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Xenon Pharmaceuticals Inc.  
Form 10-Q  
August 13, 2015

UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 10 Q

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

For the quarterly period ended June 30, 2015

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: 001-36687

XENON PHARMACEUTICALS INC.

(Exact name of registrant as specified in its charter)

Canada 98-0661854  
(State or other jurisdiction of (I.R.S. Employer

incorporation or organization) Identification Number)

200-3650 Gilmore Way

Burnaby, British Columbia V5G 4W8

Canada

(Address of principal executive offices)

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(604) 484-3300

(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, or a non-accelerated filer, or a smaller reporting company. See the definitions of "large accelerated filer," "accelerated filer" and "smaller reporting company" in Rule 12b-2 of the Exchange Act. (Check one):

Large accelerated filer

Accelerated filer

Non-accelerated filer  (Do not check if a smaller reporting company) Smaller reporting company

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

Indicate the number of shares outstanding of each of the issuer's classes of common stock, as of the latest practicable date:

The number of registrant's common shares outstanding as of August 7, 2015 was 14,286,858

XENON PHARMACEUTICALS INC.

QUARTERLY REPORT ON FORM 10-Q

FOR THE QUARTER ENDED JUNE 30, 2015

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The accompanying notes are an integral part of these financial statements.

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XENON PHARMACEUTICALS INC.

Statement of Shareholders' Equity (Deficit)

(Unaudited)

(Expressed in thousands of U.S. dollars except per share data)

	Series A convertible preferred shares		Series B convertible preferred shares		Series E convertible preferred shares		Common shares		Additional paid-in capital	Accumulated deficit	Accumulated other comprehensive income (loss)
	Shares	Amount	Shares	Amount	Shares	Amount	Shares	Amount			
of											
31,	1,151,468	\$2,939	994,885	\$8,683	4,322,126	\$90,866	1,344,627	\$6,147	\$29,722	\$(116,752)	\$2,511
for										13,018	
of											
	(1,151,468)	(2,939)	(994,885)	(8,683)	(4,322,126)	(90,866)	7,725,924	102,488			
t of							5,095,000	38,373			
t											(3,501)
n											
tion									760		
							13,365	124	(124 )		

of											
on											
uant											
of											
31,	—	\$—	—	\$—	—	\$—	14,181,333	\$147,157	\$30,346	\$(103,734)	\$(990 )
the											
n											
on											
uant											
tion											
of											
ons											
of											
	—	\$—	—	\$—	—	\$—	14,267,174	\$147,824	\$29,314	\$(111,801)	\$(990 )

(1) At June 30, 2015, our accumulated other comprehensive loss is entirely related to historical cumulative translation adjustments from the application of U.S. dollar reporting when the functional currency of the Company was the Canadian dollar. See Note 3 – Changes in significant accounting policies.

The accompanying notes are an integral part of these financial statements.

## XENON PHARMACEUTICALS INC.

## Statements of Cash Flows

(Unaudited)

(Expressed in thousands of U.S. dollars)

	Six Months Ended June 30,	
	2015	2014
<b>Operating activities:</b>		
Net income (loss)	\$(7,988 )	\$2,603
<b>Adjustments to reconcile net income (loss) to net cash used in operating activities:</b>		
Depreciation and amortization	492	350
Stock-based compensation	3,446	373
Deferred tenant inducements	(32 )	(33 )
Unrealized foreign exchange loss	2,353	8
<b>Changes in operating assets and liabilities:</b>		
Accounts receivable	31	73
Prepaid expenses, and other current assets	221	18
Accounts payable and accrued expenses	(350 )	(126 )
Deferred revenue	(6,144 )	(6,333 )
Net cash used in operating activities	(7,971 )	(3,067 )
<b>Investing activities:</b>		
Purchases of property, plant and equipment	(190 )	(497 )
Purchase of marketable securities	—	(2,946 )
Proceeds from marketable securities	1,818	4,568
Net cash provided by investing activities	1,628	1,125
<b>Financing activities:</b>		
Deferred financing fees	—	(730 )
Proceeds from issuance of common shares	213	4
Net cash provided by (used in) financing activities	213	(726 )
Effect of exchange rate changes on cash and cash equivalents	(1,550 )	(195 )
Decrease in cash and cash equivalents	(7,680 )	(2,863 )
Cash and cash equivalents, beginning of period	72,026	37,950
Cash and cash equivalents, end of period	\$64,346	\$35,087
<b>Supplemental disclosures:</b>		
Interest received	\$268	\$238
<b>Supplemental disclosures of non-cash transactions:</b>		

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Issuance of common shares on conversion of subscription rights	—	27
Fair value of options exercised on a cashless basis	189	—

The accompanying notes are an integral part of these financial statements.

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XENON PHARMACEUTICALS INC.

Notes to Financial Statements

(Unaudited)

(Expressed in thousands of U.S. dollars except numbers of shares and per share amounts)

1. Nature of the business:

Xenon Pharmaceuticals Inc. (the “Company”), incorporated in 1996 under the British Columbia Business Corporations Act and continued federally in 2000 under the Canada Business Corporation Act, is a clinical-stage biopharmaceutical company discovering and developing a pipeline of differentiated therapeutics for orphan indications that it intends to commercialize on its own, and for larger market indications that it intends to partner with global pharmaceutical companies.

2. Basis of presentation:

These financial statements are presented in U.S. dollars.

The accompanying unaudited interim financial statements have been prepared in accordance with United States generally accepted accounting principles (“U.S. GAAP”) and pursuant to the rules and regulations of the United States Securities and Exchange Commission (“SEC”) for interim financial information. Accordingly, these financial statements do not include all of the information and footnotes required for complete financial statements and should be read in conjunction with the audited financial statements and notes for the year ended December 31, 2014 and included in the Company’s 2014 Annual Report on Form 10-K filed with the SEC on March 12, 2015.

These unaudited interim financial statements reflect all adjustments, consisting of normal recurring adjustments, which, in the opinion of management, are necessary for a fair presentation of results for the interim periods presented. The results of operations for the three and six month periods ended June 30, 2015 and 2014 are not necessarily indicative of results that can be expected for a full year. These unaudited interim financial statements follow the same significant accounting policies as those described in the notes to the audited financial statements of the Company included in the Company’s 2014 Annual Report on Form 10-K for the year ended December 31, 2014, with the exception of the policies described in note 3(a).

Certain comparative figures have been reclassified to conform to the financial statement presentation adopted for the current interim period.

3. Changes in significant accounting policies:

(a) Functional currency:

The Company’s reporting currency is the U.S. dollar. The functional currency of the Company changed to U.S. dollars from Canadian dollars on January 1, 2015 based on management’s analysis of the changes in the primary economic environment in which the Company operates. The change in functional currency is accounted for prospectively from January 1, 2015 and prior year financial statements have not been restated for the change in functional currency. Past translation gains and losses from the application of the U.S. dollar as the reporting currency while the Canadian dollar was the functional currency are included as part of the cumulative foreign currency translation adjustment, which is reported as a component of shareholders’ equity under accumulated other comprehensive loss.

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For periods commencing January 1, 2015, monetary assets and liabilities denominated in foreign currencies are translated into U.S. dollars using exchange rates in effect at the balance sheet date. Opening balances related to non-monetary assets and liabilities are based on prior period translated amounts, and nonmonetary assets and nonmonetary liabilities incurred after January 1, 2015 are translated at the approximate exchange rate prevailing at the date of the transaction. Revenue and expense transactions are translated at the approximate exchange rate in effect at the time of the transaction. Foreign exchange gains and losses are included in the statement of operations and comprehensive income (loss) as foreign exchange gain (loss).

(b) Liability classified stock options:

The Company granted stock options with exercise prices denominated in Canadian dollars under its Amended and Restated Stock Option Plan to members of its board of directors and certain consultants prior to the Company's initial public offering ("IPO") in November 2014. Following the change in functional currency on January 1, 2015, described in note

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3(a), the options denominated in Canadian dollars that were granted to members of the Company's board of directors and certain consultants were subject to liability accounting with fair value calculated using the Black-Scholes option-pricing model. The liability classified stock options are measured at fair value at each reporting period with changes in fair value recognized in the statement of operations and comprehensive income (loss) as general and administrative stock based compensation expense.

#### 4. Future changes in accounting policies:

In May 2014, the FASB issued amendments to clarify the principles of recognizing revenue and to develop a common revenue standard that would remove inconsistencies in revenue requirements, leading to improved comparability of revenue recognition practices across entities and industries. The amendments stipulate that an entity should recognize revenue to depict the transfer of promised goods or services to customers in an amount that reflects the consideration to which the entity expects to be entitled in exchange for those goods or services. Additional disclosure will also be required about the nature, amount, timing and uncertainty of revenue and cash flows arising from customer contracts, including significant judgments and changes in judgments, and assets recognized from costs incurred to obtain or fulfill a contract. In April 2015, the FASB voted to propose a deferral of the effective date of the new revenue standard by one year. The new guidance would be effective for public entities for fiscal years beginning after December 15, 2017 instead of the originally contemplated effective date of December 15, 2016. Entities are permitted to adopt in accordance with the original effective date if they choose. The Company is currently evaluating the new guidance to determine the impact it will have on the Company's financial position, results of operations and cash flows.

In August 2014, the FASB issued amendments requiring management to assess an entity's ability to continue as a going concern. For each reporting period, management will be required to evaluate whether there are conditions or events that raise substantial doubt about a company's ability to continue as a going concern within one year from the date the financial statements are issued. These amendments will be effective for public entities for the annual period ending after December 15, 2016, and for annual periods and interim periods thereafter. The adoption of these amendments in fiscal 2017 is not expected to have a material impact on the Company's financial statements.

#### 5. Net income (loss) per common share:

Basic net income (loss) per common share is computed by dividing the net income (loss) attributable to common shareholders by the weighted average number of common shares outstanding for the period. Diluted net income (loss) per common share is computed by adjusting net income (loss) attributable to common shareholders to reallocate undistributed earnings based on the potential impact of dilutive securities.

Prior to the Company's IPO, net income (loss) per share was calculated under the two-class method as the Company had outstanding shares that met the definition of participating securities. The two-class method determines net income (loss) per share for each class of common and participating securities according to dividends declared or accumulated and participation rights in undistributed earnings. The two-class method requires income available to common shareholders for the period to be allocated between common and participating securities based upon their respective rights to receive dividends as if all income for the period had been distributed. All of the outstanding redeemable convertible preferred shares converted to common shares upon the consummation of the Company's IPO.

As the Company reported a net loss attributable to common shareholders for the six months ended June 30, 2015 and no net income was attributable to common shareholders for the three and six months ended June 30, 2014, all stock options were anti-dilutive and were excluded from the diluted weighted average shares outstanding for those periods.

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For the three months ended June 30, 2015, common shares of 389,283 were excluded from the calculation of income per common share because their inclusion would be anti-dilutive.

The following is a reconciliation of the numerators and denominators of basic and diluted net income (loss) per common share:

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	Three Months Ended June 30, 2015		Six Months Ended June 30, 2014	
<b>Numerator:</b>				
Net income (loss) attributable to common shareholders used to compute net income (loss) per common share:				
Basic	\$1,168	\$—	\$(7,988)	) \$—
Adjustment for change in fair value of liability classified stock options	(2,244)	) —	—	—
Diluted	\$(1,076)	) \$—	\$(7,988)	) \$—
<b>Denominator:</b>				
Weighted average number of common shares:				
Basic	14,241,827	1,347,237	14,227,203	1,346,274
Adjustment for dilutive effect of stock options	888,151	—	—	—
Diluted	15,129,978	1,347,237	14,227,203	1,346,274
Net income (loss) per common share - basic	\$0.08	\$—	\$(0.56)	) \$—
Net loss per common share - diluted	\$(0.07)	) \$—	\$(0.56)	) \$—

#### 6. Fair value of financial instruments:

U.S. GAAP establishes a fair value hierarchy for inputs to be used to measure fair value of financial assets and liabilities. This hierarchy prioritizes the inputs to valuation techniques used to measure fair value into three levels: Level 1 (highest priority), Level 2, and Level 3 (lowest priority).

- Level 1 - Unadjusted quoted prices in active markets for identical assets or liabilities that the Company has the ability to access at the balance sheet date.
  - Level 2 - Inputs other than quoted prices included within Level 1 that are observable for the asset or liability, either directly or indirectly. Level 2 inputs include quoted prices for similar assets or liabilities in active markets, quoted prices for identical or similar assets or liabilities in markets that are not active, inputs other than quoted prices that are observable for the asset or liability (i.e., interest rates, yield curves, etc.), and inputs that are derived principally from or corroborated by observable market data by correlation or other means (market corroborated inputs).
  - Level 3 - Inputs are unobservable and reflect the Company's assumptions as to what market participants would use in pricing the asset or liability. The Company develops these inputs based on the best information available.
- The Company's Level 1 assets include cash and cash equivalents and marketable securities with quoted prices in active markets. The carrying amount of accounts receivables, accounts payable and accrued expenses approximates fair value due to the nature and short-term of those instruments. As quoted prices for the liability classified stock options are not readily available, the Company has used a Black-Scholes pricing model to estimate fair value using Level 3 inputs as defined above.

The weighted average Black-Scholes option-pricing assumptions for liability classified stock options outstanding at June 30, 2015 are as follows:

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	June 30, 2015	
Average risk-free interest rate	1.71	%
Average expected term (in years)	4.42	
Expected volatility	75	%
Expected dividend yield	0.00	%
Expected forfeiture rate	0.00	%
Number of liability classified stock options outstanding	492,842	

7. Accounts payable and accrued expenses:

Accounts payable and accrued expenses consisted of the following:

	June 30, 2015	December 31, 2014
Trade payables	\$872	\$ 553
Employee compensation, benefits, and related accruals	731	1,077
Consulting and contracted research	432	774
Professional fees	216	180
Other	27	80
Total	\$2,278	\$ 2,664

8. Stock option plan:

The following table presents stock option activity for the period:

	Three Months Ended June 30,		Six Months Ended June 30,	
	2015	2014	2015	2014
Outstanding, beginning of period	1,785,436	1,445,320	1,484,218	1,333,099
Granted	33,474	—	380,438	157,231
Exercised <sup>(1)</sup>	(55,155 )	—	(99,811 )	(772 )
Forfeited and expired	(18,737 )	(2,579 )	(19,827 )	(46,817 )
Outstanding, end of period	1,745,018	1,442,741	1,745,018	1,442,741
Exercisable, end of period	1,126,629	1,034,518	1,126,629	1,034,518

(1) During the six months ended June 30, 2015, 53,442 stock options were exercised for the same number of common shares for cash. In the same period, the Company issued 32,399 common shares for the cashless exercise of 46,369 stock options.

The fair value of each option issued to employees and non-employees is estimated using the Black-Scholes option-pricing model with the following weighted-average assumptions:

	Three Months Ended June 30,		Six Months Ended June 30,	
	2015	2014	2015	2014
Average risk-free interest rate	1.71 %	1.97 %	1.71 %	1.97 %
Average expected term (in years)	6.04	6.20	6.23	6.20

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Expected volatility	75 %	74 %	75 %	74 %
Expected dividend yield	0.00%	0.00%	0.00%	0.00%
Expected forfeiture rate	0.00%	0.00%	0.00%	0.00%

The weighted-average fair value of options granted during the six months ended June 30, 2015 was \$11.96 (six months ended June 30, 2014 - \$6.57) per option.

9. Collaboration agreements:

The Company has entered into a number of collaboration agreements with multiple deliverables under which it may have received non-refundable upfront payments. The Company generally recognizes revenue from upfront payments ratably over the term of its estimated period of performance of research under its collaboration agreements in the event that such arrangements represent a single unit of accounting. The collaborations may also include contractual milestone payments, which relate to the achievement of prespecified research, development, regulatory and commercialization events. The milestone events coincide with the progression of product candidates from research and development, to regulatory approval and through to commercialization. The process of successfully discovering a new product candidate, having it selected by the collaborator for development and having it approved and ultimately sold for a profit is highly uncertain. As such, the milestone payments that the Company may earn from its collaborators involve a significant degree of risk to achieve.

The following table is a summary of the revenue recognized from the Company's collaborations for the three and six months ended June 30, 2015 and 2014:

	Three Months Ended June 30,		Six Months Ended June 30,	
	2015	2014	2015	2014
Teva:				
Recognition of upfront payment	\$2,908	\$3,095	\$5,784	\$6,120
Research funding	45	87	90	167
Genentech:				
Recognition of upfront payment	181	969	360	1,755
Research funding	910	1,145	1,820	2,255
Total collaboration revenue	\$4,044	\$5,296	\$8,054	\$10,297

#### 10. Commitments and contingencies:

The Company has entered into license and research agreements with third parties that include indemnification provisions that are customary in the industry. These indemnification provisions generally require the Company to compensate the other party for certain damages and costs incurred as a result of third party claims or damages arising from these transactions.

The maximum amount of potential future indemnification is unlimited; however, the Company currently holds commercial and product liability insurance. This insurance limits the Company's exposure and may enable it to recover a portion of any future amounts paid. Historically, the Company has not made any indemnification payments under such agreements and the Company believes that the fair value of these indemnification obligations is minimal. Accordingly, the Company has not recognized any liabilities relating to these obligations for any period presented.

#### 11. Subsequent event:

On August 7, 2015, the Company entered into a priority access agreement with Medpace, Inc. ("Medpace") for the provision of certain clinical development services. An officer and director of Medpace is a beneficial owner of more than 5% of the Company's common shares. Under the terms of the agreement, the Company has committed to using Medpace non-exclusively for clinical development services over the five year term of the agreement. In consideration for priority access to Medpace resources and preferred service rates, the Company has committed to \$7,000 of services over the term of the agreement, \$1,700 of which was prepaid upon signing of the agreement and an additional \$1,300 will be paid during the remainder of 2015.

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## ITEM 2. MANAGEMENT'S DISCUSSION AND ANALYSIS OF FINANCIAL CONDITION AND RESULTS OF OPERATIONS

This section should be read in conjunction with our unaudited financial statements and related notes included in Part I, Item 1 of this report and our audited financial statements and related notes thereto and management's discussion and analysis of financial condition and results of operations for the year ended December 31, 2014 included in our Annual Report on Form 10-K filed with the U.S. Securities and Exchange Commission on March 12, 2015 and with the securities commissions in British Columbia, Alberta and Ontario on March 12, 2015.

