rent as of September 30, 2017 represents the net excess of rent expense over the actual cash paid for rent and the tenant improvement allowances received.

(g) Other comprehensive (loss) income

The Company follows the provisions of FASB ASC Topic 220, *Comprehensive Income*, which establishes standards for the reporting and display of comprehensive income and its components. Comprehensive income is defined to include all changes in equity during a period except those resulting from investments by owners and distributions to owners. Comprehensive loss includes gains and losses related to changes in the fair value of available for sale securities and foreign currency translation.

The accumulated balances related to each component of other comprehensive income (loss) are summarized as follows:

	Net unrealized (losses) gain on available for sale securities, net of tax	Foreign currency translation adjustments	Accumulated other comprehensive (loss) income
Balance as of December 31, 2016	$ (801,717)	$ 7,421	$ (794,296)
Current period other comprehensive income, net of tax	984,501	42,239	1,026,740
Balance as of September 30, 2017	$ 182,784	$ 49,660	$ 232,444

Pursuant to the intraperiod tax guidance included in ASC 740, *Accounting for Income Taxes*, the Company recorded an income tax benefit of $0.8 million during the nine months ended September 30, 2017 as a result of the unrealized gain on available for sale securities with an offsetting tax expense in other comprehensive income (loss).

(h) Recent accounting pronouncements

In February 2016, the FASB issued Accounting Standards Update (ASU) No. 2016-02, "*Leases.*" ASU 2016-02 requires that lease arrangements longer than 12 months result in an entity recognizing an asset and liability. ASU 2016-02 is effective for interim and annual periods beginning after December 15, 2018, and early adoption is permitted. The Company is currently evaluating the impact of the updated guidance on the Company's consolidated financial statements.

In May 2014, the FASB issued updated guidance regarding the accounting for, and disclosures of, revenue recognition, with an effective date for annual and interim periods beginning after December 15, 2017. The update provides a single comprehensive model for accounting for revenue from contracts with customers. The model requires that revenue recognized reflect the actual consideration to which the entity expects to be entitled in exchange for the goods or services defined in the contract, including in situations with multiple performance obligations. The Company plans to adopt this guidance using the modified prospective method and believes adopion will have an immaterial impact on its consolidated financial statements as it relates to the Pfizer Inc. (Pfizer) collaboration agreement discussed in note 12.

In January 2016, the FASB issued ASU No. 2016-01, "*Financial Instruments-Overall: Recognition and Measurement of Financial Assets and Financial Liabilities.*" ASU 2016-01 changes accounting for equity investments, financial liabilities under the fair value option, and presentation and disclosure requirements for financial instruments. ASU 2016-01 does not apply to equity investments in consolidated subsidiaries or those accounted for under the equity method of accounting. In addition, the FASB clarified guidance related to the valuation allowance assessment when recognizing deferred tax assets resulting from unrealized losses on available-for-sale debt securities. Equity investments with readily determinable fair values will be measured at fair value with changes in fair value recognized in net income. Companies have the option to either measure equity investments without readily determinable fair values at fair value or at cost, adjusted for changes in observable prices, minus impairment. Changes in measurement under either alternative will be recognized in net income. Companies that elect the fair value option for financial liabilities must recognize changes in fair value related to instrument-specific credit risk in other comprehensive income (OCI). Companies must assess valuation allowances for deferred tax assets related to available-

for-sale debt securities in combination with their other deferred tax assets. ASU 2016-01 will be effective beginning the first quarter of 2018 and early adoption is available to publicly traded companies to record fair value changes for financial liabilities under the fair value option resulting from instrument-specific credit risk in OCI. The Company currently is evaluating the impact of the updated guidance on the Company's consolidated financial statements.

(4) Marketable securities

The following table summarizes the available-for-sale securities held at December 31, 2016 and September 30, 2017:

Description	Amortized cost	Unrealized gains	Unrealized losses	Fair value
December 31, 2016				
U.S. government agency	$ 133,690,267	$ 10,907	$ (85,714)	$ 133,615,460
Corporate securities	$ 126,253,903	$ —	$ (726,579)	$ 125,527,324
September 30, 2017				
U.S. government agency	$ 218,260,834	$ 847	$ (175,794)	$ 218,085,887
Corporate securities	$ 209,218,241	$ 1,275,323	$ (114,478)	$ 210,379,086

No available-for-sale securities held as of September 30, 2017 had remaining maturities greater than two years.

(5) 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, 2016:			
Assets:			
Money market funds (included in cash and cash equivalents)	$ 53,452,424	—	—
Corporate securities (included in cash and cash equivalents)	5,029,838	—	—
Marketable securities - U.S. government agencies	133,615,460	—	—
Marketable securities - corporate securities	122,144,692	3,382,632	—
At September 30, 2017:			
Assets:			
Money market funds (included in cash and cash equivalents)	$ 144,551,878	—	—
Marketable securities - U.S. government agencies	218,085,887	—	—
Marketable securities - corporate securities	204,802,817	5,576,269	—

(a) Cash and cash equivalents

The Company considers all highly liquid investments that have maturities of three months or less when acquired to be cash equivalents. Cash equivalents as of September 30, 2017 consisted of money market funds.

(b) Marketable securities

The Company classifies its marketable security investments as available-for-sale securities and the securities are stated at fair value. No material realized gains or losses were recognized on the maturity of available-for-sale securities during the nine months ended September 30, 2017 and, as a result, the Company did not reclassify any amount out of accumulated other comprehensive (loss) income for the same period. In addition, as part of the license and stock purchase agreements entered into with Selecta Biosciences, Inc. (Selecta) (note 12), the Company purchased restricted common shares of Selecta. The investment is classified as available-for-sale and is stated at fair value.

(6) Impairment of acquired in-process research and development

The acquired in-process research and development (IPR&D) asset was an indefinite-lived intangible asset and was assessed for impairment annually, or more frequently if impairment indicators existed. During the nine months ended September 30, 2017, the Company determined that it would no longer pursue product candidates utilizing the technology acquired from Genable Technologies, Ltd. in March 2016 and, accordingly, recorded an impairment charge of $15.7 million within its consolidated statement of operations. Additionally, the Company recognized an income tax benefit of $1.0 million related to the reversal of the deferred tax liability associated with the IPR&D during the nine months ended September 30, 2017.

(7) Accrued expenses

Accrued expenses consist of the following:

	December 31, 2016	September 30, 2017
Compensation and benefits	$ 9,613,275	$ 9,208,714
Consulting and professional fees	995,614	2,788,783
Research and development	2,717,777	1,818,065
Other	500,254	1,861,880
Total accrued expenses	$ 13,826,920	$ 15,677,442

(8) 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.

In 2013 and 2014, the Company issued restricted stock to various employees, directors and consultants of the Company. The vesting terms of the restricted stock issued varied, but primarily, shares vested 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.

Additionally, in 2014, 200,000 restricted shares of common stock were issued to The Trustees of the University of Pennsylvania in connection with a license agreement, of which 100,000 shares have vested. The remaining shares are subject to certain milestone-based vesting conditions. No milestone vesting conditions were achieved in 2016 or during the nine months ended September 30, 2017.

For the nine months ended September 30, 2016, the Company recorded compensation expense of $47,481 and $1.3 million in general and administrative expense and research and development expense, respectively, related to the restricted shares. For the nine months ended September 30, 2017, the Company recorded compensation expense of $29,850 and $6.7 million in general and administrative expense and research and development expense, respectively, related to the restricted shares.

The following table summarizes restricted stock activity:

	Number of shares	Weighted-average grant date fair value
Nonvested shares at December 31, 2016	174,876	$ 5.78
Shares canceled	(3,107)	$ 1.15
Shares vested	(65,633)	$ 3.71
Nonvested shares at September 30, 2017	106,136	$ 7.20

(9) Stock incentive plans

The Company's 2015 Stock Incentive Plan (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. In January 2017, the number of shares of common stock authorized for issuance under the 2015 Plan automatically increased, pursuant to the terms of the 2015 Plan, by 1,234,641 shares. As of September 30, 2017, 687,195 shares were available for future grants under the 2015 Plan.

In January 2017, the number of shares of common stock authorized for issuance under the 2015 Employee Stock Purchase Plan (the 2015 ESPP) automatically increased, pursuant to the terms of the 2015 ESPP, by 308,660 shares. The 2015 ESPP provides participating employees with the opportunity to purchase an aggregate of 791,476 shares of common stock. For the nine months ended September 30, 2017, 11,804 shares were issued under the 2015 ESPP.

Stock-based compensation expense

Stock-based compensation expense by award type was as follows:

	Nine months ended September 30,	
	2016	2017
Stock options	$ 15,647,182	$ 21,238,088
Restricted stock	326,913	5,624,797
Employee stock purchase plan	—	259,599
	$ 15,974,095	$ 27,122,484

Of the $27.1 million of stock-based compensation expense incurred during the nine months ended September 30, 2017, $11.1 million is classified as research and development expense and $16.0 million is classified as general and administrative expense in the consolidated statements of operations and comprehensive income (loss). Of the $16.0 million of stock-based compensation expense incurred during the nine months ended September 30, 2016, $6.8 million is classified as research and development expense and $9.2 million is classified as general and administrative expense in the consolidated statements of operations and comprehensive income (loss).

Stock options

The following table summarizes stock option activity:

	Number of options	Weighted-average exercise price
Outstanding at December 31, 2016	4,181,993	$ 33.25
Granted	701,300	$ 56.78
Exercised	(768,321)	$ 22.18
Canceled	(343,913)	$ 40.69
Outstanding at September 30, 2017	3,771,059	$ 39.20
Vested at September 30, 2017	1,361,776	$ 30.39

Restricted stock

The following table summarizes restricted common stock activity:

	Number of shares		Weighted-average grant date fair value
Nonvested shares at December 31, 2016	76,933	$	49.90
Shares granted	658,600	$	62.98
Shares vested	(35,463)	$	55.62
Shares canceled	(24,503)	$	55.91
Nonvested shares at September 30, 2017	675,567	$	62.13

Included in the above table are non-vested restricted stock grants to certain employees and consultants totaling 19,500 shares for which the vesting provisions are based on the achievement of certain Company milestones.

(10) Related-party transactions

As of December 31, 2016 and September 30, 2017, the Children's Hospital of Philadelphia (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 nine months ended September 30, 2016 and 2017, the Company recorded $0.7 million and $0.6 million, respectively, of general and administrative expense related to the reimbursement of such patent costs in the accompanying consolidated statements of operations and comprehensive income (loss).

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 nine months ended September 30, 2016 and 2017, the Company recorded $5.4 million and $4.4 million, respectively, as research and development expense.

As of December 31, 2016, $1.1 million and $0.9 million were recorded in accrued expenses and accounts payable, respectively, as amounts due to CHOP. As of September 30, 2017, $0.1 million and $0.4 million were recorded in accrued expenses and accounts payable, respectively, as amounts due to CHOP.

(11) Commitments and contingencies

In January 2017, the Company amended its lease for office space in Philadelphia to lease an additional 24,800 square feet that will commence on January 1, 2018, and terminate on December 31, 2028. The additional leased space will increase the Company's future minimum lease payments by $11.5 million over the life of the lease.

(12) Collaboration and license agreements

(a) Pfizer

In December 2014, the Company entered into a global collaboration agreement with Pfizer for the development and commercialization of *SPK-FIX* product candidates for the treatment of hemophilia B. Under the agreement, the Company granted Pfizer an exclusive worldwide license to any factor IX gene therapy that it develops, manufactures or commercializes prior to December 31, 2024. The Company is 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. During the nine month periods ended September 30, 2016 and 2017, the Company

recognized $3.9 million and $4.7 million, respectively, of revenue related to the upfront payment. As of September 30, 2017, there is $4.4 million of current deferred revenue related to this payment. During the nine month periods ended September 30, 2016 and 2017, the Company recorded $1.2 million and $2.6 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 $230.0 million in aggregate milestone payments, $110.0 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 November 2017, the Company amended its collaboration agreement with Pfizer. Under the amendment, the Company will receive from Pfizer an initial $10.0 million cash payment and up to an additional $15.0 million in potential milestone payments upon completion of certain transition activities.

(b) Selecta

In December 2016, the Company entered into a License and Option Agreement (the License Agreement) with Selecta that provides the Company with exclusive worldwide rights to Selecta's proprietary Synthetic Vaccine Particles (SVP™) platform technology for co-administration with gene therapy targets. Under the terms of the License Agreement, Selecta has granted the Company certain exclusive, worldwide, royalty-bearing licenses to Selecta's intellectual property and know-how relating to its SVP technology to research, develop and commercialize gene therapies for factor VIII, an essential blood clotting protein relevant to the treatment of hemophilia A, which is the initial target under the license. In addition, for a specified period of time, the Company may exercise options to research, develop and commercialize gene therapies utilizing the SVP technology for up to four additional targets, subject to the Company's payment of the applicable option exercise fee, in a range of $1.4 million to $2.0 million depending on the incidence of the applicable indication, to Selecta in each case.

Pursuant to a letter agreement (Letter Agreement), entered into between the Company and Selecta on June 6, 2017, Selecta agreed to reimburse the Company for all costs and expenses related to research and development for any licensed products for a specified amount of time, up to an agreed upon cap. Additionally, the Company has agreed to reimburse Selecta in respect of full-time equivalents and out-of-pocket costs incurred in performing certain tasks or assistance specifically requested by the Company. Selecta retains the responsibility to manufacture the Company's preclinical, clinical and commercial requirements for the SVP technology, subject to the terms of the License Agreement.

In connection with the execution of the License Agreement, the Company paid Selecta an upfront payment of $10.0 million in December 2016. An additional payment of $2.5 million was made in June 2017 pursuant to the terms of the License Agreement and the Letter Agreement. An additional payment of $2.5 million is due to Selecta within 12 months of execution of the agreement. On a target-by-target basis, the Company will be responsible to pay up to an aggregate of $430.0 million in milestone payments for each target, with up to $65.0 million being based on the Company's achievement of specified development and regulatory milestones and up to $365.0 million for commercial milestones, as well as tiered royalties on global net sales at percentages ranging from mid-single to low-double digits. For a period of 3 years, the Company has the right to fund up to 50% of any development or regulatory milestone payable to Selecta by issuing to Selecta shares of the Company's common stock having a fair market value equal to the percentage of such development or regulatory milestone, as applicable. The License Agreement will continue on a country-by-country and product-by-product basis until the expiration of the Company's royalty payment obligations with respect to such product in such country unless earlier terminated by the parties. The License Agreement may be terminated by the Company for convenience upon 90 days' notice and the Company will not be required to make any payments. Either party may terminate the License Agreement on a target-by-target basis for material breach with respect to such target.

In connection with the License Agreement, the Company entered into a Stock Purchase Agreement (SPA) with Selecta pursuant to which the Company purchased 197,238 unregistered shares of Selecta's common stock for $5.0 million in December 2016 and an additional 324,362 unregistered shares of Selecta's common stock for $5.0 million in June 2017. The fair value of these

shares is classified as available-for-sale securities as of September 30, 2017. Under the terms of the SPA, the Company will purchase additional shares of Selecta's common stock for an aggregate of $5.0 million in 2017, unless the License Agreement is terminated.

In December 2016, the Company accounted for payments under the License Agreement and SPA as a basket transaction and allocated the $15.0 million in cash payments to the shares of Selecta's common stock and the License Agreement in the amounts of $3.5 million and $11.5 million, respectively. The Company calculated the $3.5 million allocated to the Selecta shares acquired based on the closing market price on the date of purchase. The Company allocated the remaining $11.5 million to the License Agreement, which was expensed as acquired in-process research and development as the Company determined there was no alternative future use.

In June 2017, the Company accounted for the payments under the License Agreement, Letter Agreement and SPA as a basket transaction and allocated the $7.5 million in cash payments to the shares of Selecta's common stock and the License Agreement in the amounts of $4.4 million and $3.1 million, respectively. The Company calculated the $4.4 million allocated to the Selecta shares acquired based on the closing market price on the date of purchase. The Company allocated the remaining $3.1 million to the License Agreement, which was expensed as acquired in-process research and development as the Company determined there was no alternative future use.

In October 2017, under the terms of the SPA, the Company made an additional payment of $2.5 million and purchased additional shares of Selecta's common stock for an aggregate of $5.0 million.

Item 2. 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 in conjunction with our financial statements and related notes appearing elsewhere in this Quarterly Report on Form 10-Q and the audited financial statements and notes thereto and management's discussion and analysis of financial condition and results of operations for the year ended December 31, 2016 included in our Annual Report on Form 10-K that was filed with the SEC on February 28, 2017. Some of the information contained in this discussion and analysis or set forth elsewhere in this Quarterly Report on Form 10-Q, 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 in the "Risk Factors" section of this Quarterly Report on Form 10-Q, our actual results could differ materially from the results described in, or implied by, these 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 potentially 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. We have built a pipeline of product candidates targeting orphan diseases, including rare blinding conditions, hematologic disorders and neurodegenerative diseases, including four product candidates that are in, or have completed, clinical trials.

In 2017, the U.S. Food and Drug Administration, or FDA, accepted for filing the biologics license application, or BLA, for LUXTURNA™ (voretigene neparvovec) and granted it Priority Review with a Prescription Drug User Fee Act, or PDUFA, date of January 12, 2018. On October 12, 2017, FDA's Cellular, Tissue and Gene Therapies Advisory Committee unanimously recommended approval of LUXTURNA. In August 2017, our manufacturing facility underwent a successful preapproval inspection by FDA. LUXTURNA has received orphan product designation and also has been designated by FDA as a "rare pediatric disease" and, therefore, we may qualify for a rare pediatric disease priority review voucher if LUXTURNA receives marketing approval.

Our clinical pipeline includes our hemophilia programs consisting of *SPK-9001*, our lead product candidate in the *SPK-FIX* program addressing hemophilia B, a product candidate for hemophilia A, currently in Phase 1/2 clinical trial, as well as *SPK-7001*, a product candidate targeting choroideremia, or CHM, currently in a Phase 1/2 clinical trial. We retain global rights to all of our product candidates other than *SPK-FIX* product candidates, which we licensed to Pfizer Inc., or Pfizer.

LUXTURNA is intended to treat a genetic blinding condition, or inherited retinal disease, or IRD, caused by biallelic mutations in the *RPE65* gene. Patients suffering from *RPE65*-mediated IRD 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.

In October 2015, we announced positive top-line results from our pivotal Phase 3 clinical trial of LUXTURNA, the first successfully completed randomized controlled Phase 3 trial of a gene therapy for genetic disease in the United States. The Phase 3 trial demonstrated a statistically significant improvement of vision in subjects that were progressing toward complete blindness. In August 2016, we announced positive one-year follow-up data from the Phase 3 trial on the nine control subjects that crossed over after one year and received LUXTURNA.

LUXTURNA continues to demonstrate long-lasting effects as measured by both multi-luminance mobility test, or MLMT, and full-field light sensitivity threshold testing, or FST. Specifically, a cohort of eight subjects participated in our second Phase 1 clinical trial, and that would have met the eligibility criteria for the Phase 3 trial, continue to experience durable improvement over four years from time of administration, with observation ongoing. Further, in the continuation of the Phase 3 trial, the original intervention group (n = 20) that received LUXTURNA demonstrated sustained benefit three years post-treatment as measured by the bilateral MLMT and FST.

We possess global rights to LUXTURNA. If approved, we intend to commercialize LUXTURNA globally, initially in the United States and Europe. We employ small, targeted market development and medical affairs groups to build and promote access to the product through centers that specialize in treating IRDs. We believe that this approach is more patient-centered and will provide the foundation for future market development 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, educating stakeholders, developing a high-quality delivery and distribution model, ensuring market access and building a patient-centric organization.

RPE65-mediated IRD historically has been clinically diagnosed based on clinical presentation and findings and has been characterized most frequently as Leber congenital amaurosis, or LCA, or retinitis pigmentosa, or RP, among over 20 other clinical classifications. We estimate that LCA affects approximately one in every 81,000 individuals and RP affects

approximately one in every 4,500 individuals. Because there are no current pharmacologic treatments for IRDs and there are known to be over 220 different genes causing IRDs, there are limited epidemiology data from which to derive population estimates. Additionally, epidemiology estimates vary based on geography. We are aware of studies that estimate the prevalence of *RPE65* mutations within the LCA population from approximately 6% to 16% and within the RP population from approximately 1% to 3%. Based on our own assessment of the epidemiology data, we believe the prevalent population is up to approximately 6,000 individuals with *RPE65* mutations in the United States, Europe and select additional markets in the Americas and Asia/Pacific.

SPK-7001 is our lead product candidate for the treatment of CHM, an IRD caused by mutations in the *REP-1* gene. We have completed enrollment of ten participants in two dose cohorts of our Phase 1/2 trial for *SPK-7001* and continue to follow subjects in the trial. In July we completed enrollment of five additional subjects in the trial who are at an earlier stage of disease. To date, *SPK-7001* has been well tolerated and we have not observed any product candidate-related serious adverse events, or SAEs, in this trial. We have received orphan product designation for *SPK-7001* 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 $15.0 million milestone payment in each of December 2015 and 2016 and are eligible to receive up to an additional $230.0 million in aggregate milestone payments, as well as royalties calculated as a low-teen percentage of net product sales. In November 2017, we amended our global collaboration agreement with Pfizer. Under the terms of this amendment, we will receive a $10.0 million upfront payment and up to an additional $15.0 million in potential milestone payments. In July 2016, FDA granted breakthrough therapy designation to *SPK-9001,* our lead product candidate in our *SPK-FIX* program.

Over the past year, Pfizer and we provided periodic updates at medical meetings on the progress of the ongoing Phase 1/2 trial of *SPK-9001,* most recently in July 2017 at the International Society of Hemostasis and Thrombosis Congress. As of the data cutoff date of June 5, 2017, the annualized bleeding rate for the ten trial participants had been reduced by 96% and the annualized infusion rate had been reduced by 99%, with five of the ten participants having been followed for over 12 months. One of the ten participants has infused factor IX concentrates as a precaution against suspected bleeds. No participants developed factor IX inhibitors and no SAEs have been reported.

In our *SPK-FVIII* program for the treatment of hemophilia A, we recently initiated a dose-escalating Phase 1/2 clinical trial for our lead product candidate, *SPK-8011.* On August 2, 2017, we announced top-line preliminary data from the trial. To date, five participants have been infused in the trial and there have been no SAEs reported, including no factor VIII inhibitors and no thrombotic events. As of the August 1, 2017 data cutoff, the first two participants, who received a single administration of *SPK-8011* at an initial dose of 5×10^{11} vector genomes (vg)/kg body weight, had been followed for 23 weeks and 12 weeks, respectively. During this time, there was a steady and consistent rise in factor VIII activity levels that stabilized at levels of 11% and 14% of normal, respectively. Based on these data, we elected to double the dose and infused two participants at a dose of 1×10^{12} vg/kg body weight. We recently infused one participant at a dose of 2×10^{12} vg/kg body weight. Interim data from the Phase 1/2 trial will be presented at the American Society of Hematology conference in December. We retain global commercialization rights to the *SPK-FVIII* program.

We are developing neurodegenerative disease product candidates that are intended to address TPP1 deficiency, which is a form of Batten disease, and Huntington's disease, among others. We have received orphan product designation in the United States for *SPK-TPP1* for the treatment of CLN2 disease (neuronal ceroid lipofuscinosis (NCL)) caused by TPP1 deficiency.

We have never been profitable and have incurred net losses since inception. We have an accumulated deficit of $444.0 million as of September 30, 2017. 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 nine months ended September 30, 2016 and 2017, we incurred $60.3 million and $104.7 million of research and development expenses, respectively, and $31.6 million and $74.8 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 September 30, 2017, 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 $858.2 million.

- On February 4, 2015, we completed 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. 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.

- 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.

- On June 20, 2016, we closed a follow-on offering whereby we sold 3,025,000 shares of common stock at a price to the public of $45.00 per share. The aggregate net proceeds received by us from the follow-on offering were $127.6 million, net of underwriting discounts and commissions and offering expenses payable by us.

- On August 9, 2017, we closed a follow-on offering whereby we sold 5,296,053 shares of common stock at a price to the public of $76.00 per share. The aggregate net proceeds received by us from the follow-on offering were $379.9 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 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. During the nine month periods ended September 30, 2016 and 2017, we recognized $3.9 million and $4.7 million of revenue and, as of September 30, 2017, there was $4.4 million of current deferred revenue 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:

- regulatory submissions and approval for LUXTURNA;
- expanding our medical affairs group;
- certain pre-launch activities for LUXTURNA;

- the Phase 1/2 clinical trials for *SPK-7001* and *SPK-8011*;
- research and development for additional product candidates addressing other IRDs;
- research and development for our preclinical programs; 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;
- the scope, terms and timing of regulatory approvals;
- the expense of filing, prosecuting, defending and enforcing patent claims and other intellectual property rights;
- the cost, timing and our ability to manufacture sufficient clinical and commercial supplies for any product candidates and products that we may develop; and
- the risks disclosed in the section entitled "Risk Factors" beginning on page 24 of this Quarterly Report on Form 10-Q.