### Forward-Looking Statements

Certain statements contained in this Quarterly Report on Form 10-Q may constitute forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended and Canadian Securities laws. The words or phrases "would be," "will allow," "intends to," "may," "believe," "plan," "will likely result," "are expected to," "will continue," "is anticipated," "estimate," "project," or similar expressions or the negative of such words or phrases, are intended to identify "forward-looking statements." You should read these statements carefully because they discuss future expectations, contain projections of future results of operations or financial condition, or state other "forward-looking" information. These statements relate to our future plans, objectives, expectations, intentions and financial performance and the assumptions that underlie these statements. These forward-looking statements include, but are not limited to:

- our ability to identify additional products or product candidates using our Extreme Genetics discovery platform;
- the initiation, timing, cost, progress and success of our research and development programs, preclinical studies and clinical trials;
- our ability to advance product candidates into, and successfully complete, clinical trials;
- our ability to recruit sufficient numbers of patients for our future clinical trials for orphan or more common indications;
- our ability to achieve profitability;
- our ability to obtain funding for our operations, including research funding;
- our ability to receive milestones, royalties and sublicensing fees under our collaborations, and the timing of such payments;
- the implementation of our business model and strategic plans;
- our ability to develop and commercialize product candidates for orphan and niche indications independently;
- our commercialization, marketing and manufacturing capabilities and strategy;
- our ability to find families to support our Extreme Genetics discovery platform;
- our ability to discover genes and drug targets;
- our ability to protect our intellectual property and operate our business without infringing upon the intellectual property rights of others;
- our expectations regarding federal, state and foreign regulatory requirements;
- the therapeutic benefits, effectiveness and safety of our product candidates;
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- the accuracy of our estimates of the size and characteristics of the markets that may be addressed by our products and product candidates;
- the rate and degree of market acceptance and clinical utility of Glybera and future products, if any;
  - the timing of, and our and our collaborators' ability to obtain and maintain regulatory approvals for our product candidates;
  - our ability to maintain and establish collaborations;
  - our use of proceeds from our initial public offering and the concurrent private placement completed in November 2014;
  - our expectations regarding market risk, including interest rate changes and foreign currency fluctuations;
  - our belief in the sufficiency of our cash flows to meet our needs for at least the next 12 to 24 months;

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- our ability to engage and retain the employees required to grow our business;
- our future financial performance and projected expenditures;
- developments relating to our competitors and our industry, including the success of competing therapies that are or become available; and
- estimates of our expenses, future revenue, capital requirements and our needs for additional financing.

These forward-looking statements are subject to certain risks and uncertainties that could cause actual results to differ materially from those anticipated in the forward-looking statements. Factors that might cause such a difference include, but are not limited to, those discussed in this report in Part I, Item 1A — “Risk Factors,” and elsewhere in this report. Forward-looking statements are based on our management’s beliefs and assumptions and on information currently available to our management. These statements, like all statements in this report, speak only as of their date, and we undertake no obligation to update or revise these statements in light of future developments. In this report, “we,” “our,” “us,” “Xenon,” and “the Company” refer to Xenon Pharmaceuticals Inc. Unless otherwise noted, all dollar amounts in this report are expressed in United States dollars.

## Overview

We are a clinical-stage biopharmaceutical company discovering and developing a pipeline of differentiated therapeutics for orphan indications that we intend to commercialize on our own, and for larger market indications that we intend to partner with global pharmaceutical companies. We have built a core enabling discovery platform for the discovery of validated drug targets by studying rare human diseases with extreme traits, including diseases caused by mutations in ion channels, known as channelopathies. We have an integrated platform that includes in-house capabilities for human genetics, small molecule drug discovery, as well as preclinical and clinical development.

Our business was founded on our proprietary discovery platform, which we refer to as Extreme Genetics. Extreme Genetics involves the study of families where individuals exhibit inherited severe traits, or phenotypes. By identifying and characterizing single-gene defects responsible for these phenotypes, we gain insights into human disease biology to better select targets for therapeutic intervention. Our Extreme Genetics discovery platform has yielded the first approved gene therapy product in the European Union, or the EU, and a broad development pipeline and multiple pharmaceutical partnerships. We believe that our Extreme Genetics discovery platform enhances the likelihood of discovering a drug target that has a major effect in humans. From these discoveries, we can gain an improved understanding of how a drug that modulates the target might act when given to a human.

Our pharmaceutical partners include Teva Pharmaceutical Industries, Ltd., or Teva (through its subsidiary, Ivax International GmbH), Genentech, Inc., or Genentech, and Merck & Co., Inc., or Merck (through its affiliate, Essex Chemie AG). Our pharmaceutical collaborations have generated in aggregate over \$155.0 million in non-equity funding to date with the potential to provide us with over \$1.0 billion in future milestone payments, as well as royalties and co-promotion income on product sales.

To date, our Extreme Genetics discovery platform has yielded:

- Glybera, developed by our licensee uniQure Biopharma B.V., or uniQure, the first, and currently the only, gene therapy approved in the EU for the treatment of the orphan disorder lipoprotein lipase deficiency, or LPLD. uniQure has reported that its commercialization partner, Chiesi Farmaceutici S.p.A., or Chiesi, has submitted price and reimbursement dossiers in key European countries in order to make Glybera accessible to patients. Chiesi has sole control over commercialization in Europe and neither uniQure nor Xenon will be providing additional guidance regarding commercialization progress. uniQure has also reported that in early 2016, it expects to commence a pivotal clinical study for Glybera to support a future regulatory submission in the U.S.;
- TV-45070 (formerly XEN402), a product candidate being developed in collaboration with Teva for the treatment of pain. Teva is currently conducting a randomized, double-blind, placebo-controlled Phase 2b clinical trial in patients with postherpetic neuralgia, or PHN, with results expected in the second half of 2016. TV-45070 is a topically applied small-molecule inhibitor of the sodium channel Nav1.7 and other sodium channels, including those that are expressed in the pain-sensing peripheral nervous system;
- GDC-0276, a product candidate being developed in collaboration with Genentech for the treatment of pain. In September 2014, Genentech initiated a Phase 1 clinical trial for GDC-0276, which is expected to complete patient enrollment in the second half of 2015. GDC-0276 is a selective, oral Nav1.7 small-molecule inhibitor being developed for the treatment of pain. Xenon and Genentech also have an active research collaboration focused on other orally selective small molecule inhibitors of Nav1.7; and

Proprietary preclinical programs, including XEN801, a stearyl Co-A desaturase, or SCD1, inhibitor for the treatment of acne, and a sodium channel inhibitor for the orphan disorder Dravet Syndrome, or DS. We anticipate filing an investigational new drug, or IND, equivalent application for XEN801 in August 2015 and an IND for our DS program in 2016.

We have funded our operations through the sale of equity securities, funding received from our licensees and collaborators and, to a lesser extent, government funding. For the six months ended June 30, 2015, we recognized revenues, consisting primarily of funding from our collaborators of approximately \$8.1 million. This compares to \$10.3 million for the six months ended June 30, 2014.

Though our revenue from our collaboration and license agreements resulted in net income of \$13.0 million for the year ended December 31, 2014 and \$12.0 million for the year ended December 31, 2013, we do not expect to have sustained profitability for the foreseeable future. We had a net loss of \$8.0 million for the six months ended June 30, 2015 and had an accumulated deficit of \$111.8 million as of June 30, 2015, from expenses incurred in connection with our research programs and from general and administrative costs associated with our operations.

We have not generated any royalty revenue or other revenue from product sales, and we expect that our revenue in the near term will be substantially dependent on our collaboration agreements. Given the uncertain nature of clinical development of our current and future product candidates and the commercialization of current and future products, we cannot predict when or whether we will receive further milestone payments under our current or future collaboration agreements or whether we will be able to report either revenue or net income in future years.

We expect to continue to incur significant expenses and operating losses for at least the next 12 to 24 months. We anticipate that our expenses will increase substantially as we:

- continue our research and preclinical and clinical development of our product candidates;
- seek regulatory and marketing approvals for any of our product candidates that successfully complete clinical trials;
- make milestone and other payments under our in-license agreements;
- maintain, protect and expand our intellectual property portfolio;
- attract, hire and retain skilled personnel; and
- create additional infrastructure to support our operations as a public company and otherwise.

#### Recent Developments

In May 2015 we amended our collaborative research and license agreement with Genentech, and its affiliate, F. Hoffman-La Roche Ltd., to leverage the work performed in our ongoing Nav1.7 pain collaboration with Genentech for use in our research and development program directed towards modulators of Nav1.6 for use in the field of treating epilepsy, including Dravet Syndrome. Pursuant to the amendment, we obtained a worldwide, non-exclusive, revocable license under intellectual property previously licensed by us to Genentech and intellectual property developed under

the Nav1.7 collaboration that is necessary or useful to make and use certain Nav1.6 modulators for use in the field, excluding commercialization. We obtained a right of first negotiation for a certain period of time to obtain a worldwide, exclusive license under the intellectual property licensed to us to commercialize certain Nav1.6 modulators to treat any disease in the field. We also granted Genentech a right of first negotiation to enter into a drug research and development collaboration with us for our Nav1.6 program. Genentech can terminate the license upon 90 days' notice after the third anniversary of the amendment or at any time upon our uncured material breach.

Pursuant to the amendment, we granted Genentech a worldwide exclusive license under intellectual property developed under our Nav1.6 program. The license permits Genentech to develop and commercialize compounds identified or first made in our Nav1.6 program for all uses outside the field of epilepsy and to develop and commercialize compounds (other than certain compounds identified or first made in our Nav1.6 program) for all uses. If Genentech reaches certain development milestones for and/or sells certain compounds identified or first made in our Nav1.6 program that are covered by a patent licensed to Genentech under the amendment, products containing such compound would be included in the products subject to the royalty and milestone obligations payable to us under the original agreement.

On July 1, 2015, we and our partner Teva announced top line results from a double-blind, placebo-controlled Phase 2b study designed to evaluate the safety and efficacy of topically applied TV-45070 (4% and 8% ointment) in patients with chronic pain due to osteoarthritis, or OA, of the knee. Results from this trial showed that TV-45070 4% and 8% did not demonstrate statistically significant difference from placebo in efficacy endpoints of reductions in pain due to OA. TV-45070 did demonstrate a favorable safety and tolerability profile, with no drug-related serious adverse events. The most common adverse events were application site dermal skin reactions which were mostly mild and less frequent than seen with other topical analgesics. There were no cardiac or CNS safety issues. We and Teva are working to fully analyze the data from the OA trial, but at this time, there are no plans for further development of TV-45070 in OA. Teva is continuing an ongoing randomized, double-blind, placebo-controlled Phase 2b clinical trial in patients with PHN, with results expected in the second half of 2016.

On August 7, 2015, we entered into a priority access agreement with Medpace, Inc., or Medpace, for the provision of certain clinical development services. Dr. August Troendle, an officer and director of Medpace, is a beneficial owner of more than 5% of our common shares.

Under the terms of our priority access agreement with Medpace, we have committed to using Medpace non-exclusively for clinical development services over the five year term of the agreement. In consideration for priority access to Medpace resources and preferred service rates, we have committed to retain Medpace for \$7.0 million of services over the term of the agreement, or the Minimum Commitment. A prepayment of \$1.7 million was paid to Medpace upon signing of the agreement and an additional \$1.3 million will be paid during the remainder of 2015. Any portion of the \$3.0 million payment made during 2015 that is not used within the first three years of the agreement term will be forfeited to Medpace. If we do not meet the Minimum Commitment prior to the expiration of the five year term of the priority access agreement, we have agreed to give Medpace the exclusive right to perform all of our subsequent outsourced clinical development work until the Minimum Commitment has been satisfied, subject to the availability of appropriate Medpace resources and reasonable service rates. If we decide not to retain Medpace for the provision of clinical development services, we may satisfy our obligations under the priority access agreement by paying Medpace an amount equal to half of the unsatisfied portion of the Minimum Commitment.

## Financial Operations Overview

### Revenue

To date, our revenue has been primarily derived from collaboration and licensing agreements as well as, to a lesser extent, government funding. In addition, we have received nominal royalties from a diagnostic license. To date, we have not generated any royalty revenue from product sales, and do not otherwise anticipate generating revenue from product sales other than from sales of Glybera under our license to uniQure for the foreseeable future, if ever.

The following table is a summary of revenue recognized from our current collaboration and licensing agreements for the three and six months ended June 30, 2015 and 2014 (in thousands):

Three Months		Six Months	
Ended June 30,		Ended June 30,	
2015	2014	2015	2014

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Teva:				
Recognition of upfront payment	\$2,908	\$3,095	\$5,784	\$6,120
Research funding	45	87	90	167
Genentech:				
Recognition of upfront payment	181	969	360	1,755
Research funding	910	1,145	1,820	2,255
Total collaboration revenue	\$4,044	\$5,296	\$8,054	\$10,297

Pursuant to the terms of our collaborative development and license agreement with Teva, we received an upfront payment of \$41.0 million. We determined that the various deliverables under this agreement should be considered as a single unit of accounting. As such, the \$41.0 million upfront payment is being recognized as revenue ratably over the expected period of research performance of pre-commercial activities, which is the three-year period from December 2012 through December 2015.

Pursuant to the terms of our December 2011 collaborative development and license agreement with Genentech, we received an upfront payment of \$10.0 million. We determined that the various deliverables under this agreement should be considered as a single unit of accounting. As such, the \$10.0 million upfront payment was recognized as revenue ratably over the expected period of research performance, which was the three-year period from December 2011 through December 2014. In September 2013, we received a \$5.0 million milestone payment for the selection of a compound for good laboratory practices, or GLP, toxicology studies. We recognized the milestone payment upon achievement in August 2013. In August 2014, we received an \$8.0 million milestone payment

for the approval of the GDC-0276 Clinical Trial Application by Health Canada. We recognized the milestone payment upon achievement in August 2014.

Pursuant to the terms of our March 2014 agreement with Genentech, we received an upfront payment of \$1.5 million. We determined that the various deliverables under this agreement should be considered as a single unit of accounting. As such, the \$1.5 million upfront payment is being recognized as revenue ratably over the expected period of research performance, which is the two-year period from March 2014 to March 2016.

As our other internal and partnered products are in various stages of clinical and preclinical development, we do not expect to generate any revenue from product sales other than from our share of revenue related to our agreement with uniQure for at least the next several years. We expect that revenue for the next several years will be derived from our agreement with uniQure and our eligibility to receive a share of the compensation received by uniQure relating to the technology or products licensed by us, and full-time equivalents, or FTEs, and milestone payments under our current collaboration agreements and any additional collaboration agreements that we may enter into in the future. We cannot provide any assurance as to the extent or timing of future milestone payments or royalty payments or that we will receive any future payments at all.

We expect that any revenue we generate will fluctuate quarter to quarter as a function of the timing and amount of milestones and other payments from our existing collaborations and any future collaborations.

The following table is a summary of our deferred revenue for our collaboration and licensing agreements as of June 30, 2015 and December 31, 2014 (in thousands):

	June	
	30, 2015	December 31, 2014
Teva	\$ 5,113	\$ 10,897
Genentech	522	882
Total deferred revenue	\$ 5,635	\$ 11,779

We expect such deferred revenue remaining as of June 30, 2015 to be recognized as revenue in the applicable fiscal years ending December 31, 2015 and 2016 based on our accounting policy for revenue recognition for each collaboration agreement.

#### Operating Expenses

The following table summarizes our operating expenses for the three and six months ended June 30, 2015 and 2014 (in thousands):

	Three Months Ended		Six Months Ended	
	June 30, 2015	2014	June 30, 2015	2014
Research and development	\$3,669	\$2,566	\$7,096	\$5,099

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General and administrative	2,058	1,213	3,629	2,513
General and administrative - stock based compensation	(1,880)	141	3,269	277
Total operating expenses	\$3,847	\$3,920	\$13,994	\$7,889

Research and Development Expenses

Research and development expenses represent costs incurred to conduct research on our product candidates in collaboration with Teva and Genentech, as well as further research and development of our other proprietary product candidates.

Research and development expenses consist of costs incurred in performing research and development activities, including salary, related benefits and share-based compensation for employees engaged in scientific research and development, third-party contract costs relating to research, formulation, manufacturing, preclinical studies and clinical trial activities, third-party license and collaboration fees, laboratory consumables and allocated facility-related costs.

Project-specific expenses reflect costs directly attributable to our clinical development candidates and our preclinical candidates once nominated and selected for further development. All remaining research and development expenses are reflected in early-stage discovery programs. At any given time, we have several active early-stage research and drug discovery programs. Our personnel and infrastructure are typically deployed over multiple projects and are not directly linked to any individual internal early-stage research or



drug discovery program. Therefore, we do not maintain financial information for our internal early-stage research and internal drug discovery programs on a project-specific basis.

We expense all research and development costs as incurred. We expect that our research and development expenses will increase in the future as we advance our proprietary product candidates into clinical development, conduct our development activities under our agreements with Teva and Genentech, advance our internal drug discovery programs into preclinical development and continue our early-stage research. The increase in expense will likely include added personnel and third-party contracts related to research, formulation, manufacturing, preclinical studies and clinical trial activities as well as third-party license and collaboration fees and laboratory consumables.

Clinical development timelines, likelihood of regulatory approval and commercialization and associated costs are uncertain and difficult to estimate and can vary significantly. We anticipate determining which research and development projects to pursue as well as the level of funding available for each project based on the scientific research and preclinical and clinical results of each product candidate and related regulatory action. We expect our research and development expenses to continue to represent our largest category of operating expense for at least the next 12 to 24 months.

#### General and Administrative Expenses

General and administrative expenses consist primarily of salary and related benefits of our executive, finance, business development and administrative functions, travel expenses, allocated facility-related costs not otherwise included in research and development expenses, and professional fees for auditing, tax and legal services, including legal expenses for intellectual property protection. Following our initial public offering (“IPO”) in November 2014, we have been incurring additional general and administrative expenses as a public company, including costs of additional personnel, additional professional fees for audit, accounting and legal services, director fees, enhanced business and accounting systems, costs related to investor relations and increased premiums for directors’ and officers’ liability insurance.

We expect that general and administrative expenses will increase in the future as we expand our operating activities to support increased research and development activities, and the potential build of commercial infrastructure for our option for co-promotion of TV-45070 in the U.S., if and when regulatory approval is received.

#### General and Administrative Expenses – Stock Based Compensation

General and administrative stock based compensation expenses consist of share-based compensation of our directors and executives and our finance, business development and administrative functions and starting in the quarter ended March 31, 2015, includes changes in the fair value of our liability classified stock options for options granted to directors and certain consultants prior to our IPO.

General and administrative stock based compensation expenses will be primarily driven by changes in fair value of our liability classified stock options. We expect to see future changes in the fair value of our liability classified stock options and these changes will largely depend on the change in our share price and any change in our assumed rate of share price volatility and other Black-Scholes option-pricing assumptions.

#### Other Income (Expense)

Interest Income. Interest income consists of income earned on our cash and investment balances. Our interest income has not been significant due to the levels of cash and investment balances and low interest earned on such balances. We anticipate that our interest income will continue to fluctuate depending on timing of payments from collaborative

partners, our cash and investment balances, and interest rates.

Foreign Exchange Gain (Loss). On January 1, 2015, our functional currency changed from the Canadian dollar to the U.S. dollar based on our analysis of the changes in the primary economic environment in which we operate. We will continue to incur substantial expenses in Canadian dollars and will remain subject to risks associated with foreign currency fluctuations. For the three and six months ended June 30, 2015, net foreign exchange gains and losses comprise gains and losses from the impact of foreign exchange fluctuations on our monetary assets and liabilities that are denominated in currencies other than the U.S. dollar (principally the Canadian dollar). See Part I, Item 3 – “Foreign Currency Exchange Risk” below.

#### Critical Accounting Policies and Significant Judgments and Estimates

Our management’s discussion and analysis of our financial condition and results of operations is based on our financial statements, which have been prepared in conformity with generally accepted accounting principles in the U.S., or U.S. GAAP. The

preparation of our financial statements requires us to make estimates and assumptions that affect the reported amounts of assets and liabilities and the revenue and expenses incurred during the reported periods. We base estimates on our historical experience, known trends and various other factors that we believe are reasonable under the circumstances, the results of which form the basis for making judgments about the carrying value of assets and liabilities that are not apparent from other sources. Actual results may differ from these estimates under different assumptions or conditions.

During the six months ended June 30, 2015, we had the following changes in our critical accounting policies:

**Functional Currency.** Our reporting currency is the U.S. dollar. Our functional currency changed to U.S. dollars from Canadian dollars on January 1, 2015 based on management's analysis of the changes in the primary economic environment in which we operate. The change in functional currency is accounted for prospectively from January 1, 2015 and prior year financial statements have not been restated for the change in functional currency. Past translation gains and losses from the application of the U.S. dollar as the reporting currency while the Canadian dollar was the functional currency are included as part of the cumulative foreign currency translation adjustment, which is reported as a component of shareholders' equity under accumulated other comprehensive loss.

For periods commencing January 1, 2015, monetary assets and liabilities denominated in foreign currencies are translated into U.S. dollars using exchange rates in effect at the balance sheet date. Opening balances related to non-monetary assets and liabilities are based on prior period translated amounts, and nonmonetary assets and nonmonetary liabilities incurred after January 1, 2015 are translated at the approximate exchange rate prevailing at the date of the transaction. Revenue and expense transactions are translated at the approximate exchange rate in effect at the time of the transaction. Foreign exchange gains and losses are included in the statement of operations and comprehensive income (loss) as foreign exchange gain (loss).

**Liability Classified Stock Options.** Prior to our IPO, we granted stock options with exercise prices denominated in Canadian dollars under our Amended and Restated Stock Option Plan to directors and certain consultants. Following the change in our functional currency on January 1, 2015, the options denominated in Canadian dollars that were granted to directors and certain consultants were subject to liability accounting with fair value calculated using the Black-Scholes option-pricing model. The liability classified stock options are measured at fair value at each reporting period with changes in fair value recognized in the statement of operations and comprehensive income (loss) as general and administrative stock based compensation expense.

The valuation of liability classified stock options is a critical accounting estimate due to the value of liabilities recorded and the assumptions that are required to calculate the liability, resulting in the classification of our liability classified stock options as a level 3 financial instrument.

There have been no other significant and material changes in our critical accounting policies during the three and six months ended June 30, 2015, as compared to those disclosed in "Management's Discussion and Analysis of Financial Conditions and Results of Operations - Critical Accounting Policies and Significant Judgments and Estimates" included in our 2014 Annual Report on Form 10-K filed with the SEC on March 12, 2015. We believe that the accounting policies discussed in the Annual Report are critical to understanding our historical and future performance, as these policies relate to the more significant areas involving management's judgments and estimates.

Results of Operations

Comparison of Three and Six Months Ended June 30, 2015 and 2014

The following table summarizes the results of our operations for the three and six months ended June 30, 2015 and 2014 together with changes in those items (in thousands):

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	Three Months		Change	Six Months Ended		Change
	Ended June 30, 2015	2014	2015 vs. 2014 Increase/(Decrease)	June 30, 2015	2014	2015 vs. 2014 Increase/(Decrease)
Collaboration revenue	\$4,044	\$5,296	\$ (1,252 )	\$8,054	\$10,297	\$ (2,243 )
Royalties	2	2	—	2	2	—
Research and development expenses	3,669	2,566	1,103	7,096	5,099	1,997
General and administrative expenses	2,058	1,213	845	3,629	2,513	1,116
General and administrative - stock based compensation	(1,880)	141	(2,021 )	3,269	277	2,992
Other:						
Interest income	163	137	26	315	278	37
Foreign exchange gain (loss)	806	(285 )	1,091	(2,365)	(85 )	(2,280 )
Net income (loss)	\$1,168	\$1,230	\$ (62 )	\$(7,988)	\$2,603	\$ (10,591 )

### Revenue

Revenue decreased by \$1.3 million and \$2.2 million in the three and six months ended June 30, 2015 as compared to the three and six months ended June 30, 2014, respectively. In 2014, we recognized revenues relating to the upfront payment from the December 2011 collaborative development and license agreement with Genentech which was fully recognized by December 2014. The remaining decrease as compared to the same periods in 2014 was due to less FTE funding from Genentech and Teva and the change in the foreign exchange rate between the U.S. and Canadian dollar.

### Research and Development Expenses

The following table summarizes research and development expenses for the three and six months ended June 30, 2015 and 2014 together with changes in those items (in thousands):

	Three Months		Change	Six Months Ended June		Change
	Ended June 30, 2015	2014	2015 vs. 2014 Increase/(Decrease)	30, 2015	2014	2015 vs. 2014 Increase/(Decrease)
Teva collaboration (TV-45070) expenses	58	290	\$ (232 )	93	534	\$ (441 )
Genentech collaboration (GDC-0276) expenses	651	1,339	(688 )	1,479	2,571	(1,092 )
XEN801 expenses	1,000	171	829	1,832	276	1,556
Preclinical and discovery program expenses	1,960	766	1,194	3,692	1,718	1,974
Total research and development expenses	\$3,669	\$2,566	\$ 1,103	\$7,096	\$5,099	\$ 1,997

Research and development expenses increased by \$1.1 million and \$2.0 million in the three and six months ended June 30, 2015 as compared to the three and six months ended June 30, 2014, respectively. These increases were primarily attributable to additional expenses for our XEN801 program for IND-enabling studies and in preparation for clinical development. There was also increased spending on our other preclinical and discovery programs, mostly related to our Nav1.6 sodium channel inhibitor program, partially offset by decreases in Teva and Genentech

collaboration expenses.

General and Administrative Expenses

The following table summarizes general and administrative expenses for the three and six months ended June 30, 2015 and 2014 together with changes in those items (in thousands):

	Three Months		Change 2015 vs. 2014 Increase/(Decrease)	Six Months		Change 2015 vs. 2014 Increase/(Decrease)
	Ended June 30, 2015	2014		Ended June 30, 2015	2014	
General and administrative expenses	\$2,058	\$1,213	\$ 845	\$3,629	\$2,513	\$ 1,116
General and administrative - stock based compensation	(1,880)	141	(2,021 )	3,269	277	2,992
Total general and administrative expenses	\$178	\$1,354	\$ (1,176 )	\$6,898	\$2,790	\$ 4,108

General and administrative expenses increased by \$0.8 million and \$1.1 million in the three and six months ended June 30, 2015 as compared to the three and six months ended June 30, 2014, respectively. These increases were primarily due to additional expenses incurred as a public company, including costs of additional personnel, additional professional fees for audit, accounting and legal services, director fees, enhanced business and accounting systems, costs related to investor relations and increased premiums for directors' and officers' liability insurance as well as one-time severance costs resulting from an internal reorganization that occurred in the second quarter of 2015.

General and administrative stock based compensation expenses decreased by \$2.0 million and increased by \$3.0 million in the three and six months ended June 30, 2015 as compared to the three and six months ended June 30, 2014, respectively. For the six months ended June 30, 2015, we recognized a \$2.7 million expense due to the fair value adjustment upon the reclassification of stock option awards granted to directors and certain consultants to liability classification. For the three months ended June 30, 2015, we recognized a recovery of \$2.2 million due to the decrease in fair value of our liability classified stock options resulting from the decline in our common share price from the preceding quarter. The remaining change is due to an increase in share-based compensation expense for equity classified awards as a result of higher grants in the three and six months ended June 30, 2015 compared to the same periods in 2014.

#### Other Income (Expense)

The following table summarizes our other income (expense) for the three and six months ended June 30, 2015 and 2014 together with changes in those items (in thousands):

	Three Months Ended June 30,		Change	Six Months Ended June 30,		Change
	2015	2014	2015 vs. 2014	2015	2014	2015 vs. 2014
			Increase/(Decrease)			Increase/(Decrease)
Other income (expense):	\$969	\$(148)	\$ 1,117	\$(2,050)	\$193	\$ (2,243 )

The change in other income (expense) was primarily driven by the change in foreign exchange gain (loss). We recorded a foreign exchange gain of \$0.8 million for the three months ended June 30, 2015, which was primarily unrealized gains arising largely from the translation of \$52.0 million of cash and cash equivalents and marketable securities denominated in Canadian dollars to U.S. dollars and a 1% increase in the value of the Canadian dollar during the three month period. During the six months ended June 30, 2015, we recorded a foreign exchange loss of \$2.4 million largely due to a 7% decrease in the value of the Canadian dollar during the six month period.

#### Liquidity and Capital Resources

To date, we have financed our operations primarily through funding received from collaboration and license agreements, private placements of our common and preferred shares and our initial public offering, as well as through the receipt of government funding. As of June 30, 2015, we had cash and cash equivalents and marketable securities of \$73.7 million. We received \$38.5 million of proceeds, net of underwriting discounts and commissions but before offering expenses, from our initial public offering and \$4.1 million of proceeds, net of underwriters' fees but before offering expenses, from the concurrent private placement to an affiliate of Genentech. Our initial public offering and

concurrent private placement each closed in November 2014.

We have incurred significant operating losses since inception. We had an \$8.0 million net loss for the six months ended June 30, 2015 and an accumulated deficit of \$111.8 million from inception through June 30, 2015. We expect to continue to incur significant expenses in excess of our revenue and expect to incur operating losses over the next several years. Our net losses may fluctuate significantly from quarter to quarter and year to year. We expect to continue to incur significant expenses and operating losses for the foreseeable future as we continue our research and preclinical and clinical development of our product candidates; expand the scope of our current studies for our product candidates; initiate additional preclinical, clinical or other studies for our product candidates, including under our collaboration agreements; change or add additional manufacturers or suppliers; seek regulatory and marketing approvals for any of our product candidates that successfully complete clinical studies; seek to identify and validate additional product candidates; acquire or in-license other product candidates and technologies; make milestone or other payments under our in-license agreements including, without limitation, our agreements with the University of British Columbia, or UBC, and the Memorial University of Newfoundland, or MUN; maintain, protect and expand our intellectual property portfolio; attract and retain skilled personnel; establish a sales, marketing and distribution infrastructure to commercialize any products for which we or one of our collaborators may obtain marketing approval, and maintain commercial rights; create additional infrastructure to support our operations as a public company and our product development and planned future commercialization efforts; and experience any delays or encounter issues with any of the above.

Until such time as we can generate substantial product revenue, if ever, we expect to finance our cash needs through a combination of collaboration agreements and equity or debt financings. Except for any obligations of our collaborators to reimburse us



for research and development expenses or to make milestone payments under our agreements with them, we do not have any committed external sources of capital. To the extent that we raise additional capital through the future sale of equity or debt, the ownership interest of our shareholders will be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect the rights of our existing common shareholders. If we raise additional funds through collaboration agreements in the future, we may have to relinquish valuable rights to our technologies, future revenue streams or product candidates or grant licenses on terms that may not be favorable to us. If we are unable to raise additional funds through equity or debt financings when needed, we may be required to delay, limit, reduce or terminate our product development or future commercialization efforts or grant rights to develop and market product candidates that we would otherwise prefer to develop and market ourselves.

Our future capital requirements are difficult to forecast and will depend on many factors, including:

- the number and characteristics of the future product candidates we pursue;
- the scope, progress, results and costs of independently researching and developing any of our future product candidates, including conducting preclinical research and clinical trials;
- whether our existing collaborations continue to generate substantial milestone payments and, ultimately, royalties on future approved products for us;
- the timing of, and the costs involved in, obtaining regulatory approvals for any future product candidates we develop independently;
- the cost of future commercialization activities, including activities required pursuant to our option to co-promote TV-45070, if exercised by us, and the cost of commercializing any future products we develop independently that are approved for sale;
- the cost of manufacturing our future product candidates and products, if any;
- our ability to maintain existing collaborations and to establish new collaborations, licensing or other arrangements and the financial terms of such agreements;
- the costs involved in preparing, filing, prosecuting, maintaining, defending and enforcing patents, including litigation costs and the outcome of such litigation; and
- the timing, receipt and amount of sales of, or royalties on, Glybera, and our future products, if any.

Based on our research and development plans and our timing expectations related to the progress of our programs, we expect that our existing cash and cash equivalents and marketable securities as of the date of this report and research funding that we expect to receive under our existing collaborations, will enable us to fund our operating expenses and capital expenditure requirements for at least the next 12 to 24 months. We have based this estimate on assumptions that may prove to be wrong, and we could use our capital resources sooner than we expect. Additionally, the process of testing drug candidates in clinical trials is costly, and the timing of progress in these trials remains uncertain.

### Cash Flows

The following table shows a summary of our cash flows for the six months ended June 30, 2015 and 2014 (in thousands):

	Six Months Ended June 30,	
	2015	2014
Net cash used in operating activities	\$(7,971)	\$(3,067)
Net cash provided by investing activities	1,628	1,125
Net cash provided by (used in) financing activities	213	(726)

### Operating Activities

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For the six months ended June 30, 2015, net cash used by operating activities totaled \$8.0 million, compared to \$3.1 million for the same period in 2014. The change is primarily related to the increase in operating expenses in 2015, the \$1.5 million upfront payment received from Genentech for the pain genetics collaboration entered into in March 2014 and \$0.5 million less FTE funding from Genentech and Teva for the six months ended June 30, 2015 as compared to the same period in 2014.

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### Investing Activities

For the six months ended June 30, 2015, net cash provided by investing activities totaled \$1.6 million, compared to \$1.1 million for the same period in 2014. The change was driven primarily by an increase in proceeds from the sale of marketable securities, net of purchases, and a decrease in the purchase of property, plant and equipment.

### Financing Activities

For the six months ended June 30, 2015, net cash provided by financing activities totaled \$0.2 million, compared to net cash used in financing activities of \$0.7 million for the same period in 2014. Net cash used in financing activities in 2014 consisted primarily of deferred financing costs in connection with our IPO which closed in November 2014 and net cash provided by financing activities in 2015 consisted exclusively of proceeds from the issuance of common shares from the exercise of stock options.

### Contractual Obligations and Commitments

Our future significant contractual obligations as of December 31, 2014 were reported in our Annual Report on Form 10-K, filed with the SEC on March 12, 2015. As of June 30, 2015, there have been no other material changes from the contractual commitments previously disclosed in the Annual Report on Form 10-K.

### Inflation

We do not believe that inflation has had a material effect on our business, financial condition or results of operations in the last three fiscal years.

### Off-Balance Sheet Arrangements

We do not engage in any off-balance sheet financing activities. We do not have any interest in entities referred to as variable interest entities, which include special purposes entities and other structured finance entities.

### Outstanding Share Data

As of August 7, 2015, we had 14,286,858 common shares issued and outstanding and outstanding options to purchase an additional 1,721,322 common shares.

### Recent Accounting Pronouncements

In May 2014, the Financial Accounting Standards Board, or FASB, issued amendments to clarify the principles of recognizing revenue and to develop a common revenue standard that would remove inconsistencies in revenue requirements, leading to improved comparability of revenue recognition practices across entities and industries. The amendments stipulate that an entity should recognize revenue to depict the transfer of promised goods or services to customers in an amount that reflects the consideration to which the entity expects to be entitled in exchange for those goods or services. Additional disclosure will also be required about the nature, amount, timing and uncertainty of revenue and cash flows arising from customer contracts, including significant judgments and changes in judgments, and assets recognized from costs incurred to obtain or fulfill a contract. In April 2015, the FASB voted to propose a deferral of the effective date of the new revenue standard by one year. The new guidance would be effective for public entities for fiscal years beginning after December 15, 2017 instead of the originally contemplated effective date of December 15, 2016. Entities are permitted to adopt in accordance with the original effective date if they choose. We are currently evaluating the new guidance to determine the impact it will have on our financial position, results of

operations and cash flows.

In August 2014, the FASB issued amendments requiring management to assess an entity's ability to continue as a going concern. For each reporting period, management will be required to evaluate whether there are conditions or events that raise substantial doubt about a company's ability to continue as a going concern within one year from the date the financial statements are issued. These amendments will be effective for public entities for the annual period ending after December 15, 2016, and for annual periods and interim periods thereafter. The adoption of these amendments in fiscal 2017 is not expected to have a material impact on our financial statements.

The Jumpstart Our Business Startups Act of 2012, or JOBS Act, provides that an emerging growth company can take advantage of an extended transition period for complying with new or revised accounting standards. This allows an emerging growth company to delay the adoption of certain accounting standards until those standards would otherwise apply to private companies. However, we previously chose to "opt out" of such extended transition period, and as a result, we will comply with new or revised accounting standards on the relevant dates on which adoption of such standards is required for non-emerging growth companies. Section 107 of

the JOBS Act provides that our decision to opt out of the extended transition period for complying with new or revised accounting standards is irrevocable.

### Item 3. Quantitative and Qualitative Disclosures About Market Risk

We are exposed to various market risks in the ordinary course of our business, including changes in interest rates and currency exchange rates. Market risk is the potential loss arising from adverse changes in interest rates and exchange rates.

#### Foreign Currency Exchange Risk

On January 1, 2015, our functional currency changed from the Canadian dollar to the U.S. dollar based on our analysis of the changes in the primary economic environment in which we operate.

The principal market risk we face is foreign currency exchange rate risk. We face this risk, in part, as a result of entering into transactions denominated in and holding currencies other than U.S. dollars, particularly those denominated in Canadian dollars and Euros. We also hold non-U.S. dollar denominated cash and cash equivalents, marketable securities, accounts receivable and accounts payable, which are denominated in Canadian dollars.

Changes in foreign currency exchange rates can create significant foreign exchange gains or losses to us. Our current foreign currency risk is with the Canadian dollar, as a majority of our non-U.S. dollar denominated expenses are denominated in Canadian dollars and the majority of our cash and cash equivalents and marketable securities are held in Canadian dollars. To limit our exposure to volatility in currency markets, we estimate our anticipated expenses that will be denominated in Canadian and U.S. dollars and then purchase a corresponding amount of Canadian or U.S. dollars at the current spot rate. Once these estimated expense amounts are acquired, we do not hedge our exposure and thus assume the risk of future gains or losses on the amounts of Canadian dollars held. At June 30, 2015, we held cash and cash equivalents and marketable securities of \$52.0 million denominated in Canadian dollars. A hypothetical 10% increase (decrease) in the value of the Canadian dollar would result in a foreign exchange gain (loss) of \$5.2 million being recorded in the Statement of Operations on the translation of these Canadian dollar cash and cash equivalent and marketable securities balances into the U.S. dollar functional currency.

#### Interest Rate Risk

An additional market risk we face is interest rate risk. We had cash and cash equivalents and marketable securities of \$73.7 million as of June 30, 2015. The goals of our investment policy are liquidity and capital preservation; we do not enter into investments for trading or speculative purposes and have not used any derivative financial instruments to manage our interest rate exposure. We believe that we do not have any material exposure to changes in the fair value of these assets as a result of changes in interest rates due to the short term nature of our cash and cash equivalents and marketable securities. Declines in interest rates, however, would reduce future investment income. A 10% change in interest rates during any of the periods presented would not have had a material impact on our financial statements. Such interest-earning instruments carry a degree of interest rate risk. We had no outstanding debt as of June 30, 2015.