A change in the outcome of any of these variables could mean a significant change in the expenses and timing associated with the development or commercialization 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, commercial 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 increased expenses related to costs associated with being a public company, including audit, legal, regulatory and tax-related services associated with maintaining compliance as a public company, director and officer insurance premiums and investor relations costs. Additionally, prior to the potential regulatory approval of our first product candidate, we anticipate an increase in payroll and related expenses as a result of our preparation for commercial operations, especially as it relates to sales and marketing.

Results of operations

Comparison of the three months ended September 30, 2016 and 2017

	Three months ended September 30,	
	2016	2017
	(in thousands)	
Revenues	$ 1,303	$ 1,900
Operating expenses:		
Research and development	22,384	39,341
Acquired in-process research and development	—	1,750
General and administrative	12,050	26,641
Total operating expenses	34,434	67,732
Loss from operations	(33,131)	(65,832)
Interest income, net	569	1,112
Loss before income taxes	(32,562)	(64,720)
Income tax benefit	—	(292)
Net loss	$ (32,562)	$ (65,012)

Revenues

For the three months ended September 30, 2016 and 2017, we recognized $1.3 million and $1.9 million, respectively, of revenue associated with our Pfizer agreement.

Research and development expenses

Our research and development expenses for the three months ended September 30, 2017 were $39.3 million compared with $22.4 million for the three months ended September 30, 2016. The $17.0 million increase was due to a $14.6 million increase in internal research and development expenses, primarily due to increased headcount, and an increase of $2.4 million in external research and development costs. The increase in external research and development was primarily from an increase of $2.3 million in our *SPK-FVIII* program and $0.1 million in our other clinical programs.

The following table summarizes our research and development expenses by product candidate or program for the three months ended September 30, 2016 and 2017:

	Three months ended September 30,	
	2016	2017
	(in thousands)	
External research and development expenses:		
LUXTURNA	$ 3,317	$ 3,195
SPK-CHM	314	512
SPK-FIX	423	423
SPK-FVIII	699	3,026
Programs in preclinical development	1,941	1,890
Total external research and development expenses	6,694	9,046
Total internal research and development expenses	15,690	30,295
Total research and development expenses	$ 22,384	$ 39,341

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

We recognize acquired-in-process research and development expense for licensed technologies because of the additional research and development efforts and marketing approval required for commercialization. Our acquired in-process research and development expense for the three months ended September 30, 2016 was zero. Our acquired in-process research and development expense for the three months ended September 30, 2017 was $1.8 million.

General and administrative expenses

General and administrative expenses for the three months ended September 30, 2017 were $26.6 million compared with $12.0 million for the three months ended September 30, 2016. General and administrative expenses consisted primarily of salaries and related costs, including stock-based compensation, legal and patent costs, professional fees and other operating costs. The $14.6 million increase was primarily due to an increase of $7.2 million in salaries and related costs, including stock-based compensation, as a result of increased headcount, an increase of $2.6 million in launch preparation activities for LUXTURNA and $4.8 million in legal and patent expenses, professional fees and other operating costs.

Comparison of the nine months ended September 30, 2016 and 2017

	Nine months ended September 30,	
	2016	2017
	(in thousands)	
Revenues	$ 3,880	$ 4,657
Operating expenses:		
Research and development	60,258	104,679
Acquired in-process research and development	—	5,207
Impairment of acquired in-process research and development	—	15,696
General and administrative	31,601	74,783
Total operating expenses	91,859	200,365
Loss from operations	(87,979)	(195,708)
Interest income, net	1,164	2,231
Loss before income taxes	(86,815)	(193,477)
Income tax benefit	—	1,816
Net loss	$ (86,815)	$ (191,661)

Revenues

For the nine months ended September 30, 2016 and 2017, we recognized $3.9 million and $4.7 million, respectively, of revenue associated with our Pfizer agreement.

Research and development expenses

Our research and development expenses for the nine months ended September 30, 2017 were $104.7 million compared with $60.3 million for the nine months ended September 30, 2016. The $44.4 million increase was due to a $35.4 million increase in internal research and development expenses, primarily due to increased headcount, and an increase of $9.0 million in external research and development. The increase in external research and development was primarily from an increase of $2.9 million in expenses related to LUXTURNA, $2.3 million in our *SPK-FVIII* program, $2.0 million in our other clinical programs and $1.8 million in our programs in preclinical development.

The following table summarizes our research and development expenses by product candidate or program for the nine months ended September 30, 2016 and 2017:

	Nine months ended September 30,	
	2016	2017
	(in thousands)	
External research and development expenses:		
LUXTURNA	$ 7,400	$ 10,323
SPK-CHM	955	1,596
SPK-FIX	1,026	2,424
SPK-FVIII	2,954	5,240
Programs in preclinical development	4,703	6,481
Total external research and development expenses	17,038	26,064
Total internal research and development expenses	43,220	78,615
Total research and development expenses	$ 60,258	$ 104,679

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

We recognize acquired-in-process research and development expense for licensed technologies because of the additional research and development efforts and marketing approval required for commercialization. Our acquired in-process research and development expense for the nine months ended September 30, 2016 was zero. Our acquired in-process research and development expense for the nine months ended September 30, 2017 was $5.2 million. This amount includes payments of $3.4 million related to a license agreement and a portion of a stock purchase entered into with Selecta that provides us with exclusive worldwide rights to Selecta's proprietary Synthetic Vaccine Particles (SVP™) platform technology for co-administration with gene therapy targets.

Impairment of acquired in-process research and development expense

During the nine months ended September 30, 2017, it was determined that we would no longer pursue product candidates utilizing the technology acquired from Genable in March 2016 and, accordingly, we recorded a non-cash impairment charge of $15.7 million. Additionally, we recognized an income tax benefit of $1.0 million related to the reversal of the deferred tax liability associated with the acquired in-process research and development during the nine months ended September 30, 2017.

General and administrative expenses

General and administrative expenses for nine months ended September 30, 2017 were $74.8 million compared with $31.6 million for the nine months ended September 30, 2016. General and administrative expenses consisted primarily of salaries and related costs, including stock-based compensation, legal and patent costs, professional fees and other operating costs. The $43.2 million increase was primarily due to an increase of $20.7 million in salaries and related costs, including stock-based compensation, as a result of increased headcount, an increase of $7.4 million in launch preparation activities for LUXTURNA and $15.1 million in legal and patent expenses, professional fees and other operating costs.

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:

	Nine months ended September 30,	
	2016	2017
	(in thousands)	
Net cash provided by (used in):		
Operating activities	$ (51,846)	$ (127,793)
Investing activities	(281,387)	(181,637)
Financing activities	130,318	396,839
Effect of exchange rate changes on cash and cash equivalents	—	102
Net increase (decrease) in cash and cash equivalents	$ (202,915)	$ 87,511

Net cash used in operating activities

Net cash used in operating activities was $51.8 million for the nine months ended September 30, 2016, and consisted of a net loss of $86.8 million adjusted for non-cash items, including depreciation expense of $2.6 million, stock-based compensation expense of $17.3 million, non-cash rent income of $0.5 million and a net decrease in operating assets and liabilities of $15.6 million. The significant items in the change in operating assets and liabilities include a decrease in other receivables of $15.5 million, of which $15.0 million is related to payment received from Pfizer, and an increase of $0.2 million in prepaid expenses and other assets and $4.1 million in accounts payable and accrued expenses, offset by a decrease in deferred revenue of $3.9 million.

Net cash used in operating activities was $127.8 million for the nine months ended September 30, 2017, and consisted of a net loss of $191.7 million adjusted for non-cash items, including a $15.7 million impairment charge on our acquired in-process research and development associated with our Genable acquisition from March 2016 and non-cash income tax benefit for the reversal of the deferred tax liability associated with the impairment of $1.0 million and $0.8 million related to our available for sale securities. Other non-cash items included a $5.2 million in acquired in-process research and development expense, which included a second payment and equity investment payment related to our collaboration agreement with Selecta, depreciation expense of $3.5 million, stock-based compensation expense of $33.8 million, and non-cash rent expense of $0.6 million. Net cash used in operating activities also included a net decrease in operating assets and liabilities of $6.9 million. The significant items in the change in operating assets include a decrease in other receivables of $10.7 million, primarily driven by a $15.0 million payment received on our Pfizer receivable, and an increase of $2.5 million in prepaid expenses and other assets as a result of large prepayments related to preclinical and clinical expenses. The significant items in the change in operating liabilities include an increase in accounts payable and accrued expenses of $0.8 million mainly due to an increase in accruals related to bonus and other related salary accruals as a result of increased headcount. The change in operating liabilities also includes an increase in deferred rent of $2.5 million related to tenant improvement allowances, and a decrease in deferred revenue of $4.7 million.

Net cash used in investing activities

Net cash used in investing activities for the nine months ended September 30, 2016 was $281.4 million, consisting of net purchases of marketable securities of $268.0 million, costs related to the purchase of property and equipment of $7.5 million and $5.9 million of cash consideration for the acquisition of Genable, net of cash acquired.

Net cash used in investing activities for the nine months ended September 30, 2017 was $181.6 million, consisting of net purchases of marketable securities of $167.9 million, purchases of property and equipment of $8.9 million, and payments related to our license agreements of $4.8 million.

Net cash provided by financing activities

Net cash provided by financing activities for the nine months ended September 30, 2016 was $130.3 million, which consisted of $127.6 million of net proceeds from our follow-on public offering in June 2016 and $1.8 million from the exercise of stock options, and proceeds from long-term debt of $1.6 million, offset by costs of $0.7 million paid in the first quarter of 2016 related to our follow-on offering in December 2015.

Net cash provided by financing activities for the nine months ended September 30, 2017 was $396.8 million, which consisted of $380.0 million of net proceeds from our follow-on public offering in August 2017, $17.0 million from the exercise of stock options and $0.6 million of proceeds from the issuance of common stock under our employee stock purchase plan, offset by $0.6 million in purchases of treasury stock related to the settlement for taxes of vested stock and $0.2 million in payments of long-term debt.

Funding requirements

We expect our expenses to increase compared to prior periods in connection with our ongoing activities, particularly as we prepare for commercialization, 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-launch expenses.

The expected use of our cash and cash equivalents and marketable securities of $574.9 million as of September 30, 2017 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, the timing and outcome of regulatory filings and actions, whether and when we commercialize and products, 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 and marketable securities.

Based on our planned use of our cash and cash equivalents and marketable securities, we estimate that such funds will be sufficient to enable us to prepare for commercialization of LUXTURNA, complete our Phase 1/2 trials for *SPK-7001, SPK-9001* and *SPK-8011*, advance certain of our other pipeline product candidates and fund our operating expenses and capital expenditure requirements into 2021. 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.

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, or SEC, rules.

Contractual obligations

In January 2017, we amended our lease for office space in Philadelphia to lease an additional 24,800 square feet that will commence on January 1, 2018 and terminate on December 31, 2028. The additional leased space will increase our future minimum lease payments by $11.5 million over the life of the lease.

There were no other material changes to our contractual obligations and commitments described under Management's Discussion and Analysis of Financial Condition and Results of Operations in the Annual Report on Form 10-K for the year ended December 31, 2016.

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 consolidated financial statements, which have been prepared in accordance with U.S. generally accepted accounting principles. The preparation of these consolidated 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.

There have been no material changes to our critical accounting policies from those described in Management's Discussion and Analysis of Financial Condition and Results of Operations included in our Annual Report on Form 10-K, which was filed with the SEC on February 28, 2017.

Item 3. Quantitative and Qualitative Disclosures about Market Risk

We are exposed to market risk related to changes in interest rates. As of September 30, 2017, we had cash and cash equivalents and marketable securities, including our investment in Selecta, of $574.9 million, primarily invested in U.S. government agency and corporate securities, 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. Our marketable securities are subject to interest rate risk and will fall in value if market interest rates increase. If market interest rates were to increase immediately and uniformly by 100 basis points from levels as of September 30, 2017, the net fair market value of our marketable securities would have resulted in a hypothetical decline of approximately $2.7 million.

Item 4. 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 September 30, 2017. 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 SEC'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 September 30, 2017, 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.

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 quarter ended September 30, 2017 that has materially affected, or is reasonably likely to materially affect, our internal control over financial reporting.

PART II. OTHER INFORMATION

Item 1. Legal Proceedings

We currently are not subject to any material legal proceedings.