### Item 4. Controls and Procedures

(a) Evaluation of disclosure controls and procedures. Our management, with the participation of our Chief Executive Officer and our Chief Financial Officer, have evaluated our disclosure controls and procedures (as defined in Rules 13a-15(e) and 15d-15(e) under the Securities Exchange Act of 1934, as amended) as of the end of the period covered by this quarterly report. Based on that evaluation and as a result of the restatement of our financial statements for the quarter ended March 31, 2015, our Chief Executive Officer and our Chief Financial Officer concluded that our disclosure controls and procedures were not, in design and operation, effective as of June 30, 2015. The restatement is more fully described in Note 2 to the restated unaudited interim financial statements included in Amendment No. 1 to our Quarterly Report on Form 10-Q/A for the quarter ended March 31, 2015, filed with the SEC on August 13, 2015.

(b) Changes in internal control over financial reporting. There were no changes in our internal control over financial reporting during the period ended June 30, 2015 that have materially affected, or are reasonably likely to materially affect, our internal control over financial reporting.

Inherent limitation on the effectiveness of internal control.

The effectiveness of any system of internal control over financial reporting, including ours, is subject to inherent limitations, including the exercise of judgment in designing, implementing, operating, and evaluating the controls and procedures, and the

inability to eliminate misconduct completely. Accordingly, any system of internal control over financial reporting, including ours, no matter how well designed and operated, can only provide reasonable, not absolute assurances. In addition, projections of any evaluation of effectiveness to future periods are subject to the risk that controls may become inadequate because of changes in conditions, or that the degree of compliance with the policies or procedures may deteriorate. We intend to continue to monitor and upgrade our internal controls as necessary or appropriate for our business, but cannot assure you that such improvements will be sufficient to provide us with effective internal control over financial reporting.

## PART II. OTHER INFORMATION

### Item 1. Legal Proceedings

From time to time, we may become involved in legal proceedings or be subject to claims arising in the ordinary course of our business. We are not presently a party to any legal proceedings that, in the opinion of our management, would reasonably be expected to have a material adverse effect on our business, financial condition, operating results or cash flows if determined adversely to us. Regardless of the outcome, litigation can have an adverse impact on us because of defense and settlement costs, diversion of management resources and other factors.

### Item 1A. Risk Factors

You should carefully consider the following risk factors, in addition to the other information contained in this report, including the section of this report captioned “Management’s Discussion and Analysis of Financial Condition and Results of Operations” and our financial statements and related notes. If any of the events described in the following risk factors and the risks described elsewhere in this report occurs, our business, operating results and financial condition could be seriously harmed. This report on Form 10-Q also contains forward-looking statements that involve risks and uncertainties. Our actual results could differ materially from those anticipated in the forward-looking statements as a result of factors that are described below and elsewhere in this report.

### Risks Related to Our Financial Condition and Capital Requirements

We have incurred significant losses since our inception and anticipate that we will continue to incur significant losses for the foreseeable future.

We are a clinical-stage biotechnology company and, other than the years ended December 31, 2014 and 2013, we have recorded net losses in each annual reporting period since inception in 1996, and we do not expect to have sustained profitability for the foreseeable future. We had net losses of \$8.0 million for the six months ended June 30, 2015 and an accumulated deficit of \$111.8 million as of June 30, 2015.

We have devoted most of our financial resources to research and development, including our clinical and preclinical development activities. To date, we have financed our operations through the sale of equity securities, funding received from our licensees and collaborators and, to a lesser extent, government funding. We have not generated any royalty revenue from product sales and our product candidates will require substantial additional investment before

they will provide us with any product royalty revenue.

We expect to incur significant expenses and increasing operating losses for the foreseeable future as we:

- continue our research and preclinical and clinical development of our product candidates;
- expand the scope of our clinical studies for our current and prospective product candidates;
- initiate additional preclinical, clinical or other studies for our product candidates, including under our collaboration agreements;
- change or add additional manufacturers or suppliers;
- seek regulatory and marketing approvals for any of our product candidates that successfully complete clinical studies;
- seek to identify and validate additional product candidates;
- acquire or in-license other product candidates and technologies;
- make milestone or other payments under our in-license agreements including, without limitation, our agreements with the University of British Columbia, or UBC, and the Memorial University of Newfoundland;
- maintain, protect and expand our intellectual property portfolio;
- establish a sales, marketing and distribution infrastructure to commercialize any products for which we or one of our collaborators may obtain marketing approval, and for which we have maintained commercial rights;



- create additional infrastructure to support our operations as a public company and our product development and planned future commercialization efforts; and
- experience any delays or encounter issues with any of the above.

Our expenses could increase beyond expectations for a variety of reasons, including if we are required by the U.S. Food and Drug Administration, or FDA, the European Medicines Agency, or EMA, or other regulatory agencies, domestic or foreign, to perform clinical and other studies in addition to those that we currently anticipate. Our prior losses, combined with expected future losses, have had and will continue to have an adverse effect on our shareholders' equity.

We have not generated any royalty revenue from product sales and may never become profitable on a U.S. GAAP basis.

Our ability to generate meaningful revenue and achieve profitability on a U.S. GAAP basis depends on our ability, alone or with strategic collaborators, to successfully complete the development of, and obtain the regulatory approvals necessary to commercialize, our product candidates. Substantially all of our revenue since inception has consisted of upfront and milestone payments associated with our collaboration and license agreements. Revenue from these agreements is dependent on successful development of our product candidates by us or our collaborators. To date, we have not generated any royalty revenue from product sales, and do not otherwise anticipate generating revenue from product sales other than from sales of Glybera under our license to uniQure Biopharma B.V., or uniQure, for the foreseeable future, if ever. If any of our product candidates fail in clinical trials or do not gain regulatory approval, or if Glybera or any of our future products, if any, once approved, fail to achieve market acceptance or adequate market share, we may never become profitable. Although we were profitable for the years ended December 31, 2014 and 2013, we may not be able to sustain profitability in subsequent periods. Our ability to generate future revenue from product sales depends heavily on our success, and the success of our collaborators, in:

- completing research, preclinical and clinical development of our product candidates;
- seeking and obtaining regulatory and marketing approvals for product candidates for which we complete clinical studies;
- commercializing products for which we obtain regulatory and marketing approval, either with a collaborator or, if launched independently, by establishing sales, marketing and distribution infrastructure;
- negotiating favorable terms in any collaboration, licensing or other arrangements into which we may enter;
- obtaining market acceptance of products for which we obtain regulatory and marketing approval as therapies;
- addressing any competing technological and market developments;
- establishing and maintaining supply and manufacturing relationships with third parties that can provide adequate (in amount and quality) products and services to support clinical development and the market demand for any approved products in the future;
- developing a sustainable, scalable, reproducible, and transferable manufacturing processes for any of our products approved in the future;
- maintaining, protecting, expanding and enforcing our portfolio of intellectual property rights, including patents, trade secrets and know-how;
- implementing additional internal systems and infrastructure, as needed; and
- attracting, hiring and retaining qualified personnel.

The scope of our future revenue will also depend upon the size of any markets in which our product candidates receive approval and the availability of insurance coverage and the availability and amount of reimbursement from third-party payers for Glybera and future products, if any. If we are unable to achieve sufficient revenue to become profitable and

remain so, our financial condition and operating results will be negatively impacted, and our trading price might be harmed.

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We will likely need to raise additional funding, which may not be available on acceptable terms, if at all. Failure to obtain this necessary capital when needed may force us to delay, limit or terminate our product development efforts or other operations.

Since our inception, we have dedicated most of our resources to the discovery and development of our proprietary preclinical and clinical product candidates, and we expect to continue to expend substantial resources doing so for the foreseeable future. These expenditures will include costs associated with research and development, manufacturing of product candidates and products approved for sale, conducting preclinical experiments and clinical trials and obtaining and maintaining regulatory approvals, as well as commercializing any products later approved for sale. During the six months ended June 30, 2015, we incurred approximately \$7.1 million of costs associated with research and development, exclusive of costs incurred by our collaborators in developing our product candidates.

Our current cash and cash equivalents and marketable securities are not expected to be sufficient to complete clinical development of any of our product candidates and prepare for commercializing any product candidate which receives regulatory approval. Accordingly, we will likely require substantial additional capital to continue our clinical development and potential commercialization activities. Our future capital requirements depend on many factors, including but not limited to:

- the number and characteristics of the future product candidates we pursue;
- the scope, progress, results and costs of independently researching and developing any of our future product candidates, including conducting preclinical research and clinical trials;
- whether our existing collaborations continue to generate substantial milestone payments and, ultimately, royalties on future approved products for us;
- the timing of, and the costs involved in, obtaining regulatory approvals for any future product candidates we develop independently;
- the cost of future commercialization activities, including activities required pursuant to our option to co-promote TV-45070, if exercised by us, and the cost of commercializing any future products we develop independently that are approved for sale;
- the cost of manufacturing our future product candidates and products, if any;
- our ability to maintain existing collaborations and to establish new collaborations, licensing or other arrangements and the financial terms of such agreements;
- the costs involved in preparing, filing, prosecuting, maintaining, defending and enforcing patents, including litigation costs and the outcome of such litigation; and
- the timing, receipt and amount of sales of, or royalties on, Glybera, and our future products, if any.

We are unable to estimate the funds we will actually require to complete research and development of our product candidates or the funds required to commercialize any resulting product in the future.

Based on our research and development plans and our timing expectations related to the progress of our programs, we expect that our existing cash and cash equivalents and marketable securities as of the date of this report and research funding that we expect to receive under our existing collaborations, will enable us to fund our operating expenses and capital expenditure requirements for at least the next 12 to 24 months.

Our operating plan may change as a result of many factors currently unknown to us, and we may need to seek additional funds sooner than planned, through public or private equity or debt financings, government or other third-party funding, marketing and distribution arrangements and other collaborations, strategic alliances and licensing arrangements or a combination of these approaches. Raising funds in the future may present additional challenges and future financing may not be available in sufficient amounts or on terms acceptable to us, if at all.

Raising additional capital may cause dilution to our existing shareholders, restrict our operations or require us to relinquish rights to our technologies or product candidates.

The terms of any financing arrangements we enter into may adversely affect the holdings or the rights of our shareholders and the issuance of additional securities, whether equity or debt, by us, or the possibility of such issuance, may cause the market price of our shares to decline. The sale of additional equity or convertible securities would dilute all of our shareholders. The incurrence of indebtedness would result in increased fixed payment obligations and, potentially, the imposition of restrictive covenants. Those covenants may include limitations on our ability to incur additional debt, limitations on our ability to acquire, sell or license intellectual property rights and other operating restrictions that could adversely impact our ability to conduct our business. We could also be required to seek funds through arrangements with collaborators or otherwise at an earlier stage than otherwise would be desirable resulting in the loss of rights to some of our product candidates or other unfavorable terms, any of which may have a material adverse effect on our business, operating results and prospects. In addition, any additional fundraising efforts may divert our management from their day-to-day activities, which may adversely affect our ability to develop and commercialize our product candidates.

Unstable market and economic conditions may have serious adverse consequences on our business and financial condition.

Global credit and financial markets experienced extreme disruptions at various points over the last decade, characterized by diminished liquidity and credit availability, declines in consumer confidence, declines in economic growth, increases in unemployment rates, and uncertainty about economic stability. If another such disruption in credit and financial markets and deterioration of confidence in economic conditions occurs, our business may be adversely affected. If the equity and credit markets were to deteriorate significantly in the future, it may make any necessary debt or equity financing more difficult to complete, more costly, and more dilutive. Failure to secure any necessary financing in a timely manner and on favorable terms could have a material adverse effect on our growth strategy, financial performance and share price and could require us to delay or abandon development or commercialization plans. In addition, there is a risk that one or more of our current collaborators, service providers, manufacturers and other partners would not survive or be able to meet their commitments to us under such circumstances, which could directly affect our ability to attain our operating goals on schedule and on budget.

We are subject to risks associated with currency fluctuations and fair value adjustments which could impact our results of operations.

As of June 30, 2015, approximately 71% of our cash and cash equivalents and marketable securities was denominated in Canadian dollars. Historically, the majority of our operating expenses have been denominated in Canadian dollars and the majority of our revenue has been denominated in U.S. dollars and we expect this trend to continue.

Prior to December 31, 2014, our functional currency was the Canadian dollar. On January 1, 2015, our functional currency changed from the Canadian dollar to the U.S. dollar based on our analysis of the changes in the primary economic environment in which we operate. As a result, changes in the exchange rate between the Canadian dollar and the U.S. dollar could materially impact our reported results of operations and distort period to period comparisons. In particular, to the extent that foreign currency-denominated (i.e., non-U.S. dollar) monetary assets do not equal the amount of our foreign currency denominated monetary liabilities, foreign currency gains or losses could arise and materially impact our financial statements. As a result of such foreign currency fluctuations, it could be more difficult to detect underlying trends in our business and results of operations. In addition, to the extent that fluctuations in currency exchange rates cause our results of operations to differ from our expectations or the expectations of our investors, the trading price of our common shares could be adversely affected.

From time to time, we may engage in exchange rate hedging activities in an effort to mitigate the impact of exchange rate fluctuations. For example, we maintain a natural currency hedge against fluctuations in the U.S./Canadian foreign exchange rate by matching the amount of U.S. dollar and Canadian dollar investments to the expected amount of future U.S. dollar and Canadian dollar obligations, respectively. Any hedging technique we implement may fail to be effective. If our hedging activities are not effective, changes in currency exchange rates may have a more significant impact on the trading price of our common shares.

As of June 30, 2015, we had 492,842 outstanding liability classified stock options. Accordingly, the fair value of these stock options is recorded on our balance sheet as a liability, and such fair value is adjusted at each financial reporting date with the adjustment to fair value reflected in our statement of operations and comprehensive income (loss). The fair value of the liability classified stock options is determined using the Black-Scholes option-pricing model. Fluctuations in our common share price and the assumptions and factors used in the Black-Scholes model can result in adjustments to the fair value of these stock options reflected on our balance sheet and our statement of operations and comprehensive income (loss). Due to the classification of such stock options and other factors, quarterly results of operations are difficult to forecast, and period-to-period comparisons of our operating results may not be predictive of future performance. In addition, to the extent that fluctuations in fair value of liability classified stock options cause our results of operations to differ from our expectations or the expectations of our investors, the trading price of our common shares could be adversely affected.

## Risks Related to Our Business

We, or our collaborators, may fail to successfully develop our product candidates.

Our product candidates, including TV-45070 and GDC-0276 and compounds in our preclinical and discovery pipeline, are in varying stages of development and will require substantial clinical development, testing and regulatory approval prior to commercialization. It may be several more years before these product candidates or any of our other product candidates receive marketing approval, if ever. If any of our product candidates fail to become approved products, our business, growth prospects, operating results and financial condition may be adversely affected and a decline of our common share price could result. For example, in July 2015, we and our partner Teva announced top line results from a Phase 2b study designed to evaluate the safety and efficacy of topically applied TV-45070 in patients with chronic pain due to osteoarthritis, or OA, of the knee. Results from this trial showed that TV-45070 did not demonstrate statistically significant difference from placebo in efficacy endpoints of reductions in pain due to OA and neither we nor Teva have plans for further development of TV-45070 in OA, although clinical development of TV-45070 in post-herpetic neuralgia, or PHN, continues.

Our near-term operating revenue is partially dependent upon the regulatory and marketing efforts of uniQure, or its sublicensee, for the development and commercialization of Glybera.

Under the terms of our license agreement with uniQure, we rely on uniQure, or its sublicensees, to market Glybera and to obtain and maintain regulatory approval of Glybera. In July 2013, uniQure announced that it had granted to Chiesi Farmaceutici, S.p.A., or Chiesi, an Italian pharmaceutical firm, an exclusive license to commercialize Glybera in the European Union, or the EU, and certain other countries outside of North America and Japan. Despite the efforts of uniQure and Chiesi, Glybera may not gain market acceptance among physicians, patients, healthcare payers and the medical community. The commercial success of Glybera will depend on a number of factors, including:

- establishment and demonstration of clinical efficacy and safety and acceptance of the same by the medical community and regulatory authorities;
- commercialization of competing products;
- sufficient commercial supply of Glybera;
- cost-effectiveness of Glybera;
- regulatory authorities' final assessment of the benefit-risk analysis of Glybera;
- the availability of coverage and adequate reimbursement from third parties, including governmental payers, managed care organizations, and private health insurers;
- the relative cost, safety and efficacy of therapies that exist now or may be developed in the future;
- whether the product can be manufactured in commercial quantities at acceptable cost;
- marketing and distribution support for Glybera;
- cost of post-approval obligations in the EU including a post-approval clinical trial and market surveillance activities;
- maintaining the marketing approval under exceptional circumstances in the EU;
- the effect of current and future healthcare laws;
- the acceptance of gene therapies as a class of treatment; and
- any market or regulatory exclusivities applicable to the product.

To date, the FDA has never approved any gene therapy product as a treatment for any indication in the U.S. and the FDA may never approve Glybera. Glybera is approved in the EU under exceptional circumstances and full approval may never be granted or the existing approval under exceptional circumstances could be revoked. As a condition to approval of Glybera, uniQure is required to complete a post-approval clinical trial and is required to implement a disease registry as well as implement risk management procedures, distribute educational materials to healthcare

professionals and patients, implement an additional manufacturing process step, comply with certain notification obligations and undergo annual reassessment, any negative outcome of which could potentially lead to a withdrawal of marketing approval for Glybera.

Any failure of uniQure or its sublicensee to successfully commercialize Glybera or revocation of Glybera's marketing approval in the EU could have a material adverse effect on our business, growth prospects, operating results and financial condition and could result in a substantial decline in the price of our common shares.

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We and our collaborators face substantial competition in the markets for our product candidates, which may result in others discovering, developing or commercializing products before us or doing so more successfully than we or our collaborators do.

The biotechnology and pharmaceutical industries are characterized by rapidly advancing technologies, intense competition and a strong emphasis on proprietary products. We face potential competition in target discovery and product development from many different approaches and sources, including major pharmaceutical, specialty pharmaceutical and biotechnology companies, academic institutions and governmental agencies and public and private research institutions. Any product candidates that we or our collaborators successfully develop and commercialize will compete with existing products and any new products that may become available in the future.

The key competitive factors affecting the success of all of our product candidates, if approved, are likely to be their efficacy, safety, convenience and price; the effectiveness of alternative products; the level of generic competition; and the availability of coverage and adequate reimbursement from government and other third-party payers.

With respect to target discovery activities, competitors and other third parties, including academic and clinical researchers, may access rare families and identify novel targets for drug development before we do.

Many of the companies against which we are competing or against which we may compete in the future have significantly greater financial resources and expertise in research and development, manufacturing, preclinical testing, conducting clinical trials, obtaining regulatory approvals and marketing approved products than we, or our collaborators, do. Mergers and acquisitions in the pharmaceutical and biotechnology industries may result in even more resources being concentrated among a smaller number of our competitors. Smaller or early stage companies may also prove to be significant competitors, particularly through collaboration arrangements with large and established companies.

Our commercial opportunities could be reduced or eliminated if our competitors develop and commercialize products or therapies that are safer, more effective, have fewer or less severe side effects, are more convenient or are less expensive than any products that we may develop. Our competitors also may obtain FDA, EMA or other regulatory approval for their products more rapidly than we may obtain approval for ours, which could result in our competitors establishing a strong market position before we are able to enter the market. In addition, our ability to compete may be affected by decisions made by insurers or other third party payers.

To the extent that we are unable to compete effectively against one or more of our competitors in these areas, our business will not grow and our financial condition, results of operations and common share price may suffer.