Item 1A. Risk Factors

The following risk factors and other information included in this Quarterly Report on Form 10-Q 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 1 of this Quarterly Report on Form 10-Q 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 $86.8 million and $191.7 million for the nine months ended September 30, 2016 and 2017, respectively. As of September 30, 2017, we had an accumulated deficit of $444.0 million. We have financed our operations primarily through private placements of our preferred stock, our initial public offering, or IPO, which closed on February 4, 2015, and follow-on offerings which closed on December 21, 2015, June 20, 2016 and August 9, 2017. We received net proceeds from the IPO and follow-on offerings of $775.7 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 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:

- seek marketing approvals for any of our product candidates that successfully complete clinical trials;
- establish and grow a marketing and distribution infrastructure to commercialize LUXTURNA, if approved, and any other product candidates for which we may submit for and obtain marketing approval;
- continue our clinical development of our product candidates, including our Phase 1/2 clinical trials for *SPK-7001, SPK-9001* and *SPK-8011*;
- conduct Investigational New Drug, or IND, enabling studies for our preclinical programs;
- initiate additional preclinical studies and clinical trials for our other product candidates;
- seek to identify additional product candidates;
- validate a commercial-scale current good manufacturing practices, or cGMP, manufacturing facility;
- build out additional laboratory and cGMP manufacturing capacity;
- further develop our gene therapy platform;
- expand our medical affairs efforts;
- 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 unless and until such time as LUXTURNA may be approved by the U.S. Food and Drug Administration, or FDA, or other non-US regulatory authorities and we are able to successfully market and sell LUXTURNA. Our ability to generate future revenues from product sales depends heavily on our, or our collaborators', success in:

- completing research and preclinical and clinical development of our product candidates and identifying new gene therapy product candidates;
- seeking and obtaining regulatory and marketing approvals for product candidates for which we complete clinical trials;
- launching and commercializing product candidates for which we obtain regulatory and marketing approval by establishing a sales force, marketing and distribution infrastructure or, alternatively, collaborating with a commercialization partner;
- qualifying for adequate coverage and reimbursement by government and third-party payors for our product candidates;
- maintaining and enhancing a sustainable, scalable, reproducible and transferable manufacturing process for our vectors and product candidates;
- establishing and maintaining supply and manufacturing relationships with third parties that can provide adequate, in both amount and quality, products and services to support clinical development and the market demand for our product candidates, if approved;
- obtaining market acceptance of our product candidates as a viable treatment option;
- addressing any competing technological and market developments;
- implementing additional internal systems and infrastructure, as needed;
- negotiating favorable terms in any collaboration, licensing or other arrangements into which we may enter and performing our obligations in such collaborations;
- maintaining, protecting and expanding our portfolio of intellectual property rights, including patents, trade secrets and know-how;
- avoiding and defending against third-party interference or infringement claims; and
- 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, the European Medicines Agency, or 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, diagnostics and genetic testing, 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 September 30, 2017, our cash and cash equivalents and marketable securities, including our equity investment in Selecta, were $574.9 million. Our research and development expenses increased from $60.3 million for the nine months ended September 30, 2016 to $104.7 million for the nine months ended September 30, 2017. We estimate that our cash and cash equivalents and marketable securities as of September 30, 2017 will enable us to fund our operating expenses and capital expenditure requirements into 2021.

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

- the costs of preparing and submitting marketing approvals for any of our product candidates that successfully complete clinical trials;
- the cost and our ability to establish commercial infrastructure and manufacturing capabilities required to support the launch of LUXTURNA;
- whether additional clinical testing is required to secure regulatory approvals for all intended or desired indications of LUXTURNA*;*
- the scope, progress, results and costs of drug discovery, recruitment, laboratory testing, preclinical development and clinical trials for our other product candidates;
- the costs associated with the build out of additional laboratory and cGMP manufacturing capacity;
- 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. Currently, no gene therapy product has been approved for a genetic disease in the United States and only two such products have 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 products. There can be no assurance that we will not experience problems or delays in developing new products 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 LUXTURNA in our preclinical and clinical development of other product candidates, we may be unable to reduce development timelines and costs for our other 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 approved products on a timely or profitable basis, if at all. We, a collaborator or another group may uncover a previously unknown risk associated with adeno-associated virus, or AAV, and this may prolong the period of observation required for obtaining regulatory approval or may necessitate additional clinical testing.

In addition, the clinical trial requirements of FDA, EMA and other regulatory authorities and the criteria these regulators use to determine the safety and efficacy of a product candidate vary substantially according to the type, complexity, novelty and intended use and market of such product candidates. The regulatory approval process for novel product candidates such as ours can be more expensive and take longer than for other, better known or more extensively studied product candidates. Only two gene therapy products for genetic diseases, uniQure N.V.'s Glybera and GlaxoSmithKline plc's Strimvelis, have received marketing authorization from the EMA and no gene therapy products for a genetic disease have received marketing approval from FDA. Even if we are successful in developing product candidates, 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 EU, or how long it will take to commercialize our product candidates. Approvals by the EMA may not be indicative of what FDA may require for approval and vice versa.

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 Tissue and Advanced 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 announced in 2014 that the RAC will 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 approved its initiation. Conversely, FDA can put an IND on a clinical hold even if the RAC has provided a favorable review or an exemption from in-depth, public review. If we were to engage an NIH-funded institution, such as the Children's Hospital of Philadelphia, or 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, the European Commission 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 LUXTURNA 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 LUXTURNA should be indicated for the treatment of patients with any IRD mediated by *RPE65* mutations, the results from our pivotal Phase 3 clinical trial for LUXTURNA, 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 LUXTURNA, we might obtain marketing approval only to treat patients diagnosed with leber congenital amaurosis, or 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 LUXTURNA 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 LUXTURNA for 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 LUXTURNA to treat patients diagnosed with RP due to *RPE65* mutations or other *RPE65*-mediated IRDs. The inability to market LUXTURNA to treat patients with these other clinical classifications would have a material adverse effect on our projected revenues from LUXTURNA 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 LUXTURNA, 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 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 LUXTURNA. 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 multi-luminance mobility test, or MLMT, 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. The MLMT is designed to measure improvements in peripheral vision and improvements in night blindness, the two predominant visual deficits in patients with *RPE65*-mediated IRDs. The MLMT for our pivotal Phase 3 clinical trial of LUXTURNA 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 MLMT 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 dialogue pursuant to the breakthrough therapy designation of LUXTURNA, 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 MLMT 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 biologics license application, or 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. Neither the fact that FDA accepted our BLA for filing and granted it Priority Review nor the recommendation of approval of the Cellular, Tissue and Gene Therapies Advisory Committee on October 12, 2017 indicates that FDA has made any decisions about any of the above judgments, nor guarantees approval by the January 12, 2018 PDUFA date. Other regulatory authorities in the EU 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 MLMT as a result of their cognitive development, and not due to LUXTURNA. 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 LUXTURNA, 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.

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 or preliminary stages of 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 limited clinical efficacy data for the use of *SPK-7001, SPK-9001 and SPK-8011* in humans. There can be no assurance that the results seen in preclinical studies for any of our product candidates ultimately will result in success in 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 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. 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.

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

- difficulty in establishing or managing relationships with contract research organizations, or CROs, and physicians;
- different standards for the conduct of clinical trials;
- absence in some countries of established groups with sufficient regulatory expertise for review of gene therapy protocols;
- our inability to locate qualified local consultants, physicians and partners; and
- the potential burden of complying with a variety of foreign laws, medical standards and regulatory requirements, including the regulation of pharmaceutical and biotechnology products and treatment.

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

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

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

- delays in reaching a consensus with regulatory authorities on trial design;
- delays in reaching agreement on acceptable terms with prospective CROs and clinical trial sites;
- delays in opening clinical trial sites or obtaining required IRB or independent Ethics Committee approval at each clinical trial site;
- delays in recruiting suitable subjects to participate in our clinical trials;
- imposition of a clinical hold by regulatory authorities as a result of a serious adverse event or after an inspection of our clinical trial operations or trial sites;

- failure by us, any CROs we engage or any other third parties to adhere to clinical trial requirements;
- failure to perform in accordance with FDA good clinical practices, or GCP, or applicable regulatory guidelines in the EU 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 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, which we are unable to mitigate with immuno-suppressive regimens, 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 LUXTURNA to manage post-operative inflammation related to the standard vitrectomy procedure subjects undergo prior to administration of LUXTURNA. We subsequently adjusted the protocol regarding the use of local steroids and FDA released the clinical hold, allowing the trial to proceed.

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

Additionally, FDA could require us to adopt a Risk Evaluation and Mitigation Strategy, or REMS, and other non-US regulatory authorities could impose other specific obligations as a condition of approval to ensure that the benefits of our product candidates outweigh their risks, which could delay approval of our product candidates. A REMS may include, among other things, a communication plan to health care practitioners or patients, and elements to assure safe use, such as restricted distribution methods, patient registries, and other risk minimization tools. Similar programs could be imposed by EMA. 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 EU, 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 EU, 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 EU. 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 EU would be sufficient to justify the necessary investment in developing the drug or biologic product.

LUXTURNA has been granted orphan drug designation by FDA for the treatment of IRD caused by biallelic mutations to the *RPE65* gene and from the European Commission for the treatment of both LCA and RP due to *RPE65* mutations. *SPK-9001* has received both breakthrough therapy and orphan drug designation by FDA. *SPK-7001* has been granted orphan drug designation by FDA and the European Commission for the treatment of choroideremia. *SPK-TPP1* has been granted orphan product designation by FDA for the treatment of CLN2 disease (neuronal ceroid lipofuscinosis (NCL)) caused by TPP1 deficiency.

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.

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 EU. 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 EU 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 patient care. In the EU, 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 LUXTURNA for nyctalopia in patients with LCA due to *RPE65* mutations, as confirmed by genetic testing. We have received breakthrough therapy designation for *SPK-9001* for the treatment of hemophilia B. We 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 LUXTURNA and *SPK-9001* have been designated as breakthrough therapy product candidates, FDA may later decide that one or both no longer meet 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 LUXTURNA for the treatment of patients diagnosed with LCA due to *RPE65* mutations but not for the treatment of patients with RP due to *RPE65* mutations or other *RPE65*-mediated IRDs) or they may impose significant limitations in the form of narrow indications, warnings or a REMS. These regulatory authorities may require precautions or contra-indications with respect to conditions of use or they may grant approval subject to the performance of costly post-marketing clinical trials. In addition, regulatory authorities may not approve the labeling claims that are necessary or desirable for the successful commercialization of our product candidates. Any of the foregoing scenarios could materially harm the commercial prospects for our product candidates and materially and adversely affect our business, financial condition, results of operations and prospects.

Further, the regulatory authorities may require concurrent approval or the CE mark of a companion diagnostic device. For the product candidates we currently are developing, we believe that diagnoses based on symptoms, in conjunction with existing genetic tests developed and administered by laboratories certified under the Clinical Laboratory Improvement Amendments, or CLIA, are sufficient to diagnose patients and will be permitted by FDA. For future product candidates, however, it may be necessary to use FDA-cleared or FDA-approved diagnostic tests to diagnose patients or to assure the safe and effective use of product candidates in trial subjects. FDA refers to such tests as *in vitro* companion diagnostic devices. On July 31, 2014, FDA announced the publication of a final guidance document describing the agency's current thinking about the development and regulation of *in vitro* companion diagnostic devices. The final guidance articulates a policy position that, when safe and effective use of a therapeutic product depends on a diagnostic device, FDA generally will require approval or clearance of the diagnostic device at the same time that FDA approves the therapeutic product. The final guidance allows for two exceptions to the general rule of concurrent drug/device approval, namely, when the therapeutic product is intended to treat serious and life-threatening conditions for which no alternative exists, and when a serious safety issue arises for an approved therapeutic agent, and no FDA-cleared or FDA-approved companion diagnostic test is yet available. At this point, it is unclear how FDA will apply this policy to our current or future gene therapy product candidates. Should FDA deem genetic tests used for diagnosing patients for our therapies to be *in vitro* companion diagnostics requiring FDA clearance or approval, we may face significant delays or obstacles in obtaining approval of a BLA for our product candidates. In the EU, Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on in vitro diagnostic medical devices will apply from 2022 and repeal the current applicable provisions. Regulation (EU) 2017/746 will 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, or the specific obligations imposed as a condition for marketing authorization by equivalent authorities in foreign jurisdiction, particularly by the European Commission, 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, in the United States, 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 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 the EU, the advertising and promotion of our products are subject to EU laws governing promotion of medicinal products, interactions with physicians, misleading and comparative advertising and unfair commercial practices. In addition, other legislation adopted by individual EU Member States may apply to the advertising and promotion of medicinal products. These laws require that promotional materials and advertising in relation to medicinal products comply with the product's Summary of Product Characteristics, or SmPC, as approved by the competent authorities. The SmPC is the document that provides information to physicians concerning the safe and effective use of the medicinal product. It forms an intrinsic and integral part of the marketing authorization granted for the medicinal product. Promotion of a medicinal product that does not comply with the SmPC is considered to constitute off-label promotion. The off-label promotion of medicinal products is prohibited in the EU. The applicable laws at EU level and in the individual EU Member States also prohibit the direct-to-consumer advertising of prescription-only medicinal products. Violations of the rules governing the promotion of medicinal products in the EU could be penalized by administrative measures, fines and imprisonment. These

laws may further limit or restrict the advertising and promotion of our products to the general public and may also impose limitations on our promotional activities with health care professionals.