There are no approved gene therapies currently on the market for lipoprotein lipase deficiency, or LPLD, in the U.S. The current management of LPLD consists of strict adherence to an extremely low-fat diet, but compliance with such a diet is challenging. Lipid-lowering drugs are generally not effective for treating LPLD. We are not aware of any other drugs or therapies currently in development that treat LPLD by using the lipoprotein lipase, or LPL, sequence containing the LPL<sup>S447X</sup> genetic variant or otherwise.

Drug discovery and development for various pain applications is intensely competitive. There are a large number of approved products for neuropathic pain, inflammatory pain and other pain indications. These approved products include capsaicin, celecoxib, lidocaine, narcotic analgesics and pregabalin. We are also aware of clinical-stage development programs at several pharmaceutical and biotechnology companies that are targeting Nav1.7 inhibitors to develop products to treat various pain indications, including Bioline Rx Ltd., Biogen Inc. through its recent acquisition of Convergence Pharmaceuticals Limited, Dainippon Sumitomo Co., Ltd. and Pfizer, Inc. Moreover, we are aware of various other product candidates in development that target other mechanisms of action to treat various pain indications.

The novelty of gene therapy products and their lack of a commercial track record may hinder market acceptance of Glybera among physicians, patients, healthcare payers and the medical community.

Glybera is the first gene therapy product approved in the EU and no gene therapy product has been approved in the U.S. Because Glybera is the first gene therapy to be marketed in the EU, gaining market acceptance and overcoming any safety or efficacy concerns may be more challenging than for a more traditional therapy. Glybera's commercial success will depend, in part, on the success of efforts to educate the market regarding gene therapy products. In particular, the success of Glybera will depend upon physicians who treat patients with LPLD, prescribing Glybera. With respect to Glybera and any other gene therapy products we or a collaborator may develop, public perception may be influenced by claims that gene therapy is unsafe, and, if so, gene therapy may not gain the acceptance of the public or the medical community.

uniQure reported that, on April 8, 2015, it received a copy of a preliminary assessment report prepared by the rapporteur designated by the Committee for Advanced Therapies, or CAT, which is the committee that advises the EMA's Committee for Human Medicinal Products, or CHMP, on gene therapies. The preliminary report was a response to uniQure's submission to the EMA in

September 2014 of a Type II variation, which proposed an amendment to the Glybera Summary of Product Characteristics to reflect certain information from the six-year follow up data included in uniQure's final clinical study report. The preliminary assessment report, which represented the sole view of the rapporteur, stated that Glybera lacked efficacy and therefore the benefit-risk was negative. On April 24, 2015, uniQure received a copy of the final assessment report prepared by the CAT and endorsed by the CHMP, which stated that the CAT discussed the negative rapporteur recommendation on the benefit risk analysis of Glybera and did not agree with the negative view of the rapporteur and concluded by majority on the recommendation that the efficacy of Glybera be considered in its totality as defined in the initial approval taking into account the criteria at the time of the initial approval. The CAT will continue to evaluate the six-year follow up data and uniQure has provided requested supplemental information.

There can be no assurance regarding the EMA's final conclusion and any adverse outcome of this review could require conducting further post-approval studies, or could potentially result in revocation of the marketing approval for Glybera in the EU. More restrictive government regulations resulting from CAT's and CHMP's review or negative public opinion could have a negative effect on our business or financial condition and may delay or impair the commercialization of Glybera. If Glybera is not successfully commercialized, our ability to generate near term revenue could be impaired.

We have no marketed products and have not yet advanced a product candidate beyond Phase 2 clinical trials, which makes it difficult to assess our ability to develop our future product candidates and commercialize any resulting products independently.

We have no experience in Phase 3 and later stage clinical development, and related regulatory requirements or the commercialization of products. uniQure controls and has been responsible for the development and commercialization of Glybera, Teva Pharmaceutical Industries Ltd., or Teva, is responsible for the on-going clinical development of TV-45070, and Genentech Inc., or Genentech, is responsible for the on-going clinical development of GDC-0276. Accordingly, we have not yet demonstrated our ability to independently and repeatedly conduct clinical development after Phase 2, obtain regulatory approval and commercialize therapeutic products. We will need to develop such abilities if we are to execute on our business strategy to selectively develop and independently commercialize product candidates for orphan and niche indications. To execute on our business plan for the development of independent programs, we will need to successfully:

- execute our clinical development plans for later-stage product candidates;
- obtain required regulatory approvals in each jurisdiction in which we will seek to commercialize products;
- build and maintain appropriate sales, distribution and marketing capabilities;
- gain market acceptance for our future products, if any; and
- manage our spending as costs and expenses increase due to clinical trials, regulatory approvals and commercialization activities.

If we are unsuccessful in accomplishing these objectives, we would not be able to develop and commercialize any future orphan and niche disease product candidates independently, and could fail to realize the potential advantages of doing so.

If we are not successful in leveraging our Extreme Genetics discovery platform to discover product candidates in addition to TV-45070 and GDC-0276, our ability to expand our business and achieve our strategic objectives may be impaired.

We rely on our Extreme Genetics discovery platform to identify validated drug targets and develop new product candidates. To date, our Extreme Genetics discovery platform has yielded one approved product, Glybera, and two

clinical development candidates TV-45070 and GDC-0276. Use of our discovery platform requires substantial technical, financial and human resources, regardless of whether we identify any novel drug targets. Our Extreme Genetics discovery platform may initially show promise in identifying additional potential product candidates, yet fail to yield viable product candidates for clinical development or commercialization. Such failure may occur for many reasons, including the following: any product candidate may, on further study, be shown to have serious or unexpected side effects or other characteristics that indicate it is unlikely to be safe or otherwise does not meet applicable regulatory criteria; and any product candidate may not be capable of being produced in commercial quantities at an acceptable cost, or at all.

If we are unable to identify additional product candidates suitable for clinical development and commercialization, we may not be able to obtain product revenue in future periods, which likely would result in significant harm to our financial position and adversely impact our trading price.

Our approach to drug discovery is unproven, and we do not know whether we will be able to develop any products of commercial value.

Our Extreme Genetics discovery platform may not reproducibly or cost-effectively result in the discovery of product candidates and development of commercially viable products that safely and effectively treat human disease.

There are various challenges in utilizing our Extreme Genetics discovery platform to successfully identify novel drug targets, including locating families suffering from rare disorders and severe phenotypes, entering into agreements with foreign collaborators, complying with various domestic and foreign privacy laws, accessing required technologies in a timely manner and transporting DNA across national borders.

To date, only Glybera has been both developed using our Extreme Genetics discovery platform and approved for commercial sale. If the use of our Extreme Genetics discovery platform fails to identify novel targets for drug discovery, or such targets prove to be unsuitable for treating human disease, or we are unable to develop product candidates with specificity and selectivity for such targets, we will fail to develop viable products. If we fail to develop and commercialize viable products, we will not achieve commercial success.

We may encounter difficulties in managing our growth, including headcount, and expanding our operations successfully.

Our business strategy involves continued development and, where development is successful, commercialization of select successfully developed product candidates for orphan and niche indications independently. In order to execute on this strategy, we will need to build out a regulatory, sales, manufacturing, distribution and marketing infrastructure and expand our development capabilities or contract with third parties to provide these capabilities and infrastructure for us. To achieve this, we will need to identify, hire and integrate personnel who have not worked together as a group previously. We anticipate that we may need to hire additional accounting, legal and financial staff with appropriate public company experience and technical accounting and other knowledge to address the added burdens of operating as a newly public company. There are likely to be infrastructure costs associated with public company compliance as well.

As our operations expand, we expect that we will need to manage additional relationships with various strategic collaborators, suppliers and other third parties.

Dr. Gary Bridger, our Executive Vice President of Research and Development, works for us one to two days per month, pursuant to a consulting agreement. Drs. Simon Pimstone and Y. Paul Goldberg each devote a small amount of their time to clinical work outside of their duties at our company, conducting, generally, two to three outpatient clinics per month. Future growth will impose significant added responsibilities on members of management, and our management may need to divert a disproportionate amount of its attention away from our day-to-day activities and devote a substantial amount of time to managing these growth activities.

If we are to effectively manage our growth, our expenses may increase more than expected, our ability to generate and grow revenue could be reduced, and we may not be able to implement our business strategy. Our future financial performance and our ability to commercialize product candidates and compete effectively will depend, in part, on our ability to effectively manage any future growth.

If we fail to attract and retain senior management and key personnel, we may be unable to successfully develop our product candidates, perform our obligations under our collaboration agreements, conduct our clinical trials and commercialize our product candidates.

Our success depends in part on our continued ability to attract, retain and motivate highly qualified management, clinical and scientific personnel.

We could experience difficulties attracting and retaining qualified employees as competition for qualified personnel in the biotechnology and pharmaceutical field is intense. We are highly dependent upon our senior management, particularly Dr. Pimstone, our Chief Executive Officer and President; Mr. Ian Mortimer, our Chief Financial Officer and Chief Operating Officer; and Dr. Goldberg, our Vice President, Clinical Development, as well as other employees. In the near future, the loss of services of any of these individuals or one or more of our other members of senior management could materially delay or even prevent the successful development of our product candidates.

In addition, we will need to hire additional personnel as we expand our clinical development activities and develop commercial capabilities, including a sales infrastructure to support our independent commercialization efforts. We may not be able to attract and retain personnel on acceptable terms given the competition among numerous pharmaceutical and biotechnology companies for individuals with similar skill sets. The inability to recruit or loss of the services of any executive or key employee may impede the progress of our research, development and commercialization objectives.

Our employees, collaborators and other personnel 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, collaborators, vendors, principal investigators, consultants and commercial partners. Misconduct by these parties could include intentional failures to comply with the regulations of the FDA, EMA and other non-U.S. regulators, provide accurate information to the FDA, EMA and other non-U.S. regulators, comply with data privacy and security and healthcare fraud and abuse laws and regulations in the U.S. 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. Additionally, laws regarding data privacy and security, including the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act of 2009, or HITECH, as well as comparable laws in non-U.S. jurisdictions, may impose obligations with respect to safeguarding the privacy, use, security and transmission of individually identifiable health information such as genetic material.

Various laws and regulations may restrict or prohibit a wide range of pricing, discounting, marketing and promotion, sales commission, customer incentive programs and other business arrangements. Any misconduct could also involve the improper use of information obtained in the course of clinical studies, 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 governmental 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, including the imposition of significant fines or other sanctions.

A variety of risks associated with international operations could materially adversely affect our business.

Glybera has been approved for commercial sale in the EU by the EMA, subject to uniQure's compliance with certain post-approval reporting and monitoring obligations. Our collaborator for TV-45070, Teva, is based in Israel and a significant portion of the research and development activities under our collaboration with Teva are performed outside of North America. If we continue to engage in significant cross-border activities, we will be subject to risks related to international operations, including:

- different regulatory requirements for maintaining approval of drugs and biologics in foreign countries;
- reduced protection for intellectual property rights in certain countries;
- unexpected changes in tariffs, trade barriers and regulatory requirements;
- economic weakness, including inflation, political instability or open conflict 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 revenue, and other obligations incident to doing business in another country;
- workforce uncertainty in countries where labor unrest is more common than in North America;
- tighter restrictions on privacy and the collection and use of data, including genetic material, may apply in jurisdictions outside of North America, where we find some of the families with individuals that exhibit the severe phenotypes that we study; and

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

If any of these issues were to occur, our business could be materially harmed.

U.S. Holders of our shares may suffer adverse tax consequences if we are characterized as a passive foreign investment company.

Generally, for any taxable year in which 75% or more of our gross income is passive income, or at least 50% of the average quarterly value of our assets (which may be determined in part by the market value of our common shares, which is subject to change) are held for the production of, or produce, passive income, we would be characterized as a passive foreign investment company, or PFIC, for U.S. federal income tax purposes. Based on the composition of our gross income and gross assets and the nature of our business, we do not believe that we were a PFIC for the taxable years ended December 31, 2014 and 2013, although we could be a



PFIC in one or more subsequent years. Our status as a PFIC is a fact-intensive determination made on an annual basis and we cannot provide any assurance regarding our PFIC status for future taxable years.

If we are a PFIC for any subsequent year, U.S. Holders of our common shares may suffer adverse tax consequences. Gains realized by non-corporate U.S. Holders on the sale of our common shares would be taxed as ordinary income, rather than as capital gain, and the preferential tax rate applicable to dividends received on our common shares would be lost. Interest charges would also be added to taxes on gains and dividends realized by all U.S. Holders.

A U.S. Holder may avoid these adverse tax consequences by timely making a qualified electing fund election. For each year that we would meet the PFIC gross income or asset test, an electing U.S. Holder would be required to include in gross income its pro rata share of our net ordinary income and net capital gains, if any. A U.S. Holder may make a qualified electing fund election only if we commit to provide U.S. Holders with their pro rata share of our net ordinary income and net capital gains. If we are a PFIC in the current or a future tax year, we will provide our U.S. Holders with the information that is necessary in order for them to make a qualified electing fund election and to report their common shares of ordinary earnings and net capital gains for each year for which we are a PFIC.

A U.S. Holder may also mitigate the adverse tax consequences if we are a PFIC by timely making a mark-to-market election. Generally, for each year that we would meet the PFIC gross income or asset test, an electing U.S. Holder would include in gross income the increase in the value of its shares during each of its taxable years and deduct from gross income the decrease in the value of such shares during each of its taxable years. A mark-to-market election may be made and maintained only if our common shares are regularly traded on a qualified exchange, including The NASDAQ Global Market, or NASDAQ. Whether our common shares are regularly traded on a qualified exchange is an annual determination based on facts that, in part, are beyond our control. Accordingly, a U.S. Holder might not be eligible to make a mark-to-market election to mitigate the adverse tax consequences if we are characterized as a PFIC.

Acquisitions or joint ventures could disrupt our business, cause dilution to our shareholders and otherwise harm our business.

We actively evaluate various strategic transactions on an ongoing basis and may acquire other businesses, products or technologies as well as pursue strategic alliances, joint ventures or investments in complementary businesses. Any of these transactions could be material to our financial condition and operating results and expose us to many risks, including:

- disruption in our relationships with collaborators or suppliers as a result of such a transaction;
- unanticipated liabilities related to acquired companies;
- difficulties integrating acquired personnel, technologies and operations into our existing business;
- retention of key employees;
- diversion of management time and focus from operating our business to management of strategic alliances or joint ventures or acquisition integration challenges;
- increases in our expenses and reductions in our cash available for operations and other uses; and
- possible write-offs or impairment charges relating to acquired businesses.

Foreign acquisitions involve unique risks in addition to those mentioned above, including those related to integration of operations across different cultures and languages, currency risks and the particular economic, political and

regulatory risks associated with specific countries.

Also, the anticipated benefit of any strategic alliance, joint venture or acquisition may not materialize. Future acquisitions or dispositions could result in potentially dilutive issuances of our equity securities, the incurrence of debt, contingent liabilities or amortization expenses or write-offs of goodwill, any of which could harm our financial condition. We cannot predict the number, timing or size of future joint ventures or acquisitions, or the effect that any such transactions might have on our operating results.

#### Risks Related to Development, Clinical Testing and Regulatory Approval of Our Product Candidates

The regulatory approval processes of the FDA, EMA and regulators in other jurisdictions are lengthy, time-consuming and inherently unpredictable. If we, or our collaborators, are unable to obtain timely regulatory approval for our product candidates, our business will be substantially harmed.

The regulatory approval process is expensive and the time required to obtain approval from the FDA, EMA or other regulatory authorities in other jurisdictions to sell any product is uncertain and may take years. Whether regulatory approval will be granted is unpredictable and depends upon numerous factors, including the substantial discretion of the regulatory authorities. Approval policies,

regulations, or the type and amount of preclinical and clinical data necessary to gain approval may change during the course of a product candidate's clinical development and may vary among jurisdictions. Other than for Glybera in the EU, neither we nor our collaborators have obtained regulatory approval for any of our product candidates. It is possible that none of our existing product candidates or any of our future product candidates will ever obtain regulatory approval, even if we expend substantial time and resources seeking such approval.

Our product candidates could fail to receive regulatory approval for many reasons, including the following:

- the FDA, EMA or other regulatory authorities may disagree with the design or implementation of our or our collaborators' clinical trials;
- we or our collaborators may be unable to demonstrate to the satisfaction of the FDA, EMA or other regulatory authorities that a product candidate is safe and effective for its proposed indication;
- the results of clinical trials may not meet the level of statistical significance required by the FDA, EMA or other regulatory authorities for approval;
- we, or our collaborators, may be unable to demonstrate that a product candidate's clinical and other benefits outweigh its safety risks;
- the FDA, EMA or other regulatory authorities may disagree with our or our collaborators' interpretation of data from preclinical studies or clinical trials;
- the data collected from clinical trials of our product candidates may not be sufficient to support the submission of a New Drug Application, or NDA, or other submission or to obtain regulatory approval in the U.S. or elsewhere;
- the FDA, EMA or other regulatory authorities may fail to approve the manufacturing processes or facilities of third-party manufacturers with which we or our collaborators contract for clinical and commercial supplies; and
- the approval policies or regulations of the FDA, EMA or other regulatory authorities outside of the U.S. may significantly change in a manner rendering our or our collaborators' clinical data insufficient for approval.

Even if we, or our collaborators, obtain approval for a particular product, regulatory authorities may grant approval contingent on the performance of costly post-approval clinical trials, or may approve a product with a label that does not include the labeling claims necessary or desirable for the successful commercialization of that product.

Clinical drug development involves a lengthy and expensive process with uncertain timelines and uncertain outcomes. If clinical trials are prolonged or delayed, we, or our collaborators, may be unable to commercialize our product candidates on a timely basis.

Clinical testing of product candidates is expensive and, depending on the stage of development, can take a substantial period of time to complete. Clinical trial outcomes are inherently uncertain, and failure can occur at any time during the clinical development process.

Clinical trials can be halted or delayed for a variety of reasons, including those related to:

- side effects or adverse events in study participants presenting an unacceptable safety risk;
- inability to reach agreement with prospective contract research organizations, or CROs, and clinical trial sites, or the breach of such agreements;
- failure of third-party contractors, such as CROs, or investigators to comply with regulatory requirements;

delay or failure in obtaining the necessary approvals from regulators or institutional review boards, or IRBs, in order to commence a clinical trial at a prospective trial site, or their suspension or termination of a clinical trial once commenced;

- a requirement to undertake and complete additional preclinical studies to generate data required to support the submission of an NDA;
- inability to enroll sufficient patients to complete a protocol, particularly in orphan diseases;
- difficulty in having patients complete a trial or return for post-treatment follow-up;
- clinical sites deviating from trial protocol or dropping out of a trial;
- problems with drug product or drug substance storage and distribution;

- adding new clinical trial sites;
- our inability to manufacture, or obtain from third parties, adequate supply of drug substance or drug product sufficient to complete our preclinical studies and clinical trials; and
- governmental or regulatory delays and changes in regulatory requirements, policy and guidelines.