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 cGMP, requirements and adherence to commitments made in the BLA or foreign marketing application. If we, or a regulatory authority, discover previously unknown problems with a product, such as adverse events of unanticipated severity or frequency, or problems with the facility where the product is manufactured or disagrees with the promotion, marketing or labeling of that product, a regulatory authority may impose restrictions relative to that product, the manufacturing facility or us, including requiring recall or withdrawal of the product from the market or suspension of manufacturing.

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

- issue a warning letter asserting that we are in violation of the law;
- seek an injunction or impose administrative, civil or criminal penalties or monetary fines;
- suspend or withdraw regulatory approval;
- suspend any ongoing clinical trials;
- refuse to approve a pending BLA or comparable foreign marketing application (or any supplements thereto) submitted by us or our strategic partners;
- restrict the marketing or manufacturing of the product;
- seize or detain the product or otherwise require the withdrawal of the product from the market;
- refuse to permit the import or export of products; or
- refuse to allow us to enter into supply contracts, including government contracts.

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

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

Similarly to the United States, both marketing authorization holders and manufacturers of medicinal products are subject to comprehensive regulatory oversight by the EMA and the competent authorities of the individual EU Member States both before and after grant of the manufacturing and marketing authorizations. This includes control of compliance with cGMP rules, which govern quality control of the manufacturing process and require documentation policies and procedures. We and our third party manufacturers would be required to ensure that all of our processes, methods, and equipment are compliant with cGMP. Failure by us or by any of our third party partners, including suppliers, manufacturers, and distributors to comply with EU laws and the related national laws of individual EU Member States governing the conduct of clinical trials, manufacturing approval, marketing authorization of medicinal products, both before and after grant of marketing authorization, and marketing of such products following grant of authorization may result in administrative, civil, or criminal penalties. These penalties could include delays in or refusal to authorize the conduct of clinical trials or to grant marketing authorization, product withdrawals and recalls, product seizures, suspension, or variation of the marketing authorization, total or partial suspension of production, distribution, manufacturing, or clinical trials, operating restrictions, injunctions, suspension of licenses, fines, and criminal penalties.

In addition, EU legislation related to pharmacovigilance, or the assessment and monitoring of the safety of medicinal products, provides that the EMA and the competent authorities of the EU Member States have the authority to require companies to conduct additional post-approval clinical efficacy and safety studies. The legislation also governs the obligations of marketing authorization holders with respect to additional monitoring, adverse event management and reporting. Under the pharmacovigilance legislation and its related regulations and guidelines, we may be required to conduct a labor intensive collection of data regarding the risks and benefits of marketed products and may be required to engage in

ongoing assessments of those risks and benefits, including the possible requirement to conduct additional clinical studies, which may be time-consuming and expensive and could impact our profitability. Non-compliance with such obligations can lead to the variation, suspension or withdrawal of marketing authorization or imposition of financial penalties or other enforcement measures.

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., Applied Genetic Technologies Corporation, Asklepios BioPharmaceutical, Inc., Audentes Therapeutics, Inc., Adverum Biotechnologies, Inc., AveXis, Inc., Abeona Therapeutics Inc., BioMarin Pharmaceutical Inc., 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 programs, the main competitors include:

- **LUXTURNA.** While no approved pharmacologic agents exist for patients with *RPE65*-mediated IRD, 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. Novelion Therapeutics, Inc. (formally 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, including MeiraGTx and Horama SAS. 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 Inc., or Pfizer. Many other companies are developing gene therapies to treat hemophilia B, including Shire, PLC, Sangamo BioSciences, Inc., Freeline Therapeutics and uniQure N.V.
- ***SPK-FVIII*.** The standard of care for moderate to severe hemophilia A is intravenously administered FVIII protein or its derivatives. The main competitors with product candidates under development to treat hemophilia A include BioMarin Pharmaceutical Inc., Dimension Therapeutics Inc. in collaboration with Bayer HealthCare, Shire PLC, uniQure N.V., Sangamo Biosciences, Inc. in collaboration with Pfizer, Telethon Institute for Gene Therapy in collaboration with Biogen Inc., Alnylam Incorporated, Novo Nordisk A/S and Roche Holding AG.

Many of our potential competitors, alone or with their strategic partners, have substantially greater financial, technical and other resources, such as larger research and development, clinical, marketing and manufacturing organizations. Mergers and acquisitions in the biotechnology and pharmaceutical industries may result in even more resources being concentrated among a smaller number of competitors. Our commercial opportunity could be reduced or eliminated if competitors develop and commercialize products that are safer, more effective, have fewer or less severe side effects, are more convenient or are less expensive than any products that we may develop. Competitors also may obtain FDA or other regulatory approval for their products more rapidly or earlier than we may obtain approval for ours, which could result in our competitors establishing a strong market position before we are able to enter the market. Additionally, technologies developed by our competitors may render our potential product candidates uneconomical or obsolete, and we may not be successful in marketing our product candidates against competitors.

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

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

Approval of a product candidate in the United States by FDA does not ensure approval of such product candidate by regulatory authorities in other countries or jurisdictions, and approval by one foreign regulatory authority does not ensure approval by regulatory authorities in other foreign countries or by FDA. Sales of our 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 have submitted, and had validated, a marketing authorization application, or MAA, to EMA for LUXTURNA and intend to submit for approval of our other product candidates in the EU, 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 EU 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 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.

The results of the United Kingdom's referendum on withdrawal from the EU may have a negative effect on global economic conditions, financial markets and our business.

On March 29, 2017, the Government of the United Kingdom, or the UK, initiated the formal procedure of withdrawal from the EU. The procedure involves a two-year negotiation period in which the UK and the EU must conclude an agreement setting out the terms of the UK's withdrawal and the arrangements for the UK's future relationship with the EU. This negotiation period could be extended by a unanimous decision of the European Council, in agreement with the UK.

The referendum has created significant uncertainty concerning the future relationship between the UK and the EU. This includes the laws and regulations that will apply as the UK determines which EU laws to replace or replicate in the event of a withdrawal. From a regulatory perspective, the UK's withdrawal could result in significant complexity and risks. A basic requirement related to the grant of a marketing authorization for a medicinal product in the EU is the requirement that the applicant is established in the EU. Following withdrawal of the UK from the EU, marketing authorizations previously granted to applicants established in the UK may no longer be valid. Moreover, depending upon the exact terms of the UK's withdrawal, there is an arguable risk that the scope of a marketing authorization for a medicinal product granted by the European Commission pursuant to the centralized procedure would not, in the future, include the UK. In these circumstances, an authorization granted by the UK's competent authorities would always be required to place medicinal products on the UK market.

In addition, the laws and regulations that will apply after the UK withdraws from the EU may have implications for manufacturing sites that hold certification issued by the UK competent authorities. Our capability to rely on these manufacturing sites for products intended for the EU market would also depend upon the exact terms of the UK's withdrawal.

The UK referendum has also given rise to calls for the governments of other EU Member States to consider withdrawal from the EU. These developments, or the perception that they could occur, have had and may continue to have a material adverse effect on global economic conditions and the stability of global financial markets. They may significantly reduce global market liquidity and restrict the ability of key market participants to operate in certain financial markets.

Risks related to third parties

We have in the past entered, 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, as amended in June 2016 and as further amended in November 2017, 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 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;
- 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. Our collaborators are subject to similar risks with respect to product development, regulatory approval and commercialization and their business, results of operations and financial condition could be harmed should they experience any such risks, which could adversely affect our collaboration.

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

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

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

If we are unable to reach agreements with suitable collaborators on a timely basis, on acceptable terms or at all, we may have to curtail the development of a product candidate, reduce or delay its development program, delay its potential commercialization, reduce the scope of any sales or marketing activities or increase our expenditures and undertake development or commercialization activities at our own expense. If we elect to fund development or commercialization activities on our own, we may need to obtain additional expertise and additional capital, which may not be available to us on acceptable terms or at all. If we fail to enter into collaborations and do not have sufficient funds or expertise to undertake the necessary development and commercialization activities, we may not be able to further develop our product candidates and our business, financial condition, results of operations and prospects may be materially and adversely affected.

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 completed construction of our own manufacturing facility in 2014, and we may encounter difficulties in validating and operating this 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.

Before we can begin to commercially manufacture our product candidates in our own facility, we must obtain regulatory approval from FDA, which includes a review of our manufacturing process and facility. In August 2017, our GMP manufacturing facility underwent a successful preapproval inspection by FDA for LUXTURNA. A manufacturing authorization must also be obtained from the appropriate regulatory authorities of the EU Member States. In order to obtain approval, we will need to ensure that all of our processes, methods and equipment are compliant with cGMP, and perform extensive audits of vendors, contract laboratories and suppliers. If any of our vendors, contract laboratories or suppliers is found to be out of compliance with cGMP, we may experience delays or disruptions in manufacturing while we work with these third parties to remedy the violation or while we work to identify suitable replacement vendors, contract laboratories or suppliers. 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 may rely on CHOP and other third parties to conduct aspects of our product manufacturing, and these third parties may not perform satisfactorily.

While we expect to produce our commercial supply of LUXTURNA at our own facility, we may rely on CHOP for the production of certain 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 to provide for continued production of product candidates for our current and future early stage clinical trials. 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 enter into 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 or action of equivalent competent authorities in foreign jurisdictions, 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 us could materially harm our business, financial condition, results of operations and prospects.

If 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 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.

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 and other components 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 expand our market development capabilities or enter into agreements with third parties to market and sell our product candidates, we may be unable to generate any product revenue.

To successfully commercialize any products that may result from our development programs, we need to continue to expand our market development organization, either on our own or with others. The development of our own market development team is, and will continue to 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.

As part of our plan to market LUXTURNA 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 LUXTURNA to appropriate patients via sub-retinal injection. This procedure requires significant skill and training, which could take substantial time to complete after approval, before the product can be sold and administered. In addition, if we are unable to recruit or train sufficient retinal surgeons to perform the procedure properly, the availability of LUXTURNA could be substantially diminished, which would adversely affect our business, financial condition, results of operations and prospects.

We have entered into a collaboration with Pfizer for the development and commercialization of *SPK-FIX* product candidates for the treatment of hemophilia B pursuant to which Pfizer would commercialize such product candidates, and we would be eligible to receive specified milestone payments and royalties, for any product developed under the agreement. We may enter into collaborations regarding other of our product candidates with other entities to utilize their established marketing and distribution capabilities, but we may be unable to enter into such agreements on favorable terms, if at all. If any current or future collaborators do not commit sufficient resources to commercialize our products, or we are unable to develop the necessary capabilities on our own, we will be unable to generate sufficient product revenue to sustain our business. We compete with many companies that currently have extensive, experienced and well-funded medical affairs, marketing and sales operations to recruit, hire, train and retain marketing and sales personnel. We also face competition in our search for third parties to assist us with the sales and marketing efforts of our product candidates. Without an internal team or the support of a third party to perform marketing and sales functions, we may be unable to compete successfully against these more established companies.

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 EU 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.

Government price controls or other changes in pricing regulation could restrict the amount that we are able to charge for LUXTURNA, if approved, or any of our other product candidates that may be approved in the future, which would adversely affect our revenue and results of operations.

We expect that coverage and reimbursement of pharmaceutical drugs may be increasingly restricted both in the United States and internationally. The escalating cost of health care has led to increased pressure on the health care industry to reduce costs. In particular, drug pricing by pharmaceutical companies recently has come under increased scrutiny and continues to be subject to intense political and public debate in the United States and abroad. Government and private third-party payors have proposed health care reforms and cost reductions. A number of federal and state proposals to control the cost of health care, including the cost of drug treatments, have been made in the United States. Specifically, there have been several recent United States Congressional inquiries and proposed federal and state bills designed to, among other things, bring more transparency to drug pricing, review the relationship between pricing and manufacturer patient programs and reform government program reimbursement methodologies for drugs. In addition, there have been proposals to impose federal rebates on Medicare Part D drugs, which would require federally-mandated rebates on either all drugs dispensed to Medicare Part D beneficiaries or on only those drugs dispensed to certain groups of lower income beneficiaries. In some international markets, the government controls the pricing, which can affect the profitability of drugs. Current government regulations and possible future legislation regarding health care may affect coverage and reimbursement for medical treatment by third-party payors, which may render our product candidates, if approved, not commercially viable or may adversely affect our anticipated future revenues and gross margins.

We cannot predict the extent to which our business may be affected by these or other potential future legislative or regulatory developments. However, future price controls or other changes in pricing regulation or negative publicity related to the pricing of pharmaceutical drugs generally could restrict the amount that we are able to charge for our future products, which would adversely affect our anticipated revenue and results of operations.

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 prices of our product candidates will be paid by health maintenance, managed care, pharmacy benefit and similar healthcare management organizations, or will be reimbursed by government authorities, private health coverage insurers and other third-party payors. Coverage and reimbursement by a third-party payor may depend upon several factors, including the third-party payor's determination that use of a product is:

- a covered benefit under its health plan;
- safe, effective and medically necessary;
- appropriate for the specific patient;
- cost-effective; and
- neither experimental nor investigational.

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

There is significant uncertainty related to third-party coverage and reimbursement of newly approved products, including potential one-time gene therapies. 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. We cannot be assured that Medicare or Medicaid will cover our approved products or provide reimbursement at adequate levels to realize a sufficient return on our investment. Moreover, reimbursement agencies in the EU 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 EU 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 EU, Canada and other countries may put pricing pressure on us. In many countries, the prices of medical products are subject to varying price control mechanisms as part of national health systems. It also can take a significant amount of time after approval of a product to secure pricing and reimbursement for such product in many counties outside the United States. 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, average manufacturer price, 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.

In the EU, in particular, each EU Member State may restrict the range of medicinal products for which its national health insurance system provides reimbursement and can control the prices of medicinal products for human use marketed on its territory. As a result, following receipt of marketing authorization in an EU Member State, through any application route, an applicant is required to engage in pricing discussions and negotiations with the competent pricing authority in the individual EU Member States. Some EU Member States operate positive and negative list systems under which products may only be marketed once a reimbursement price has been agreed upon. Other EU Member States approve a specific price for the medicinal product or may instead adopt a system of direct or indirect controls on the profitability of the company placing the medicinal product on the market. The downward pressure on healthcare costs in general, particularly prescription drugs, has become more intense. As a result, increasingly high barriers are being erected to the entry of new products. In addition, we may face competition for our product candidates from lower priced products in foreign countries that have placed price controls on pharmaceutical products.

Health Technology Assessment, or HTA, of medicinal products, however, is becoming an increasingly common part of the pricing and reimbursement procedures in some EU Member States, including the UK, France, Germany, Ireland, Italy and Sweden. HTA is the procedure according to which the assessment of the public health impact, therapeutic impact and the

economic and societal impact of use of a given medicinal product in the national healthcare systems of the individual country is conducted. HTA generally focuses on the clinical efficacy and effectiveness, safety, cost, and cost-effectiveness of individual medicinal products as well as their potential implications for the healthcare system. Those elements of medicinal products are compared with other treatment options available on the market. The outcome of HTA regarding specific medicinal products will often influence the pricing and reimbursement status granted to these medicinal products by the competent authorities of individual EU Member States. The extent to which pricing and reimbursement decisions are influenced by the HTA of the specific medicinal product varies between EU Member States. In addition, pursuant to Directive 2011/24/EU on the application of patients' rights in cross-border healthcare, a voluntary network of national authorities or bodies responsible for HTA in the individual EU Member States was established. The purpose of the network is to facilitate and support the exchange of scientific information concerning HTAs. This may lead to harmonization of the criteria taken into account in the conduct of HTAs between EU Member States and in pricing and reimbursement decisions and may negatively affect price in at least some EU Member States.

Ethical, legal and social issues related to genetic testing may reduce demand for our products candidate, if approved.

We anticipate that prior to receiving certain gene therapies, patients would be required to undergo genetic testing. Genetic testing has raised concerns regarding the appropriate utilization and the confidentiality of information provided by genetic testing. Genetic tests for assessing a person's likelihood of developing a chronic disease have focused public attention on the need to protect the privacy of genetic information. For example, concerns have been expressed that insurance carriers and employers may use these tests to discriminate on the basis of genetic information, resulting in barriers to the acceptance of genetic tests by consumers. This could lead to governmental authorities restricting genetic testing or calling for limits on or regulating the use of genetic testing, particularly for diseases for which there is no known cure. Any of these scenarios could decrease demand for our product candidates, if approved.

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 EU 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;
- 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 two gene therapy products for genetic diseases approved to date in the EU. 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 EU, a variety of risks associated with international operations could materially adversely affect our business.

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

- different regulatory requirements for approval of drugs and biologics in foreign countries;
- reduced protection for intellectual property rights;
- unexpected changes in tariffs, trade barriers and regulatory requirements;
- economic weakness, including inflation, or political instability in particular foreign economies and markets;
- compliance with tax, employment, immigration and labor laws for employees living or traveling abroad;
- foreign currency fluctuations, which could result in increased operating expenses and reduced revenues, and other obligations incident to doing business in another country;
- workforce uncertainty in countries where labor unrest is more common than in the United States;
- production shortages resulting from any events affecting raw material supply or manufacturing capabilities abroad; and
- business interruptions resulting from geopolitical actions, including war and terrorism or natural disasters including earthquakes, typhoons, floods and fires.

Risks related to our business operations

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

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

Additionally, because we have limited resources, we may forego or delay pursuit of opportunities with certain programs or product candidates or for indications that later prove to have greater commercial potential. Our spending on current and future research and development programs may not yield any commercially viable products. If we do not accurately evaluate the commercial potential for a particular product candidate, we may 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 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 is, and will continue to 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 EU and other jurisdictions, provide accurate information to FDA, the European Commission and other regulatory authorities, comply with healthcare fraud and abuse laws and regulations in the United States and abroad, report financial information or data accurately or disclose unauthorized activities to us. In particular, sales, marketing and business arrangements in the healthcare industry are subject to extensive laws and regulations intended to prevent fraud, misconduct, kickbacks, self-dealing and other abusive practices. These laws and regulations restrict or prohibit a wide range of pricing, discounting, marketing and promotion, sales commission, customer incentive programs and other business arrangements. Such misconduct also could involve the improper use of information obtained in the course of clinical trials or interactions with FDA or other regulatory authorities, which could result in regulatory sanctions and cause serious harm to our reputation. We have adopted a code of conduct applicable to all of our employees, but it is not always possible to identify and deter employee misconduct, and the precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from government investigations or other actions or lawsuits stemming from a failure to comply with these laws or regulations. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business, financial condition, results of operations and prospects, including the imposition of significant fines or other sanctions.

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

Our industry is highly regulated and changes in law may adversely impact our business, operations or financial results. The Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act, or the PPACA, is a sweeping measure intended to, among other things, expand healthcare coverage within the United States, primarily through the imposition of health insurance mandates on employers and individuals and expansion of the Medicaid program.

Several provisions of the law may affect us and increase certain of our costs. For example, the Medicaid rebate rate was increased and the volume of rebated drugs has been expanded to include beneficiaries in Medicaid managed care organizations. Among other things, the PPACA also expanded the 340B drug discount program (excluding orphan drugs), including the creation of new penalties for non-compliance, included a 50% discount on brand name drugs for Medicare Part D participants in the coverage gap, or "donut hole," and imposed a new fee on certain manufacturers and importers of branded prescription drugs (excluding orphan drugs under certain conditions). The law also revised the definition of "average manufacturer price," or AMP, for reporting purposes, which could increase the amount of the Medicaid drug rebates paid to states, and created a new Patient-Centered Outcomes Research Institute to oversee clinical effectiveness research.

In addition, other legislative changes have been adopted since the PPACA was enacted. These changes include aggregate reductions in Medicare payments to providers of 2% per fiscal year, which went into effect on April 1, 2013 and, following passage of the Bipartisan Budget Act of 2015, will remain in effect through 2025 unless additional Congressional action is taken. In January 2013, President Obama signed into law the American Taxpayer Relief Act of 2012, which, among other things, further reduced Medicare payments to several types of providers and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. These new laws may result in additional reductions in Medicare and other healthcare funding, which could have a material adverse effect on our customers and, accordingly, our financial operations.

We anticipate that the PPACA, as well as other healthcare reform measures that may be adopted in the future, may result in more rigorous coverage criteria and an additional downward pressure on the reimbursement our customers may receive for our products. Further, there have been, and there may continue to be, judicial and Congressional challenges to certain aspects of the PPACA. Additional legislative and regulatory changes to the PPACA, its implementing regulations and guidance and its policies, remain possible in the 115th U.S. Congress and under the Trump Administration. However, it remains unclear how any new legislation or regulation might affect the prices we may obtain for any of our product candidates, including LUXTURNA, for which regulatory approval is obtained. Any reduction in reimbursement from Medicare and other government programs may result in a similar reduction in payments from private payors. The implementation of cost containment measures or other healthcare reforms may prevent us from being able to generate revenue, attain profitability or commercialize our products.

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.

In the United States, the research, manufacturing, distribution, sale, and promotion of drugs and biologic products are potentially subject to regulation by various federal, state, and local authorities in addition to FDA, including CMS, other divisions of the United States Department of Health and Human Services, or HHS, (e.g., the Office of Inspector General), the United States Department of Justice offices of the United States Attorney, and state and local governments. If we obtain FDA or other non-US regulatory authorities' approval for any of our product candidates and begin commercializing those products in the United States or elsewhere, 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 Anti-Kickback Statute, the federal civil and criminal False Claims Act and Physician Payments Sunshine Act and regulations and equivalent provisions in other countries. These laws will impact, among other things, our proposed sales, marketing and educational programs. In addition, we may be subject to patient privacy laws by both the federal government and the states in which we conduct our business. The laws that will affect our operations include, but are not limited to:

- the federal 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. Liability may be established under the federal Anti-Kickback Statute without proving actual knowledge of the statute or specific intent to violate it. There are a number of statutory exemptions and regulatory safe harbors protecting some common activities from prosecution; however, those

exceptions and safe harbors are drawn narrowly. Failure to meet all of the requirements of a particular statutory exception or regulatory safe harbor does not make the conduct per se illegal under the Anti-Kickback Statute, but the legality of the arrangement will be evaluated on a case-by-case basis based on the totality of the facts and circumstances. We seek to comply with the exemptions and safe harbors whenever possible, but our practices may not in all cases meet all of the criteria for safe harbor protection from anti-kickback liability. Moreover, there are no safe harbors for many common practices, such as educational and research grants or patient assistance programs. Violations of the Anti-Kickback Statute are subject to significant civil, criminal, and administrative penalties, including damages, fines, imprisonment, and exclusion from government-funded healthcare programs like Medicare and Medicaid;

- the federal civil False Claims Act, which prohibits any person from knowingly presenting, or causing to be presented, a false or fraudulent claim for payment of government funds; or knowingly and improperly avoiding, decreasing, or concealing an obligation to pay money to the federal government. In recent years, several pharmaceutical and other healthcare companies have faced enforcement actions under the federal False Claims Act for allegedly submitting false or misleading pricing information to government health care programs and providing free product to customers with the expectation that the customers would bill federal programs for the product. Other companies have faced enforcement actions for causing false claims to be submitted because of the company marketing a product for unapproved, and thus non-reimbursable, uses. Federal enforcement agencies also have showed increased interest in pharmaceutical companies' product and patient assistance programs, including reimbursement and co-pay support services, and a number of investigations into these programs have resulted in significant civil and criminal settlements. In addition, the government may assert that a claim including items or services resulting from a violation of the federal anti-kickback statute constitutes a false or fraudulent claim for purposes of the federal civil False Claims Act. The civil False Claims Act also permits an individual acting as a "whistleblower" to bring actions on behalf of the federal government alleging violations of the statute and to share in any monetary recovery. False Claims Act liability is potentially significant because the statute provides for treble damages and mandatory penalties of $10,781 to $21,563 per false claim or statement. Because of the potential for large monetary exposure, healthcare and pharmaceutical companies often resolve allegations without admissions of liability for significant and material amounts to avoid the uncertainty of treble damages and per claim penalties that may awarded in litigation proceedings. Companies may be required, however, to enter into corporate integrity agreements with the government, which may impose substantial costs on companies to ensure compliance. Criminal prosecution is possible for making or presenting a false or fictitious or fraudulent claim to the federal government;
- the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, which imposes criminal and civil liability for, among, other things, executing, or attempting to execute, a scheme to defraud any healthcare benefit program or knowingly and willfully falsifying, concealing, or covering up a material fact or making any materially false, fictitious, or fraudulent statement or representation, or making or using any false writing or document knowing the same to contain any materially false, fictitious or fraudulent statement or entry, in connection with the delivery of, or payment for, healthcare benefits, items, or services;
- HIPAA and its implementing regulations, which impose 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;
- numerous other federal and state laws and regulations that address privacy and data security, including state data breach notification laws, state health information privacy laws, and federal and state consumer protection laws (e.g., Section 5 of the Federal Trade Commission Act, or FTC Act), govern the collection, use, disclosure and protection of health-related and other personal information, many of which differ from each other in significant ways, thus complicating compliance efforts;
- the federal Physician Payment Sunshine Act, being implemented as the Open Payments Program, imposes annual reporting requirements on certain manufacturers of drugs, devices, or biologics for payments and other transfers of value by them ,directly or indirectly, to physicians and teaching hospitals, as well as ownership and investment interests held by physicians and their immediate family members. A manufacturer's failure to submit timely, accurately and completely the required information for all payments, transfers of value or ownership or investment interests may result in civil monetary penalties of up to an aggregate of $150,000 per year, and up to an aggregate of $1 million per year for "knowing failures." Manufacturers must submit reports by the 90th day of each calendar year; and
- analogous state laws and regulations, such as state anti-kickback and false claims laws, may apply to sales or marketing arrangements and claims involving healthcare items or services reimbursed by non-governmental third-party payors, including private insurers. Several states also require pharmaceutical companies to report expenses relating to the marketing and promotion of pharmaceutical products in those states and to report gifts and payments to

individual health care providers in those states. Some of these states also prohibit certain marketing-related activities, including the provision of gifts, meals, or other items to certain health care providers. In addition, several states require pharmaceutical companies to implement compliance programs or marketing codes.