The results of any Phase 3 or other pivotal clinical trial may not be adequate to support marketing approval. These clinical trials are lengthy and, with respect to non-orphan indications, usually involve many hundreds to thousands of patients. In addition, if the FDA, EMA or another applicable regulator disagrees with our or our collaborator's choice of the key testing criterion, or primary endpoint, or the results for the primary endpoint are not robust or significant relative to the control group of patients not receiving the experimental therapy, such regulator may refuse to approve our product candidate in the region in which it has jurisdiction. The FDA, EMA or other applicable non-U.S. regulators also may require additional clinical trials as a condition for approving any of these product candidates.

We could also encounter delays if a clinical trial is suspended or terminated by us, by our collaborators, by the IRBs of the institutions in which such trial is being conducted, by any Data Safety Monitoring Board for such trial, or by the FDA, EMA or other regulatory authorities. Such authorities may impose such a suspension or termination due to a number of factors, including failure to conduct the clinical trial in accordance with regulatory requirements or our clinical protocols, inspection of the clinical trial operations or trial site by the FDA, EMA or other regulatory authorities resulting in the imposition of a clinical hold, product candidate manufacturing problems, unforeseen safety issues or adverse side effects, failure to demonstrate a benefit from using a drug, changes in governmental regulations or administrative actions or lack of adequate funding to continue the clinical trial. In addition, delays can occur due to safety concerns arising from trials or other clinical data regarding another company's product candidate in the same compound class as one of ours.

If we or our collaborators experience delays in the completion of, or termination of, any clinical trial of one of our product candidates, the commercial prospects of the product candidate will be harmed, could shorten the patent protection period during which we may have the exclusive right to commercialize our products and our or our collaborators' ability to commence product sales and generate product revenue from the product will be delayed. In addition, any delays in completing our clinical trials will increase our costs and slow down our product candidate development and approval process. Any of these occurrences may harm our business, financial condition and prospects significantly. In addition, many of the factors that cause, or lead to, a delay in the commencement or completion of clinical trials may also ultimately lead to the denial of regulatory approval of our product candidates.

Our TV-45070 and GDC-0276 product candidates for treatment of pain target novel molecular mechanisms. Regulatory authorities may require more extensive studies of the long-term effects of such product candidates for regulatory approval, which could delay development of our product candidates or our future product candidates based on novel mechanisms.

Our clinical trials may fail to demonstrate adequately the safety and efficacy of our product candidates, which could prevent or delay regulatory approval and commercialization.

Before obtaining regulatory approvals for the commercial sale of our products, we must demonstrate through lengthy, complex and expensive preclinical testing and clinical trials that the product candidate is both safe and effective for use in each target indication. Clinical trials often fail to demonstrate safety and efficacy of the product candidate studied for the target indication. Most product candidates that commence clinical trials are never approved as products. For example, in July 2015, we and our partner Teva announced top line results from a Phase 2b study designed to evaluate the safety and efficacy of topically applied TV-45070 in patients with chronic pain due to OA of the knee. Results from this trial showed that TV-45070 did not demonstrate statistically significant difference from placebo in efficacy endpoints of reductions in pain due to OA and neither we nor Teva have plans for further development of TV-45070 in OA, although clinical development of TV-45070 in PHN continues.

In the case of our product candidates, we are seeking to develop treatments for diseases for which there is relatively limited clinical experience, and, in some cases our clinical trials use novel end points and measurement methodologies, which adds a layer of complexity to our clinical trials and may delay regulatory approval. In addition, our focus on orphan and niche markets may cause us to select target indications that are in more challenging therapeutic areas. For example, clinical trials for pain, the indication for which TV-45070 and GDC-0276 are being developed, are inherently difficult to conduct. The primary measure of pain is subjective patient feedback, which can be influenced by factors outside of our control, and can vary widely from day to day for a particular patient, and from patient to patient and site to site within a clinical study. The placebo effect also tends to have a more significant impact on pain trials.

If our product candidates are not shown to be both safe and effective in clinical trials, we will not be able to obtain regulatory approval or commercialize these product candidates and products. In such case, we would need to develop other compounds and



erythromelalgia, or EM, by the FDA. If we seek orphan drug designations for other indications or in other jurisdictions, such as for TV-45070 in the EU, we may fail to receive such orphan drug designations and, even if we succeed, such orphan drug designations may fail to result in or maintain orphan drug exclusivity upon approval, which would harm our competitive position.



Results of earlier clinical trials may not be predictive of the results of later-stage clinical trials.

The results of preclinical studies and early clinical trials of our product candidates may not be predictive of the results of later-stage clinical trials. Interpretation of results from early, usually smaller, studies that suggest a clinically meaningful response in some patients, requires caution. Results from later stages of clinical trials enrolling more patients may fail to show the desired safety and efficacy results or otherwise fail to be consistent with the results of earlier trials of the same product candidates. Later clinical trial results may not replicate earlier clinical trials for a variety of reasons, including differences in trial design, different trial endpoints (or lack of trial endpoints in exploratory studies), patient population, number of patients, patient selection criteria, trial duration, drug dosage and formulation and lack of statistical power in the earlier studies. These uncertainties are enhanced where the diseases under study lack established clinical endpoints and validated measures of efficacy, as is often the case with orphan diseases for which no drugs have been developed previously. For example, our results for two small exploratory clinical trials for primary EM pain, one using a topical formulation and the other an oral formulation of TV-45070, used novel measures of efficacy assessment. While these studies provided promising results, further larger clinical trials will be necessary to confirm and extend these observations.

Changes in methods of product candidate manufacturing or formulation may result in additional costs or delay.

As product candidates are developed through preclinical to late stage clinical trials towards approval and commercialization, it is common that various aspects of the development program, such as manufacturing methods and formulation, are altered along the way in an effort to optimize processes and results. Such changes carry the risk that they will not achieve these intended objectives. Any of these changes could cause our product candidates to perform differently and affect the results of planned clinical trials or other future clinical trials conducted with the altered materials. This could delay completion of clinical trials, require the conduct of bridging clinical trials or the repetition of one or more clinical trials, increase clinical trial costs, delay approval of our product candidates and/or jeopardize our or our collaborators' ability to commence product sales and generate revenue.

Even if we obtain and maintain approval for our product candidates from one jurisdiction, we may never obtain approval for our product candidates in other jurisdictions, which would limit our market opportunities and adversely affect our business.

Sales of our approved products are, and will be, subject to U.S. and foreign regulatory requirements governing clinical trials and marketing approval, and we plan to seek regulatory approval to commercialize our product candidates in North America, the EU and in additional foreign countries. Clinical trials conducted in one country may not be accepted by regulatory authorities in other countries and regulatory approval in one country does not ensure approval in any other country, while a failure or delay in obtaining regulatory approval in one country may have a negative effect on the regulatory approval process in others. For example, approval in the U.S. by the FDA does not ensure approval by regulatory authorities in other countries or jurisdictions, and approval by one foreign regulatory authority, such as the EMA for Glybera, does not ensure approval by regulatory authorities in other countries, including by the FDA. Approval procedures vary among jurisdictions and can be lengthy and expensive, and involve requirements and administrative review periods different from, and greater than, those in the U.S., including additional preclinical studies or clinical trials. Even if our product candidates are approved, regulatory approval for any product may be withdrawn by the regulatory authorities in a particular jurisdiction.

Even if a product is approved, the FDA or the EMA, 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 clinical trials or reporting as conditions of approval. In many countries outside the U.S., 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 a product is also subject to approval.

Regulatory authorities in countries outside of the U.S. and the EMA also have their own requirements for approval of product candidates with which we must comply prior to marketing in those countries. Obtaining foreign regulatory approvals and compliance with such foreign regulatory requirements could result in significant delays, difficulties and costs for us and could delay or prevent the introduction of our current and any future products, in certain countries.

If we fail to receive applicable marketing approvals or comply with the regulatory requirements in international markets, 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 will be adversely affected.

We work with outside scientists and their institutions in executing our business strategy of developing product candidates using our Extreme Genetics discovery platform. These scientists may have other commitments or conflicts of interest, which could limit our access to their expertise and harm our ability to leverage our discovery platform.

We work with scientific advisors and collaborators at academic research institutions in connection with our Extreme Genetics discovery platform. These scientific advisors serve as our link to the various families with extreme phenotypes in that these advisors may:

- identify families as potential candidates for study;
- obtain their consent to participate in our research;
- perform medical examinations and gather medical histories;
- conduct the initial analysis of suitability of the families to participate in our research based on the foregoing; and
- collect data and biological samples from the family members periodically in accordance with our study protocols.

These scientists and collaborators are not our employees, rather they serve as either independent contractors or the primary investigators under research collaboration agreements that we have with their sponsoring academic or research institution. Such scientists and collaborators may have other commitments that would limit their availability to us. Although our scientific advisors generally agree not to do competing work, if an actual or potential conflict of interest between their work for us and their work for another entity arises, we may lose their services. It is also possible that some of our valuable proprietary knowledge may become publicly known through these scientific advisors if they breach their confidentiality agreements with us, which would cause competitive harm to our business.

#### Risks Related to Commercialization

If, in the future, we are unable to establish our own sales, marketing and distribution capabilities or enter into licensing or collaboration agreements for these purposes, we may not be successful in independently commercializing any future products.

We do not have a sales or marketing infrastructure and, as a company, have no sales, marketing or distribution experience. Our strategy involves, in part, building our own commercial infrastructure to selectively commercialize future products in niche or orphan indications. Where we believe such involvement would advance our business, we seek to retain the right to participate in the future development and commercialization of such products. For example, we have a co-promotion option for TV-45070 with Teva in the U.S.

To develop internal sales, distribution and marketing capabilities, we will have to invest significant amounts of financial and management resources, some of which will need to be committed prior to any confirmation that any of our proprietary product candidates will be approved. For any future products for which we decide to perform sales, marketing and distribution functions ourselves, we could face a number of additional risks, including:

- our inability to recruit and retain adequate numbers of effective sales and marketing personnel to or develop alternative sales channels;
- the inability of sales personnel to obtain access to physicians or persuade adequate numbers of physicians to prescribe any future products;
- the lack of complementary products to be offered by sales personnel, which may put us at a competitive disadvantage relative to companies with more extensive product lines; and

unforeseen costs and expenses associated with creating and maintaining an independent sales and marketing organization.

Where and when appropriate, we may elect to utilize contract sales forces or distribution partners to assist in the commercialization of our product candidates. If we enter into arrangements with third parties to perform sales, marketing and distribution services for a product, the resulting revenue or the profitability from this revenue to us is likely to be lower than if we had sold, marketed and distributed that product ourselves. In addition, we may not be successful in entering into arrangements with third parties to sell, market and distribute our product candidates or may be unable to do so on terms that are favorable to us. We likely will have little control over such third parties, and any of these third parties may fail to devote the necessary resources and attention to sell, market and distribute our current or any future products effectively.

Even if we receive regulatory approval to commercialize any of the product candidates that we develop independently, we will be subject to ongoing regulatory obligations and continued regulatory review, which may result in significant additional expense.

Any regulatory approvals that we receive for our product candidates we commercialize will be subject to limitations on the approved indicated uses for which the product may be marketed or subject to certain conditions of approval, and may contain requirements for potentially costly post-approval trials, including Phase 4 clinical trials, and surveillance to monitor the safety and efficacy of the marketed product.

For any approved product, we will need to ensure continued compliance with extensive regulations and requirements regarding the manufacturing processes, labeling, packaging, distribution, adverse event reporting, storage, advertising, promotion and recordkeeping for the product. These requirements include submissions of safety and other post-approval information and reports, as well as continued compliance with current good manufacturing practices, or cGMP, and current good clinical practices, or cGCP, for any clinical trials that we or our collaborators conduct post-approval. Later discovery of previously unknown problems with a product, including adverse events of unanticipated severity or frequency, or with third-party manufacturers or manufacturing processes, or failure to comply with regulatory requirements, may result in, among other things:

- restrictions on the marketing or manufacturing of the product, withdrawal of the product from the market or voluntary or mandatory product recalls;
- fines, warning letters or holds on any post-approval clinical trials;
- refusal by the FDA, EMA or another applicable regulatory authority to approve pending applications or supplements to approved applications filed by us or our collaborators, or suspension or revocation of product license approvals;
- product seizure or detention, or refusal to permit the import or export of products;
- and
- injunctions or the imposition of civil or criminal penalties.

Occurrence of any of the foregoing could have a material and adverse effect on our business and results of operations.

If the market opportunities for any product that we or our collaborators develop are smaller than we believe they are, our revenue may be adversely affected and our business may suffer.

We intend to focus our independent product development on treatments for rare diseases. Our projections of both the number of people who have these diseases, as well as the subset of people with these diseases who have the potential to benefit from treatment with our product candidates, are based on estimates. Currently, most reported estimates of the prevalence of these diseases are based on studies of small subsets of the population in specific geographic areas, which are then extrapolated to estimate the prevalence of the diseases in the U.S. or elsewhere. For example, studies estimate the prevalence of LPLD to be approximately 1:1,000,000, and the prevalence of Dravet Syndrome, or DS, to be 7,500-15,000 patients in the U.S. These estimates may prove to be incorrect. If the prevalence of such diseases is smaller than we have projected, then, even if our products are approved, we may not be able to successfully commercialize them.

Even if we or our collaborators receive approval to commercialize our products, unfavorable pricing regulations and challenging third-party coverage and reimbursement practices could harm our business.

Our or any collaborators' ability to commercialize any products successfully will depend, in part, on the extent to which coverage and reimbursement for these products and related treatments will be available from government healthcare programs, private health insurers, managed care plans, and other organizations. Government authorities and third-party payers, such as private health insurers and health maintenance organizations, decide which medications they will pay for and establish reimbursement levels. A primary trend in the U.S. healthcare industry is cost containment. Government authorities and third-party payers have attempted to control costs by limiting coverage and the amount of reimbursement for particular medications. Increasingly, third-party payers are requiring that drug companies provide them with predetermined discounts from list prices and are challenging the prices charged for medical products. We cannot be sure that coverage and reimbursement will be available for any product that we or any collaborator commercialize and, if reimbursement is available, the level of reimbursement. In addition, coverage and reimbursement may impact the demand for, or the price of, any product candidate for which we or a collaborator obtains marketing approval. If coverage and reimbursement are not available or reimbursement is available only to limited levels, we or our collaborators may not be able to successfully commercialize any product candidate for which marketing approval is obtained.

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

Our target patient populations in orphan and niche indications, where we intend to selectively develop and commercialize products independently, are relatively small. In order for therapies that are designed to treat smaller patient populations to be commercially viable, the reimbursement for such therapies needs to be higher, on a relative basis, to account for the lack of volume. Accordingly, we will need to implement a coverage and reimbursement strategy for any approved product that accounts for the smaller potential market size. If we are unable to establish or sustain coverage and adequate reimbursement for our current and any future products from third party payers or the government, the adoption of those products and sales revenue will be adversely affected, which, in turn, could adversely affect the ability to market or sell those products.

Recently enacted and future legislation may increase the difficulty and cost for us to commercialize any products that we or our collaborators develop and affect the prices we may obtain.

The U.S. and some foreign jurisdictions are considering or have enacted a number of legislative and regulatory proposals to change the healthcare system in ways that could affect our ability to sell any of our products profitably, once such products are approved for sale. Among policy makers and payers in the U.S. and elsewhere, there is significant interest in promoting changes in healthcare systems with the stated goals of containing healthcare costs, improving quality and/or expanding access. In the U.S., the pharmaceutical industry has been a particular focus of these efforts and has been significantly affected by major legislative initiatives.

In March 2010, the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act of 2010, collectively, PPACA, was enacted, which includes measures that have significantly changed, or will significantly change, the way healthcare is financed by both governmental and private insurers. Among the provisions of PPACA of importance to the pharmaceutical industry are the following:

- an annual, nondeductible fee on any entity that manufactures or imports certain branded prescription drugs and biologic agents, apportioned among these entities according to their market share in certain government healthcare programs, that began in 2011;
- an increase in the rebates a manufacturer must pay under the Medicaid Drug Rebate Program to 23% and 13% of the average manufacturer price for branded and generic drugs, respectively;

- a new Medicare Part D coverage gap discount program, in which manufacturers must agree to offer 50% point-of-sale discounts to negotiated prices of applicable brand drugs to eligible beneficiaries during their coverage gap period, as a condition for the manufacturer's outpatient drugs to be covered under Medicare Part D;
- extension of manufacturers' Medicaid rebate liability to covered drugs dispensed to individuals who are enrolled in Medicaid managed care organizations;
- expansion of eligibility criteria for Medicaid programs by, among other things, allowing states to offer Medicaid coverage to additional individuals and by adding new mandatory eligibility categories for certain individuals with income at or below 133% of the Federal Poverty Level beginning in 2014, thereby potentially increasing manufacturers' Medicaid rebate liability;
- expansion of the entities eligible for discounts under the Public Health Service pharmaceutical pricing program;



- new requirements under the federal Open Payments program, created under Section 6002 of the PPACA and its implementing regulations that manufacturers of drugs, devices, biologics and medical supplies for which payment is available under Medicare, Medicaid or the Children’s Health Insurance Program (with certain exceptions) report annually to the U.S. Department of Health and Human Services, or HHS, information related to “payments or other transfers of value” made or distributed to physicians (defined to include doctors, dentists, optometrists, podiatrists and chiropractors) and teaching hospitals and that applicable manufacturers and applicable group purchasing organizations report annually to the HHS ownership and investment interests held by physicians (as defined above) and their immediate family members, with data collection required beginning August 1, 2013 and reporting to the Centers for Medicare & Medicaid Services, or CMS, required by March 31, 2014 and by the 90th day of each subsequent calendar year, and disclosure of such information to be made on a publicly available website by September 2014;
- a requirement to annually report drug samples that manufacturers and distributors provide to physicians, effective April 1, 2012;
- expansion of healthcare fraud and abuse laws, including the False Claims Act and the Anti-Kickback Statute, new government investigative powers, and enhanced penalties for noncompliance;
- a licensure framework for follow-on biologic products;
- a new Patient-Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research;
- creation of the Independent Payment Advisory Board which, beginning in 2014, will have authority to recommend certain changes to the Medicare program that could result in reduced payments for prescription drugs and those recommendations could have the effect of law even if Congress does not act on the recommendations; and
- establishment of a Center for Medicare Innovation at CMS to test innovative payment and service delivery models to lower Medicare and Medicaid spending, potentially including prescription drug spending that began on January 1, 2011.

In the EU, similar political, economic and regulatory developments may affect our ability to profitably commercialize our current or any future products. In addition to continuing pressure on prices and cost containment measures, legislative developments at the EU or member state level may result in significant additional requirements or obstacles that may increase our operating costs. In international markets, reimbursement and healthcare payment systems vary significantly by country, and many countries have instituted price ceilings on specific products and therapies. Glybera and our future products, if any, might not be considered medically reasonable and necessary for a specific indication or cost-effective by third-party payers. An adequate level of reimbursement might not be available for such products and third-party payers’ reimbursement policies might adversely affect our or our collaborators’ ability to sell Glybera and any future products profitably.

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

We cannot predict the likelihood, nature or extent of government regulation that may arise from future legislation or administrative action, either in the U.S. or abroad. If we or our collaborators are slow or unable to adapt to changes in

existing requirements or the adoption of new requirements or policies, or if we or our collaborators are not able to maintain regulatory compliance, our product candidates may lose any marketing approval that may have been obtained and we may not achieve or sustain profitability, which would adversely affect our business.

Foreign governments tend to impose strict price controls, which may adversely affect our future profitability.