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. Even if we are not determined to have violated these laws, government investigations into these issues typically require the expenditure of significant resources and generate negative publicity, which could harm our financial condition and divert the attention of our management from operating our business.

In the EU, interactions between pharmaceutical companies and physicians are also governed by strict laws, regulations, industry self-regulation codes of conduct and physicians' codes of professional conduct in the individual EU Member States. 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 EU. The provision of benefits or advantages to physicians is also governed by the national anti-bribery laws of EU Member States, such as the UK Bribery Act 2010. The UK Bribery Act applies to any company incorporated in or "carrying on business" in the UK, irrespective of where in the world the alleged bribery activity occurs, which could have implications for our interactions with physicians both in and outside of the UK. Infringement of these laws could result in substantial fines and imprisonment.

Payments made to physicians in certain EU Member States must be publicly 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 EU Member States. These requirements are provided in the national laws, industry codes or professional codes of conduct, applicable in the EU Member States. Failure to comply with these requirements could result in reputational risk, public reprimands, administrative penalties, fines or imprisonment.

EU Member States, Switzerland and other countries have also adopted data protection laws and regulations, which impose significant compliance obligations. In the EU, the collection and use of personal health data is currently governed by the provisions of the EU Data Protection Directive. The EU Data Protection Directive and the national implementing legislation of the EU Member States impose strict obligations and restrictions on the ability to collect, analyze and transfer personal data, including health data from clinical trials and adverse event reporting. In particular, these obligations and restrictions concern the consent of the individuals to whom the personal data relates, the information provided to the individuals, notification of data processing obligations to the competent national data protection authorities and the security and confidentiality of the personal data. Data protection authorities from the different EU Member States may interpret the EU Data Protection Directive and national laws differently and impose additional requirements, which add to the complexity of processing personal data in the EU.

Guidance on implementation and compliance practices are often updated or otherwise revised. For example, the EU Data Protection Directive prohibits the transfer of personal data to countries outside of the European Economic Area that are not considered by the European Commission to provide an adequate level of data protection. These countries include the United States.

The judgment by the Court of Justice of the European Union in the Schrems case (Case C-362/14 Maximillian Schrems v. Data Protection Commissioner) determined the safe harbor framework, which was relied upon by many United States entities as a basis for transfer of personal data from the EU to the United States, to be invalid. United States entities therefore, had only the possibility to rely on the alternate procedures for such data transfer provided in the EU Data Protection Directive.

On February 29, 2016, however, the European Commission announced an agreement with the United States Department of Commerce, or the DOC, to replace the invalidated safe harbor framework with a new "Privacy Shield". On July 12, 2016, the European Commission adopted a decision on the adequacy of the protection provided by the Privacy Shield. The Privacy Shield is intended to address the requirements set out by the Court of Justice of the European Union in its Schrems judgment by imposing more stringent obligations on companies, providing stronger monitoring and enforcement by the DOC and the Federal Trade Commission, and making commitments on the part of public authorities regarding access to information. United States entities have been able to certify to the DOC their compliance with the privacy principles of the Privacy Shield since August 1, 2016 and rely on the Privacy Shield certification to transfer of personal data from the EU to the United States.

In September 2016, the Irish privacy advocacy group Digital Rights Ireland brought an action for annulment of the European Commission decision on the adequacy of the Privacy Shield before the Court of Justice of the EU (Case T-670/16). In October 2016, a further action for annulment was brought by three French digital rights advocacy group, La Quadrature du

Net, French Data Network and the Fédération FDN (Case T-738/16). Both cases are currently pending before the European Court of Justice. If the Court of Justice of the EU invalidates the Privacy Shield, it will no longer be possible to rely on the Privacy Shield certification to transfer personal data from the EU to entities in the United States. Adherence to the Privacy Shield is not, however, mandatory. Entities based in the United States are permitted to rely either on their adherence to the Privacy Shield or on the other authorized means and procedures to transfer personal data provided by the EU Data Protection Directive.

In addition, the General EU Data Protection Regulation, or GDPR, intended to replace the current EU Data Protection Directive entered into force on May 24, 2016 and will apply from May 25, 2018. The GDPR will introduce new data protection requirements in the EU and substantial fines for breaches of the data protection rules. The GDPR will increase our responsibility and liability in relation to personal data that we process, and we may be required to put in place additional mechanisms to ensure compliance with the new data protection rules.

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.

Failure to comply with the requirements of the GDPR and the applicable national data protection laws of the EU Member States may result in fines and other administrative penalties. The GDPR will introduce substantial fines for breaches of the data protection rules. 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.

If we fail to comply with data protection laws and regulations, we could be subject to government enforcement actions (which could include civil or criminal penalties), private litigation and/or adverse publicity, which could negatively affect our operating results and business.

We may be subject to data protection laws and regulations (i.e., laws and regulations that address privacy and data security). In the United States, numerous federal and state laws and regulations, including state data breach notification laws, state health information privacy laws, and federal and state consumer protection laws (e.g., Section 5 of the FTC Act and HIPAA), govern the collection, use, disclosure, and protection of health-related and other personal information. Failure to comply with data protection laws and regulations could result in government enforcement actions and create liability for us (which could include civil and/or criminal penalties), private litigation and/or adverse publicity that could negatively affect our operating results and business.

If we participate in the Medicaid Drug Rebate program or other governmental pricing programs, failure to comply with reporting and payment obligations under these programs could result in additional reimbursement requirements, penalties, sanctions and fines which could have a material adverse effect on our business, financial condition, results of operations and growth prospects.

If we are able to successfully commercialize a product candidate or candidates, and if we participate in the Medicaid Drug Rebate program or other governmental pricing programs, we will have certain price reporting obligations to the Medicaid Drug Rebate program, Medicare and/or other governmental pricing programs, such as state Medicaid supplemental rebate programs. If we participate in the Medicaid Drug Rebate program, we will be required to pay a rebate to each state Medicaid program for our covered outpatient drugs that are dispensed to Medicaid beneficiaries and paid for by a state Medicaid program as a condition of having federal funds being made available to the states for our drugs under Medicaid and Medicare Part B. Such rebates are based on pricing data that would be reported by us on a monthly and quarterly basis to CMS, the federal agency that administers the Medicaid Drug Rebate program. These data may include the AMP and, for certain drugs, best price, which, in general, represents the lowest price available from the manufacturer to any entity in the United States in any pricing structure, calculated to include all sales and associated rebates, discounts and other price concessions. Our failure to comply with any required price reporting and rebate payment obligations could negatively impact our financial results.

The PPACA made significant changes to the Medicaid Drug Rebate program, such as expanding rebate liability from fee-for-service Medicaid utilization to include the utilization of Medicaid managed care organizations as well and changing the definition of AMP. The PPACA also increased the minimum Medicaid rebate, changed the calculation of the rebate for certain innovator products that qualify as line extensions of existing drugs; and capped the total rebate amount at 100% of AMP. Finally, the PPACA requires pharmaceutical manufacturers of branded prescription drugs to pay a branded prescription drug fee to the federal government. Congress could enact additional legislation that further increases Medicaid drug rebates or other costs and charges associated with participating in the Medicaid Drug Rebate program. CMS issued a final regulation, which became effective on April 1, 2016, to implement the changes to the Medicaid Drug Rebate program under the PPACA.

Federal law requires that any company that participates in the Medicaid Drug Rebate program also participate in the Public Health Service's 340B program in order for federal funds to be available for the manufacturer's drugs under Medicaid and Medicare Part B. The 340B program requires participating manufacturers to agree to charge statutorily defined covered entities no more than the 340B "ceiling price" for the manufacturer's covered outpatient drugs. These 340B covered entities include a variety of community health clinics and other entities that receive health services grants from the Public Health Service, as well as hospitals that serve a disproportionate share of low-income patients. The PPACA expanded the list of covered entities to include certain free-standing cancer hospitals, critical access hospitals, rural referral centers and sole community hospitals, but exempts "orphan drugs" from the ceiling price requirements for these covered entities. The 340B ceiling price is calculated using a statutory formula based on AMP and the rebate amount for the covered outpatient drug as calculated under the Medicaid Drug Rebate program, and, in general, products subject to Medicaid price reporting and rebate liability are also subject to the 340B ceiling price calculation and discount requirement. Any additional future changes to the definition of AMP and the Medicaid rebate amount under the PPACA or otherwise could affect our 340B ceiling price calculations and negatively impact our results of operations.

The PPACA obligates the Secretary of the HHS to update the agreement that manufacturers must sign to participate in the 340B program to obligate a manufacturer to offer the 340B price to covered entities if the manufacturer makes the drug available to any other purchaser at any price and to report to the government the ceiling prices for its drugs. The Health Resources and Services Administration, or HRSA, recently updated the agreement with participating manufacturers. The PPACA also obligates the Secretary of the HHS to create regulations and processes to improve the integrity of the 340B program. On January 5, 2017, HRSA issued a final regulation regarding the calculation of the 340B ceiling price and the imposition of civil monetary penalties on manufacturers that knowingly and intentionally overcharge covered entities. The effective date of the regulation had been delayed until July 1, 2018. Implementation of this final rule and the issuance of any other final regulations and guidance could affect our obligations under the 340B program in ways we cannot anticipate. In addition, legislation may be introduced that, if passed, would further expand the 340B program to additional covered entities or would require participating manufacturers to agree to provide 340B discounted pricing on drugs used in an inpatient setting.

Federal law also requires that a company that participates in the Medicaid Drug Rebate program report average sales price information each quarter to CMS for certain categories of drugs that are paid under the Medicare Part B program. Manufacturers calculate the average sales price based on a statutorily defined formula as well as regulations and interpretations of the statute by CMS. CMS uses these submissions to determine payment rates for drugs under Medicare Part B. Statutory or regulatory changes or CMS guidance could affect the average sales price calculations for our product candidates that achieve regulatory approval and the resulting Medicare payment rate, and could negatively impact our results of operations.

Pricing and rebate calculations vary across products and programs, are complex, and are often subject to interpretation by us, governmental or regulatory agencies and the courts. In the case of our Medicaid pricing data, if we become aware that our reporting for a prior quarter was incorrect, or has changed as a result of recalculation of the pricing data, we would be obligated to resubmit the corrected data for up to three years after those data originally were due. Such restatements and recalculations would increase our costs for complying with the laws and regulations governing the Medicaid Drug Rebate program and could result in an overage or underage in our rebate liability for past quarters. Price recalculations also may affect the ceiling price at which we will be required to offer our product candidates that achieve regulatory approval under the 340B program.

We will be liable for errors associated with our submission of pricing data if we participate in the Medicaid Drug Rebate Program. In addition to retroactive rebates and the potential for 340B program refunds, if we are found to have knowingly submitted any false price information to the government, we may be liable for civil monetary penalties in the amount of $181,071 per item of false information. If we are found to have made a misrepresentation in the reporting of our average sales price, the Medicare statute provides for civil monetary penalties of up to $13,066 for each misrepresentation for each day in which the misrepresentation was applied. Our failure to submit the required price data on a timely basis could result in a civil monetary penalty of $18,107 per day for each day the information is late beyond the due date. Such failure also could be grounds for CMS to terminate our Medicaid drug rebate agreement, pursuant to which we would participate in the Medicaid program. In the event that CMS terminates our rebate agreement, federal payments may not be available under Medicaid or Medicare Part B for our covered outpatient drugs for which we receive regulatory approval.

CMS and the HHS Office of Inspector General have pursued manufacturers that were alleged to have failed to report these data to the government in a timely manner. Governmental agencies may also make changes in program interpretations, requirements or conditions of participation, some of which may have implications for amounts previously estimated or paid. We cannot assure you that our submissions will not be found by CMS or other governmental agencies to be incomplete or incorrect.

In order to be eligible to have its products paid for with federal funds under the Medicaid and Medicare Part B programs and purchased by certain federal agencies and grantees, a manufacturer also must participate in the Department of Veterans Affairs Federal Supply Schedule, or FSS, pricing program, established by Section 603 of the Veterans Health Care Act of 1992, or the VHCA. Under this program, the manufacturer is obligated to make its innovator and single source products available for

procurement on an FSS contract and charge a price to four federal agencies, Department of Veterans Affairs, or VA, Department of Defense, or DoD, Public Health Service, and Coast Guard, that is no higher than the statutory Federal Ceiling Price, or FCP. The FCP is based on the non-federal average manufacturer price, or Non-FAMP, which we calculate and report to the VA on a quarterly and annual basis. Pursuant to applicable law, knowing provision of false information in connection with a Non-FAMP filing can subject a manufacturer to penalties of $178,156 for each item of false information. These obligations also contain extensive disclosure and certification requirements.

Moreover, pursuant to regulations issued by the DoD TRICARE Management Activity, or Tricare, now the Defense Health Agency, or DHA, to implement Section 703 of the National Defense Authorization Act for Fiscal Year 2008, manufacturers are required to provide rebates on utilization of their innovator and single source products that are dispensed to TRICARE beneficiaries by TRICARE network retail pharmacies. The formula for determining the rebate is established in the regulations and is based on the difference between the annual Non-FAMP and the FCP (these price points are required to be calculated by us under the VHCA). The requirements under the FSS and TRICARE programs could reduce the revenue we may generate from any products that are commercialized in the future and could adversely affect our business and operating results.

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 LUXTURNA or any other 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 LUXTURNA or any other 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 EU, which is undergoing a continued severe economic crisis. A weak or declining economy could strain our suppliers, possibly resulting in supply disruption, or cause delays in payments for our services by third-party payors or our collaborators. Any of the foregoing could harm our business and we cannot anticipate all of the ways in which the current economic climate and financial market conditions could adversely impact our business.

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

Natural disasters could severely disrupt our operations 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 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. Our manufacturing facility, as well as CHOP's manufacturing facility, and 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, The University of Pennsylvania, or Penn, and the University of Iowa Research Foundation, or UIRF, our licensors retain control of such activities. Therefore, we cannot be certain that these patents and applications will be prosecuted, maintained and enforced in a manner consistent with the best interests of our business. If our licensors fail to maintain such patents, or lose rights to those patents or patent applications, the rights we have licensed may be reduced or eliminated and our right to develop and commercialize any of our products that are the subject of such licensed

rights could be adversely affected. In addition to the foregoing, the risks associated with patent rights that we license from third parties will also apply to patent rights we may own in the future.

Furthermore, the research resulting in certain of our licensed patent rights and technology was funded by the United States 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 United States 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. Consequently, we will not be able to assert any such patents to prevent others from using our technology for, and developing and marketing competing products to treat, these indications. It is also possible that we will fail to identify patentable aspects of our research and development output before it is too late to obtain patent protection.

We are a party to intellectual property license agreements with CHOP, Penn and UIRF, each of which is important to our business, and we expect to enter into additional license agreements in the future. Our existing license agreements impose, and we expect that future license agreements will impose, various diligence, development and commercialization timelines, milestone payments, royalties and other obligations on us. 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.

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.

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 United States patent rights lack corresponding foreign patents or patent applications. For example, we license a United States patent from Penn that covers methods of treating patients with LCA due to *RPE65* mutations. No patents or patent applications outside the United States corresponding to this patent were ever pursued. In addition, the laws of some foreign countries do not protect intellectual property rights to the same extent as federal and state laws in the United States. Consequently, we may not be able to prevent third parties from practicing our inventions in all countries outside the United States, or from selling or importing products made using our inventions in and into the United States or other jurisdictions. Competitors may use our technologies in jurisdictions where we have not obtained patent protection to develop their own products and, further, may export otherwise infringing products to territories where we have patent protection, but enforcement is not as strong as that in the United States. These products may compete with our products and our patents or other intellectual property rights may not be effective or sufficient to prevent them from competing.

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

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

If one of our licensing partners or we initiate legal proceedings against a third party to enforce a patent covering one of our product candidates, the defendant could counterclaim that the patent covering our product candidate is invalid or unenforceable. In patent litigation in the United States, defendant counterclaims alleging invalidity or unenforceability are commonplace. Grounds for a validity challenge could be an alleged failure to meet any of several statutory requirements, including lack of novelty, obviousness, written description or non-enablement. Grounds for an unenforceability assertion could be an allegation that someone connected with 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 LUXTURNA, *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 LUXTURNA, *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 United States patent in federal court, we would need to overcome a presumption of validity.

As this burden is a high one requiring us to present clear and convincing evidence as to the invalidity of any such United States patent claim, there is no assurance that a court of competent jurisdiction would invalidate the claims of any such United States 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 United States 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 United States patent law. These include provisions that affect the way patent applications are prosecuted and also may affect patent litigation. These also include provisions that switched the United States from a "first-to-invent" system to a "first-to-file" system, allow third-party submission of prior art to the USPTO during patent prosecution and set forth additional procedures to attack the validity of a patent by the USPTO administered post grant proceedings. Under a first-to-file system, assuming the other requirements for patentability are met, the first inventor to file a patent application generally will be entitled to the patent on an invention

regardless of whether another inventor had made the invention earlier. The USPTO recently developed new regulations and procedures to govern administration of the Leahy-Smith Act, and many of the substantive changes to patent law associated with the Leahy-Smith Act, and in particular, the first to file provisions, only became effective on March 16, 2013. Accordingly, it is not clear what, if any, impact the Leahy-Smith Act will have on the operation of our business. However, the Leahy-Smith Act and its implementation could increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our issued patents, all of which could have a material adverse effect on our business, financial condition, results of operations and prospects.

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

On March 4, 2014, the USPTO issued a guidance memorandum to patent examiners entitled "2014 Procedure For Subject Matter Eligibility Analysis Of Claims Reciting Or Involving Laws Of Nature/Natural Principles, Natural Phenomena, And/Or Natural Products." 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 United States 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 FDA regulatory review process. A patent term extension cannot extend the remaining term of a patent beyond a total of 14 years from the date of product approval, only one patent may be extended and only those claims covering the approved drug, a method for using it or a method for manufacturing it may be extended. However, we may not be granted an extension because of, for example, failing to exercise due diligence during the testing phase or regulatory review process, failing to apply within applicable deadlines, failing to apply prior to expiration of relevant patents or otherwise failing to satisfy applicable requirements. Moreover, the applicable time period or the scope of

patent protection afforded could be less than we request. If we are unable to obtain patent term extension or the term of any such extension is less than we request, our competitors may obtain approval of competing products following our patent expiration, and our revenue could be reduced, possibly materially.

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

We have registered trademarks with the USPTO for the mark "SPARK" and the Spark logo and pending trademark applications in the United States and various foreign jurisdictions for marks related to our business. 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

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. 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 October 31, 2017,

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 October 31, 2017, we had outstanding options to purchase an aggregate of 3,670,942 shares of our common stock, of which options to purchase 1,394,364 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. 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;
- market conditions in the pharmaceutical and biotechnology sectors; and
- general economic, industry and market conditions.

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, cash equivalents and marketable securities and may not use them effectively.

Our management has broad discretion in the application of our cash, cash equivalents and marketable securities 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 incur substantial 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, and particularly since December 31, 2016, when we ceased being an Emerging Growth Company, we incur significant legal, accounting and other expenses that we did not incur as a private company. In addition, the Sarbanes-Oxley Act of 2002 and rules subsequently implemented by the SEC and NASDAQ have imposed various requirements on public companies, including establishment and maintenance of effective disclosure and financial controls and corporate governance practices. Our management and other personnel 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 are 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. 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.

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 2. Unregistered Sales of Equity Securities and Use of Proceeds.

Use of Proceeds from Initial Public Offering of Common Stock

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 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.

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 September 30, 2017, the entire amount of the net proceeds is included as cash and cash equivalents and marketable securities.

Item 5. Other Information

On November 6, 2017, we entered into an amendment to our collaboration agreement with Pfizer pursuant to which we have agreed to take on additional responsibility with respect to *SPK-9001* in exchange for an upfront payment and potential milestone payments. We have agreed to (1) enroll up to five additional participants in the current Phase 1/2 clinical trial who will receive *SPK-9001* manufactured using an enhanced process to test its comparability to the *SPK-9001* received by the first 10 participants enrolled in the ongoing Phase 1/2 clinical trial and (2) transfer the enhanced *SPK-9001* manufacturing process to Pfizer. One of the up to five participants already has received *SPK-9001* manufactured using the enhanced process.

We will receive an initial $10.0 million cash payment and up to an additional $15.0 million in potential milestone payments upon completion of certain transition activities. The activities outlined in the amendment will occur in parallel to Pfizer's ongoing preparation to assume responsibility for *SPK-9001* after the transfer of the IND application to Pfizer. We intend to file this amendment with the Securities and Exchange Commission as an exhibit to our Annual Report on Form 10-K for the period ending December 31, 2017.

Item 6. Exhibits

The exhibits filed as part of this Quarterly Report on Form 10-Q are set forth on the Exhibit Index below.

Exhibit Number	Description of Exhibit	Incorporated by Reference				Filed Herewith
		Form	File Number	Date of Filing	Exhibit Number	
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 Quarterly Report on Form10-Q for the quarter ended September 30, 2017, formatted in XBRL (eXtensible Business Reporting Language): (i) Consolidated Balance Sheets as of December 31, 2016 and September 30, 2017, (ii) Consolidated Statements of Operations and Comprehensive Income (Loss) for the three and nine months ended September 30, 2016 and 2017, (iii) Consolidated Statement of Stockholders' Equity for the nine months ended September 30, 2017, (iv) Consolidated Statements of Cash Flows for the nine months ended September 30, 2016 and 2017 and (v) Notes to Unaudited Consolidated Financial Statements.					X

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: November 7, 2017

SPARK THERAPEUTICS, INC.

By: /s/ Stephen W. Webster

Stephen W. Webster

Chief Financial Officer

(Principal Financial Officer)

Exhibit 31.1

CERTIFICATIONS

I, Jeffrey D. Marrazzo, certify that:

1 I have reviewed this Quarterly Report on Form 10-Q of Spark Therapeutics, Inc.;

2 Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3 Based on my knowledge, the consolidated financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4 The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5 The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: November 7, 2017

By: /s/ Jeffrey D. Marrazzo

Jeffrey D. Marrazzo

Chief Executive Officer

(Principal Executive Officer)

Exhibit 31.2

CERTIFICATIONS

I, Stephen W. Webster, certify that:

1 I have reviewed this Quarterly Report on Form 10-Q of Spark Therapeutics, Inc.;

2 Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3 Based on my knowledge, the consolidated financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4 The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5 The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: November 7, 2017

By: /s/ Stephen W. Webster

Stephen W. Webster

Chief Financial Officer

(Principal Financial Officer)

Exhibit 32.1

CERTIFICATION PURSUANT TO 18 U.S.C. SECTION 1350,
AS ADOPTED PURSUANT TO
SECTION 906 OF THE SARBANES-OXLEY ACT OF 2002

In connection with the Quarterly Report on Form 10-Q of Spark Therapeutics, Inc. (the "Company") for the period ended September 30, 2017 as filed with the Securities and Exchange Commission on the date hereof (the "Report"), I, Jeffrey D. Marrazzo, Chief Executive Officer of the Company, hereby certifies, pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, that to his knowledge:

(1) the Report fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934; and
(2) the information contained in the Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

Date: November 7, 2017

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

Exhibit 32.2

CERTIFICATION PURSUANT TO 18 U.S.C. SECTION 1350,
AS ADOPTED PURSUANT TO
SECTION 906 OF THE SARBANES-OXLEY ACT OF 2002

In connection with the Quarterly Report on Form 10-Q of Spark Therapeutics, Inc. (the "Company") for the period ended September 30, 2017 as filed with the Securities and Exchange Commission on the date hereof (the "Report"), I, Stephen W. Webster, Chief Financial Officer of the Company, hereby certifies, pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley of 2002, that to his knowledge:

(1) the Report fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934; and
(2) the information contained in the Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

Date: November 7, 2017

By: /s/ Stephen W. Webster

Stephen W. Webster
Chief Financial Officer
(Principal Financial Officer)