In most foreign countries, particularly those in the EU, prescription drug pricing and/or reimbursement is subject to governmental control. In those countries that impose price controls, pricing negotiations with governmental authorities can take considerable time after the receipt of marketing approval for a product. To obtain reimbursement or pricing approval in some countries, we or our collaborators may be required to conduct a clinical trial that compares the cost-effectiveness of our product candidate to other available therapies.

Some countries require approval of the sale price of a drug before it can be marketed. In many countries, the pricing review period begins after marketing or product licensing approval is granted. In some foreign markets, prescription pharmaceutical pricing remains subject to continuing governmental control even after initial approval is granted. As a result, we or our collaborators might obtain marketing approval for a product in a particular country, but then be subject to price regulations that delay commercial launch of the product, possibly for lengthy time periods, and negatively impact the revenue that are generated from the sale of the product in that country. If reimbursement of such products is unavailable or limited in scope or amount, or if pricing is set at unsatisfactory levels, or if there is competition from lower priced cross-border sales, our profitability will be negatively affected.

#### Risks Related to Our Dependence on Third Parties

We depend on our collaborative relationship with Teva to further develop and commercialize TV-45070, and if our relationship is not successful or is terminated, we may not be able to effectively develop and/or commercialize TV-45070, which would have a material adverse effect on our business.

We depend on Teva to collaborate with us to develop and globally commercialize TV-45070. Under the agreement, Teva controls all decision-making with respect to the clinical development and commercialization for TV-45070.

As a result of our dependence on Teva, the eventual success or commercial viability of TV-45070 is largely beyond our control. The financial returns to us, if any, depend in large part on the achievement of development and commercialization milestones, plus a share of any revenue from sales. Therefore, our success, and any associated financial returns to us and our investors, will depend in large part on Teva's performance under the agreement. We are subject to a number of additional specific risks associated with our dependence on our collaborative relationship with Teva, including:

- adverse decisions by Teva or the Joint Development Committee regarding the development and commercialization of TV-45070;
- possible disagreements as to the timing, nature and extent of our development plans, including clinical trials or regulatory approval strategy;
- loss of significant rights if we fail to meet our obligations under the agreement;
- our limited control over clinical trials of TV-45070;
- changes in key management personnel at Teva, including in members of the Joint Development Committee; and
- possible disagreements with Teva regarding the agreement, for example, with regard to ownership of intellectual property rights.

If either we or Teva fail to perform our respective obligations, any clinical trial, regulatory approval or development progress could be significantly delayed or halted, could result in costly or time-consuming litigation or arbitration and could have a material adverse effect on our business.

Decisions by Teva to emphasize other drug candidates currently in its portfolio ahead of our product candidates, or to add competitive agents to its portfolio could result in a decision to terminate the agreement, in which event, among other things, we may be responsible for paying any remaining costs of all ongoing or future clinical trials.

In addition, Teva's executive offices and a substantial percentage of their manufacturing capabilities are located in Israel. Teva's Israeli operations are dependent upon materials imported from outside Israel, and Teva also exports significant amounts of products from Israel. Accordingly, our collaboration with Teva could be materially and adversely affected by acts of terrorism or if major hostilities were to occur in the Middle East or trade between Israel and its present trading partners were curtailed, including as a result of acts of terrorism in the U.S. or elsewhere.

Any of the above discussed scenarios could adversely affect the timing and extent of our development and commercialization activities, which could cause significant delays and funding shortfalls for those activities and seriously harm our business.

Our prospects for successful development and commercialization of our partnered products and product candidates are dependent upon the research, development and marketing efforts of our collaborators.

We have no control over the resources, time and effort that our collaborators may devote to our programs and limited access to information regarding or resulting from such programs. We are dependent on uniQure, and its licensee Chiesi to successfully commercialize Glybera and on Teva, Genentech, and Merck & Co., Inc., or Merck, to fund and conduct the research and any clinical development of product candidates under our collaboration with each of them, and for the successful regulatory approval, marketing and commercialization of one or more of such products or product candidates. Such success will be subject to significant uncertainty.

Our ability to recognize revenue from successful collaborations may be impaired by multiple factors including:

- a collaborator may shift its priorities and resources away from our programs due to a change in business strategies, or a merger, acquisition, sale or downsizing of its company or business unit;
- a collaborator may cease development in therapeutic areas which are the subject of our strategic alliances;
- a collaborator may change the success criteria for a particular program or product candidate thereby delaying or ceasing development of such program or candidate;
- a significant delay in initiation of certain development activities by a collaborator will also delay payment of milestones tied to such activities, thereby impacting our ability to fund our own activities;
- a collaborator could develop a product that competes, either directly or indirectly, with our current or future products, if any;
- a collaborator with commercialization obligations may not commit sufficient financial or human resources to the marketing, distribution or sale of a product;
- a collaborator with manufacturing responsibilities may encounter regulatory, resource or quality issues and be unable to meet demand requirements;
- a collaborator may exercise its rights under the agreement to terminate our collaboration;
- a dispute may arise between us and a collaborator concerning the research or development of a product candidate or commercialization of a product resulting in a delay in milestones, royalty payments or termination of a program and possibly resulting in costly litigation or arbitration which may divert management attention and resources;
- a collaborator may not adequately protect the intellectual property rights associated with a product or product candidate; and
- a collaborator may use our proprietary information or intellectual property in such a way as to invite litigation from a third party.

If our collaborators do not perform in the manner we expect or fulfill their responsibilities in a timely manner, or at all, the clinical development, regulatory approval and commercialization efforts could be delayed, terminated or be commercially unsuccessful. Conflicts between us and our collaborators may arise. In the event of termination of one or more of our collaboration agreements, it may become necessary for us to assume the responsibility of any terminated product or product candidates at our own expense or seek new collaborators. In that event, we would likely be required to limit the size and scope of one or more of our independent programs or increase our expenditures and seek additional funding which may not be available on acceptable terms or at all, and our business would be materially and adversely affected.

We may not be successful in establishing new collaborations or maintaining our existing alliances, which could adversely affect our ability to develop future product candidates and commercialize future products.

We may seek to enter into additional product collaborations in the future, including alliances with other biotechnology or pharmaceutical companies, to enhance and accelerate the development of our future product candidates and the commercialization of any resulting products. We face significant competition in seeking appropriate collaborators and the negotiation process is time-consuming and complex. Moreover, we may not be successful in our efforts to establish other collaborations or other alternative arrangements for any future 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 collaboration effort and/or third parties may view our product candidates as lacking the requisite potential to demonstrate safety and efficacy. Even if we are successful in our efforts to establish collaborations, the terms that we agree upon may not be favorable to us and we may not be able to maintain such collaborations if, for example, development or approval of a product candidate is delayed or sales of an approved product are

disappointing.

If any of our existing collaboration agreements is terminated, or if we determine that entering into other product collaborations is in our best interest but we either fail to enter into, delay in entering into or fail to maintain such collaborations:

- the development of certain of our current or future product candidates may be terminated or delayed;
- our cash expenditures related to development of our product candidates would increase significantly and we may need to seek additional financing sooner than expected;

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- we may be required to hire additional employees or otherwise develop expertise, such as clinical, regulatory, sales and marketing expertise, which we do not currently have;
- we will bear all of the risk related to the development of any such product candidates; and
- the competitiveness of any product that is commercialized could be reduced.

We intend to rely on third-party manufacturers to produce our clinical product candidate supplies. Any failure by a third-party manufacturer to produce acceptable supplies for us may delay or impair our ability to initiate or complete our clinical trials or commercialize approved products.

We do not currently own or operate any manufacturing facilities nor do we have any in-house manufacturing experience or personnel. We rely on our collaborators to manufacture product candidates licensed to them or work with multiple third party contract manufacturers to produce sufficient quantities of materials required for the manufacture of our product candidates for preclinical testing and clinical trials and intend to do so for the commercial manufacture of our products. If we are unable to arrange for such third-party manufacturing sources, or fail to do so on commercially reasonable terms, we may not be able to successfully produce, sufficient supply of product candidate or we may be delayed in doing so. Such failure or substantial delay could materially harm our business.

Reliance on third-party manufacturers entails risks to which we would not be subject if we manufactured product candidates ourselves, including reliance on the third party for regulatory compliance and quality control and assurance, volume production, the possibility of breach of the manufacturing agreement by the third party because of factors beyond our control (including a failure to synthesize and manufacture our product candidates in accordance with our product specifications) and the possibility of termination or nonrenewal of the agreement by the third party at a time that is costly or damaging to us. In addition, the FDA, EMA and other regulatory authorities require that our product candidates be manufactured according to cGMP and similar foreign standards. Pharmaceutical manufacturers and their subcontractors are required to register their facilities and/or products manufactured at the time of submission of the marketing application and then annually thereafter with the FDA and certain state and foreign agencies. They are also subject to periodic unannounced inspections by the FDA, state and other foreign authorities. Any subsequent discovery of problems with a product, or a manufacturing or laboratory facility used by us or our collaborators, may result in restrictions on the product or on the manufacturing or laboratory facility, including marketed product recall, suspension of manufacturing, product seizure, or a voluntary withdrawal of the drug from the market. Any failure by our third-party manufacturers to comply with cGMP or failure to scale up manufacturing processes, including any failure to deliver sufficient quantities of product candidates in a timely manner, could lead to a delay in, or failure to obtain, regulatory approval of any of our product candidates.

We rely on third parties to monitor, support, conduct and/or oversee clinical trials of the product candidates that we are developing independently and, in some cases, to maintain regulatory files for those product candidates. We may not be able to obtain regulatory approval for our product candidates or commercialize any products that may result from our development efforts, if we are not able to maintain or secure agreements with such third parties on acceptable terms, if these third parties do not perform their services as required, or if these third parties fail to timely transfer any regulatory information held by them to us.

We rely on entities outside of our control, which may include academic institutions, CROs, hospitals, clinics and other third-party collaborators, to monitor, support, conduct and/or oversee preclinical and clinical studies of our current and future product candidates. We also rely on third parties to perform clinical trials on our current and future product candidates when they reach that stage. As a result, we have less control over the timing and cost of these studies and the ability to recruit trial subjects than if we conducted these trials with our own personnel.

If we are unable to maintain or enter into agreements with these third parties on acceptable terms, or if any such engagement is terminated prematurely, we may be unable to enroll patients on a timely basis or otherwise conduct our trials in the manner we anticipate. In addition, there is no guarantee that these third parties will devote adequate time and resources to our studies or perform as required by our contract or in accordance with regulatory requirements, including maintenance of clinical trial information regarding our product candidates. If these third parties fail to meet expected deadlines, fail to transfer to us any regulatory information in a timely manner, fail to adhere to protocols or fail to act in accordance with regulatory requirements or our agreements with them, or if they otherwise perform in a substandard manner or in a way that compromises the quality or accuracy of their activities or the data they obtain, then clinical trials of our future product candidates may be extended or delayed with additional costs incurred, or our data may be rejected by the FDA, EMA or other regulatory agencies.

Ultimately, we are responsible for ensuring that each of our clinical trials is conducted in accordance with the applicable protocol, legal, regulatory and scientific standards, and our reliance on third parties does not relieve us of our regulatory responsibilities.



We and our CROs are required to comply with cGCP regulations and guidelines enforced by the FDA, the competent authorities of the member states of the EEA and comparable foreign regulatory authorities for products in clinical development. Regulatory authorities enforce these cGCP regulations through periodic inspections of clinical trial sponsors, principal investigators and clinical trial sites. If we or any of our CROs fail to comply with applicable cGCP regulations, the clinical data generated in our clinical trials may be deemed unreliable and our submission of marketing applications may be delayed or the FDA may require us to perform additional clinical trials before approving our marketing applications. Upon inspection, the FDA could determine that any of our clinical trials fail or have failed to comply with applicable cGCP regulations. In addition, our clinical trials must be conducted with product produced under the cGMP regulations enforced by the FDA, and our clinical trials may require a large number of test subjects. Our failure to comply with these regulations may require us to repeat clinical trials, which would delay the regulatory approval process and increase our costs. Moreover, our business may be implicated if any of our CROs violates federal or state fraud and abuse or false claims laws and regulations or healthcare privacy and security laws.

If any of our clinical trial sites terminates for any reason, we may experience the loss of follow-up information on patients enrolled in our ongoing clinical trials unless we are able to transfer the care of those patients to another qualified clinical trial site. Further, if our relationship with any of our CROs is terminated, we may be unable to enter into arrangements with alternative CROs on commercially reasonable terms, or at all.

Switching or adding CROs or other suppliers can involve substantial cost and require extensive management time and focus. In addition, there is a natural transition period when a new CRO or supplier commences work. As a result, delays may occur, which can materially impact our ability to meet our desired clinical development timelines. If we are required to seek alternative supply arrangements, the resulting delays and potential inability to find a suitable replacement could materially and adversely impact our business.

#### Risks Related to Intellectual Property

We could be unsuccessful in obtaining or maintaining adequate patent protection for one or more of our products or product candidates.

Our commercial success will depend, in large part, on our ability to obtain and maintain patent and other intellectual property protection with respect to our product candidates. Patents might not be issued or granted with respect to our patent applications that are currently pending, and issued or granted patents might later be found to be invalid or unenforceable, be interpreted in a manner that does not adequately protect our current product or any future products, or fail to otherwise provide us with any competitive advantage. The patent position of biotechnology and pharmaceutical companies is generally uncertain because it involves complex legal and factual considerations. The standards applied by the U.S. Patent and Trademark Office, or USPTO, and foreign patent offices in granting patents are not always applied uniformly or predictably. For example, there is no uniform worldwide policy regarding patentable subject matter or the scope of claims allowable in biotechnology and pharmaceutical patents. Consequently, patents may not issue from our pending patent applications. As such, we do not know the degree of future protection that we will have on our proprietary products and technology, if any, and a failure to obtain adequate intellectual property protection with respect to our product candidates and proprietary technology could have a material adverse impact on our business.

Periodic maintenance fees, renewal fees, annuity fees and various other governmental fees on patents and/or applications will be due to be paid to the USPTO and various governmental patent agencies outside of the U.S. in several stages over the lifetime of the patents and/or applications. We employ reputable law firms and other professionals and rely on such third parties to effect payment of these fees with respect to the patents and patent applications that we own, and we rely upon our licensors or our other collaborators to effect payment of these fees with respect to the patents and patent applications that we license. The USPTO and various non-US governmental patent agencies require compliance with a number of procedural, documentary, fee payment and other similar provisions during the patent application process. We employ reputable law firms and other professionals to help us comply with respect to the patents and patent applications that we own, and we rely upon our licensors or our other collaborators to effect compliance with respect to the patents and patent applications that we license. In many cases, an inadvertent lapse can be cured by payment of a late fee or by other means in accordance with the applicable rules. However, there are situations in which noncompliance can result in abandonment or lapse of the patent or patent application, resulting in partial or complete loss of patent rights in the relevant jurisdiction. In such an event, our competitors might be able to enter the market and this circumstance would have a material adverse effect on our business.

Our intellectual property rights will not necessarily provide us with competitive advantages.

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.

The following examples are illustrative:

- others may be able to make compounds that are similar to our product candidates but that are not covered by the claims of the patents that we or our collaborators own or have exclusively licensed;
- others may independently develop similar or alternative technologies without infringing our intellectual property rights;
- issued patents that we own or have exclusively licensed may not provide us with any competitive advantages, or may be held invalid or unenforceable, as a result of legal challenges by our competitors;
- we may obtain patents for certain compounds many years before we obtain marketing approval for products containing such compounds, and because patents have a limited life, which may begin to run prior to the commercial sale of the related product, the commercial value of our patents may be limited;
- 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 fail to develop additional proprietary technologies that are patentable;
- the laws of certain foreign countries may not protect our intellectual property rights to the same extent as the laws of the U.S., or we may fail to apply for or obtain adequate intellectual property protection in all the jurisdictions in which we operate; and
- the patents of others may have an adverse effect on our business, for example by preventing us from marketing one or more of our product candidates for one or more indications.

Any of the aforementioned threats to our competitive advantage 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 U.S. can be less extensive than those in the U.S. 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 U.S. Consequently, we may not be able to prevent third parties from practicing our inventions in all countries outside the U.S., or from selling or importing products made using our inventions in and into the U.S. 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 U.S. These products may compete with our current or future products, if any, 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.

Our patents covering one or more of our products or product candidates could be found invalid or unenforceable if challenged.

Any of our intellectual property rights could be challenged or invalidated despite measures we take to obtain patent and other intellectual property protection with respect to our product candidates and proprietary technology. For example, if we were to initiate legal proceedings against a third party to enforce a patent covering one of our product candidates, the defendant could counterclaim that our patent is invalid and/or unenforceable. In patent litigation in the U.S. and in some other jurisdictions, defendant counterclaims alleging invalidity and/or unenforceability are commonplace. Grounds for a validity challenge could be an alleged failure to meet any of several statutory requirements, for example, lack of novelty, obviousness or non-enablement. Grounds for an unenforceability assertion could be an allegation that someone connected with prosecution of the patent withheld material information from the USPTO or the applicable foreign counterpart, or made a misleading statement, during prosecution. A litigant or the USPTO itself could challenge our patents on this basis even if we believe that we have conducted our patent prosecution in accordance with the duty of candor and in good faith. The outcome following such a challenge is unpredictable.

With respect to challenges to the validity of our patents, for example, there might be invalidating prior art, of which we and the patent examiner were unaware during prosecution. If a defendant were to prevail on a legal assertion of invalidity and/or unenforceability, we would lose at least part, and perhaps all, of the patent protection on a product candidate. Even if a defendant does not prevail on a legal assertion of invalidity and/or unenforceability, our patent claims may be construed in a manner that would limit our ability to enforce such claims against the defendant and others. The cost of defending such a challenge, particularly in a foreign jurisdiction, and any resulting loss of patent protection could have a material adverse impact on one or more of our product candidates and our business.

Enforcing our intellectual property rights against third parties may also cause such third parties to file other counterclaims against us, which could be costly to defend, particularly in a foreign jurisdiction, and could require us to pay substantial damages, cease the sale of certain products or enter into a license agreement and pay royalties (which may not be possible on commercially reasonable terms or at all). Any efforts to enforce our intellectual property rights are also likely to be costly and may divert the efforts of our scientific and management personnel.

Patent protection and patent prosecution for some of our product candidates is dependent on, and the ability to assert patents and defend them against claims of invalidity is maintained by, third parties.

There have been and may be times in the future when certain patents that relate to our product candidates or any approved products are controlled by our licensees or licensors. Although we may, under such arrangements, have rights to consult with our collaborators on actions taken as well as back-up rights of prosecution and enforcement, we have in the past and may in the future relinquish rights to prosecute and maintain patents and patent applications within our portfolio as well as the ability to assert such patents against infringers. Currently, some of these rights relating to the patent portfolios for Glybera, TV-45070, GDC-0276 and some of our earlier stage product candidates are held by our collaborators.

If any current or future licensee or licensor with rights to prosecute, assert or defend patents related to our product candidates fails to appropriately prosecute and maintain patent protection for patents covering any of our product

candidates, or if patents covering any of our product candidates are asserted against infringers or defended against claims of invalidity or unenforceability in a manner which adversely affects such coverage, our ability to develop and commercialize any such product candidate may be adversely affected and we may not be able to prevent competitors from making, using and selling competing products.

We may be involved in lawsuits to protect or enforce our patents or the patents of our licensors, which could be expensive, time consuming and unsuccessful.

Competitors may infringe our patents or the patents of our licensors. To counter infringement or unauthorized use, we may be required to file infringement claims, which can be expensive and time-consuming. In addition, in an infringement proceeding, a court may decide that a patent of ours or one of our licensors is not valid or is unenforceable, or may refuse to stop the other party in such infringement proceeding from using the technology at issue on the grounds that our patents do not cover the technology in question. An adverse result in any litigation or defense proceedings could put one or more of our patents at risk of being invalidated, held unenforceable or interpreted narrowly, and could put any of our patent applications at risk of not yielding an issued patent.

Interference proceedings, derivation proceedings, entitlement proceedings, ex parte reexamination, inter partes reexamination, inter partes review, post-grant review, and opposition proceedings provoked by third parties or brought by the USPTO or any foreign patent authority may be used to challenge inventorship, ownership, claim scope, or validity of our patent applications. An unfavorable outcome could require us to cease using the related technology or to attempt to license rights to it from the prevailing party. Our business could be harmed if the prevailing party does not offer us a license on commercially reasonable terms, if any license is offered at all. Litigation or interference proceedings may fail and, even if successful, may result in substantial costs and distract our management and other employees.

We may not be able to prevent, alone or with our licensors, misappropriation of our trade secrets or confidential information, particularly in countries where the laws may not protect those rights as fully as in the U.S. Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation, there is a risk that some of our confidential information could be compromised by disclosure during this type of litigation. In addition, there could be public announcements of the results of hearings, motions or other interim proceedings or developments. If securities analysts or investors perceive these results to be negative, it could have a substantial adverse effect on the price of our common shares.

Claims that our product candidates or the sale or use of our future products infringe the patent or other intellectual property rights of third parties could result in costly litigation or could require substantial time and money to resolve, even if litigation is avoided.

Our commercial success depends upon our ability to develop product candidates and commercialize products that may be approved in the future, using our proprietary technology without infringing the intellectual property rights of others. Our product or product candidates or any uses of them may now and in the future infringe third-party patents or other intellectual property rights. Third parties might allege that we or our collaborators are infringing their patent rights or that we have misappropriated their trade secrets, or that we are otherwise violating their intellectual property rights, whether with respect to the manner in which we have conducted our research or to the composition, use or manufacture of the compounds we have developed or are developing with our collaborators. Such third parties might resort to litigation against us or other parties we have agreed to indemnify, which litigation could be based on either existing intellectual property or intellectual property that arises in the future.

It is possible that relevant patents or patent applications held by third parties will cover our product candidates at the time of launch and we may also fail to identify, relevant patents or patent applications held by third parties that cover our product candidates. For example, applications filed before November 29, 2000, and certain applications filed after that date that will not be filed outside the U.S. remain confidential until patents issue. Other patent applications in the U.S. and several other jurisdictions are published approximately 18 months after the earliest filing for which priority is claimed, with such earliest filing date being commonly referred to as the priority date. Furthermore, publication of discoveries in the scientific or patent literature often lags behind actual discoveries. Therefore, we cannot be certain that we or our collaborators were the first to invent, or the first to file patent applications on, our product candidates or for their uses, or that our product candidates will not infringe patents that are currently issued or that are issued in the future. In the event that a third party has also filed a patent application covering one of our product candidates or a similar invention, we may have to participate in an adversarial proceeding, known as an interference, declared by the USPTO or its foreign counterpart to determine priority of invention. Additionally, pending patent applications and patents which have been published can, subject to certain limitations, be later amended in a manner that could cover our current or future products, if any, or their use.

Defending against claims of patent infringement, misappropriation of trade secrets or other violations of intellectual property rights could be costly and time consuming, regardless of the outcome. Thus, even if we were to ultimately prevail, or to settle at an early stage, such litigation could burden us with substantial unanticipated costs. In addition, litigation or threatened litigation could result in significant demands on the time and attention of our management team, distracting them from the pursuit of other company business. Claims that our product candidates or the sale or use of our future products infringe, misappropriate or otherwise violate third-party intellectual property rights could

therefore have a material adverse impact on our business.

Most of our competitors are larger than we are and have substantially greater financial resources. They are, therefore, likely to be able to sustain the costs of complex intellectual property litigation longer than we could. In addition, the uncertainties associated with litigation could have a material adverse effect on our ability to raise the funds necessary to conduct our clinical trials, continue our internal research programs, in-license needed technology, or enter into strategic collaborations that would help us bring our product candidates to market.

In addition, any future intellectual property litigation, interference or other administrative proceedings will result in additional expense and distraction of our personnel. An adverse outcome in such litigation or proceedings may expose us or any future strategic collaborators to loss of our proprietary position, expose us to significant liabilities, or require us to seek licenses that may not be available on commercially acceptable terms, if at all, each of which could have a material adverse effect on our business.

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Unfavorable outcomes in intellectual property litigation could limit our research and development activities and/or our ability to commercialize certain products.

If third parties successfully assert their intellectual property rights against us, we might be barred from using certain aspects of our technology, or barred from developing and commercializing certain products. Prohibitions against using certain technologies, or prohibitions against commercializing certain products, could be imposed by a court or by a settlement agreement between us and a plaintiff. In addition, if we are unsuccessful in defending against allegations that we have infringed, misappropriated or otherwise violated patent or other intellectual property rights of others, we may be forced to pay substantial damage awards to the plaintiff. There is inevitable uncertainty in intellectual property litigation and we could lose, even if the case against us is weak or flawed. If litigation leads to an outcome unfavorable to us, we may be required to obtain a license from the intellectual property owner in order to continue our research and development programs or to market any resulting product. It is possible that the necessary license will not be available to us on commercially acceptable terms, or at all. Alternatively, we may be required to modify or redesign our current or future products, if any, in order to avoid infringing or otherwise violating third-party intellectual property rights. This may not be technically or commercially feasible, may render those products less competitive, or may delay or prevent the entry of those products to the market. Any of the foregoing could limit our research and development activities, our ability to commercialize one or more product candidates, or both.

In order to avoid or settle potential claims with respect to any patent or other intellectual property rights of third parties, we may choose or be required to seek a license from a third party and be required to pay license fees or royalties or both, which could be substantial. These licenses may not be available on acceptable terms, or at all. Even if we or any future collaborators were able to obtain a license, the rights may be nonexclusive, which could result in our competitors gaining access to the same intellectual property. Ultimately, we could be prevented from commercializing a product, or be forced, by court order or otherwise, to cease some or all aspects of our business operations, if, as a result of actual or threatened patent or other intellectual property claims, we are unable to enter into licenses on acceptable terms. Further, we could be found liable for significant monetary damages as a result of claims of intellectual property infringement. For example, we have received, and may in the future receive, offers to license and demands to license from third parties claiming that we are infringing their intellectual property or owe license fees and, even if such claims are without merit, we could fail to successfully avoid or settle such claims.

If Teva, uniQure, Genentech or Merck license or otherwise acquire rights to intellectual property controlled by a third party in various circumstances, for example, where a product could not be legally developed or commercialized in a country without the third-party intellectual property right or, where it is decided that it would be useful to acquire such third-party right to develop or commercialize the product, they are eligible under our collaboration agreements to decrease payments payable to us on a product-by-product basis and, in certain cases, on a country-by-country basis. Any of the foregoing events could harm our business significantly.



Interim Guidance on Patent Subject Matter Eligibility, in which it extended Myriad's "marked difference" standard for patent subject matter eligibility to all potential natural products. This standard applies to patent claims that recite not only nucleic acids (such as DNA in Myriad), but also other subject matter that could be considered a natural product, such as peptides, proteins, extracts, organisms, antibodies, chemicals, and minerals. As a consequence of the Myriad decision and the USPTO's Interim Guidance, if any of our future product candidates utilize isolated DNA, peptides, proteins or the like, we will not be able to obtain patents in the U.S. claiming such novel gene targets that we discover, which could limit our ability to prevent third parties from developing drugs directed against such targets.



product candidates, including any that are developed in combination therapies, allegedly causes injury or is found to be otherwise unsuitable during product testing, manufacturing, marketing or sale. Any such product liability claims may include allegations of defects in manufacturing, defects in design, a failure to warn of dangers inherent in the product, negligence, strict liability and a breach of warranties. Claims could also be asserted under state consumer protection acts. If we cannot successfully defend ourselves against product liability claims, we may incur substantial liabilities or be required to limit commercialization of our product candidates. Even successful defense would require significant financial and management resources. There is also risk that third parties we have agreed to indemnify could incur liability. Regardless of the merits or eventual outcome, liability claims may result in:

- decreased demand for our product candidates or any resulting products;
- injury to our reputation;
- withdrawal of clinical trial participants;
- costs to defend the related litigation;
- a diversion of management's time and our resources;
- substantial monetary awards to trial participants or patients;

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payment may be made under federal and state healthcare programs such as Medicare and Medicaid;

- federal civil and criminal false claims laws and civil monetary penalty laws, including the federal False Claims Act, which impose criminal and civil penalties, including civil whistleblower or qui tam actions, against individuals or entities for knowingly presenting, or causing to be presented, to the federal government, including the Medicare and Medicaid programs, or other third party payers claims for payment that are false or fraudulent or making a false statement to avoid, decrease or conceal an obligation to pay money to the federal government;
- HIPAA, which imposes criminal and civil liability for executing a scheme to defraud any healthcare benefit program and making false statements relating to healthcare matters;
- HIPAA, as amended by HITECH, and their respective implementing regulations, which impose obligations on covered healthcare providers, health plans, and healthcare clearinghouses, as well as their business associates that create, receive, maintain, or transmit individually identifiable health information for or on behalf of a covered entity, with respect to safeguarding the privacy, security and transmission of individually identifiable health information;







We or the third parties upon whom we depend may be adversely affected by earthquakes or other natural disasters and our business continuity and disaster recovery plans may not adequately protect us from serious disaster.

Our headquarters are located in Burnaby, British Columbia, Canada. We are vulnerable to natural disasters such as earthquakes that could disrupt our operations. If a natural disaster, power outage or other event occurred that prevented us from using all or a significant portion of our headquarters, that damaged critical infrastructure, such as the manufacturing facilities of our third-party contract manufacturers, 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. We do not carry insurance for earthquakes or other natural disasters and although our business interruption insurance applies in the event of an earthquake, we may not carry sufficient business interruption insurance to compensate us for all losses that may occur. The disaster recovery and business continuity plans we have in place currently are limited and are unlikely to prove adequate in the event of a serious disaster or similar event. We may incur substantial expenses as a result of the limited nature of our disaster recovery and business continuity plans, which, particularly when taken together with our lack of earthquake insurance, could have a material adverse effect on our business. In addition, we may lose samples or other valuable data. The occurrence of any of the foregoing could have a material adverse effect on our business.

#### Risks Related to Our Common Shares

Our stock price may be volatile, and purchasers of our common shares could incur substantial losses.

Our stock price has fluctuated in the past and is likely to be volatile in the future. The stock market in general and the market for biotechnology companies in particular have experienced extreme volatility that has often been unrelated to the operating performance of particular companies. As a result of this volatility, investors may experience losses on their investment in our common shares. The market price for our common shares may be influenced by many factors, including the following:

- actions by any of our collaborators regarding our product candidates they are developing, including announcements regarding clinical or regulatory decisions or developments or our collaboration;
- announcements by us or our competitors of new products, product candidates or new uses for existing products, significant contracts, commercial relationships or capital commitments and the timing of these introductions or announcements;
- unanticipated serious safety concerns related to Glybera or to the use of any of our products and product candidates;
- results from or delays of clinical trials of our product candidates;
- failure to obtain or delays in obtaining or maintaining product approvals or clearances from regulatory authorities;
- adverse regulatory or reimbursement announcements;
- announcements by us or our competitors of significant acquisitions, strategic collaborations, joint ventures or capital commitments;
- the results of our efforts to discover or develop additional product candidates;
- our dependence on third parties, including our collaborators, CROs, clinical trial sponsors and clinical investigators;
- regulatory or legal developments in Canada, the U.S. or other countries;
- developments or disputes concerning patent applications, issued patents or other proprietary rights;
- the recruitment or departure of key scientific or management personnel;
- our ability to successfully commercialize our future product candidates we develop independently, if approved;
- the level of expenses related to any of our product candidates or clinical development programs;
- actual or anticipated changes in estimates as to financial results, development timelines or recommendations by securities analysts;
- actual or anticipated quarterly variations in our financial results or those of our competitors;
- any change to the composition of the board of directors or key personnel;

- the recent expiration of contractual lock-up agreements with our executive officers, directors and security holders;
- sales of common shares by us or our shareholders in the future, as well as the overall trading volume of our common shares;

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- changes in the structure of healthcare payment systems;
- commencement of, or our involvement in, litigation;
- general economic, industry and market conditions in the pharmaceutical and biotechnology sectors and other factors that may be unrelated to our operating performance or the operating performance of our competitors, including changes in market valuations of similar companies; and
- the other factors described in this “Risk Factors” section.

In addition, the stock market in general, and NASDAQ and the biopharmaceutical industry in particular, have from time to time experienced volatility that often has been unrelated to the operating performance of the underlying companies. These broad market and industry fluctuations may adversely affect the market price of our common shares, regardless of our operating performance. In several recent situations where the market price of a stock has been volatile, holders of that stock have instituted securities class action litigation against the company that issued the stock. If any of our shareholders were to bring a lawsuit against us, the defense and disposition of the lawsuit could be costly and divert the time and attention of our management and harm our operating results.

Future sales of our common shares in the public market could cause our share price to fall.

Our share price could decline as a result of sales of a large number of our common shares or the perception that these sales could occur. These sales, or the possibility that these sales may occur, also might make it more difficult for us to sell equity securities in the future at a time and at a price that we deem appropriate.

Holders of approximately 6.9 million common shares have rights, subject to some conditions, to require us to file registration statements covering the sale of their common shares or to include their common shares in registration statements that we may file for ourselves or other shareholders. We have also registered the offer and sale of all common shares that we may issue under our equity compensation plans.

In addition, in the future, we may issue additional common shares or other equity or debt securities convertible into common shares in connection with a financing, acquisition, litigation settlement, employee arrangements or otherwise. Any such issuance could result in substantial dilution to our existing shareholders and could cause our common share price to decline.

Provisions in our corporate charter documents and Canadian law could make an acquisition of us, which may be beneficial to our shareholders, more difficult and may prevent attempts by our shareholders to replace or remove our current management and/or limit the market price of our common shares.

Provisions in our articles and our by-laws, as well as certain provisions under the Canada Business Corporations Act, or CBCA, and applicable Canadian securities laws, may discourage, delay or prevent a merger, acquisition or other change in control of us that shareholders may consider favorable, including transactions in which they might otherwise receive a premium for their common shares. These provisions could also limit the price that investors might be willing to pay in the future for our common shares, thereby depressing the market price of our common shares. 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 shareholders to replace or remove our current management by

making it more difficult for shareholders to replace members of our board of directors. Among other things, these provisions include the following:

- shareholders cannot amend our articles unless such amendment is approved by shareholders holding at least two-thirds of the shares entitled to vote on such approval;
- our board of directors may, without shareholder approval, issue preferred shares having any terms, conditions, rights, preferences and privileges as the board of directors may determine; and
- shareholders must give advance notice to nominate directors or to submit proposals for consideration at shareholders' meetings.

Any provision in our articles, by-laws, under the CBCA or under any applicable Canadian securities law that has the effect of delaying or deterring a change in control could limit the opportunity for our shareholders to receive a premium for their common shares, and could also affect the price that some investors are willing to pay for our common shares.

U.S. civil liabilities may not be enforceable against us, our directors, or our officers

We are governed by the CBCA and our principal place of business is in Canada. Many of our directors and officers reside outside of the U.S., and all or a substantial portion of their assets as well as all or a substantial portion of our assets are located outside

the U.S. As a result, it may be difficult for investors to effect service of process within the U.S. upon us and such directors and officers or to enforce judgments obtained against us or such persons, in U.S. courts, in any action, including actions predicated upon the civil liability provisions of U.S. federal securities laws or any other laws of the U.S. Additionally, rights predicated solely upon civil liability provisions of U.S. federal securities laws or any other laws of the U.S. may not be enforceable in original actions, or actions to enforce judgments obtained in U.S. courts, brought in Canadian courts, including courts in the Province of British Columbia.

We are governed by the corporate laws of Canada which in some cases have a different effect on shareholders than the corporate laws of Delaware, U.S.

We are governed by the CBCA and other relevant laws, which may affect the rights of shareholders differently than those of a company governed by the laws of a U.S. jurisdiction, and may, together with our charter documents, have the effect of delaying, deferring or discouraging another party from acquiring control of our company by means of a tender offer, a proxy contest or otherwise, or may affect the price an acquiring party would be willing to offer in such an instance. The material differences between the CBCA and Delaware General Corporation Law, or DGCL, that may have the greatest such effect include, but are not limited to, the following: (i) for material corporate transactions (such as mergers and amalgamations, other extraordinary corporate transactions or amendments to our articles) the CBCA generally requires a two-thirds majority vote by shareholders, whereas DGCL generally only requires a majority vote; and (ii) under the CBCA a holder of 5% or more of our common shares can requisition a special meeting of shareholders, whereas such right does not exist under the DGCL.

An active trading market for our common shares may not be maintained.

Our stock is currently traded on NASDAQ, but we can provide no assurance that we will be able to maintain an active trading market on NASDAQ or any other exchange in the future. If an active market for our common shares is not maintained, it may be difficult for our shareholders to sell the common shares they have purchased without depressing the market price for the shares or at all. Further, an inactive market may also impair our ability to raise capital by selling additional common shares and may impair our ability to enter into strategic collaborations or acquire companies or products by using our common shares as consideration.

Complying with the laws and regulations affecting public companies will increase our costs and the demands on management and could harm our operating results and our ability to accurately report our financial condition, results of operations or cash flows, which may adversely affect investor confidence in us and, as a result, the value of our common shares.

As a public company, and particularly after we cease to be an “emerging growth company,” we will incur significant legal, accounting and other expenses that we did not incur as a private company. In addition, the Sarbanes-Oxley Act of 2002, or the Sarbanes-Oxley Act, and the related rules and regulations subsequently implemented by the Securities and Exchange Commission, or SEC, the applicable Canadian securities regulators and NASDAQ impose numerous requirements on public companies, including requiring changes in corporate governance practices. Also, the Securities Exchange Act of 1934, as amended, or the Exchange Act, requires, among other things, that we file annual, quarterly and current reports with respect to our business and operating results. We anticipate that we may need to hire additional accounting and financial staff with appropriate public company experience and technical accounting knowledge to address the added burdens of operating as a public company. Our management and other personnel will need to devote a substantial amount of time to compliance with these laws and regulations. These requirements have increased and will continue to increase our legal, accounting, and financial compliance costs and have made and will continue to make some activities more time-consuming and costly. For example, we expect these rules and regulations to make it more difficult and more expensive for us to obtain director and officer liability insurance and we may be required to accept reduced policy limits and coverage or to incur substantial costs to maintain the same or similar

coverage. These rules and regulations could also make it more difficult for us to attract and retain qualified persons to serve on our board of directors or our board committees or as executive officers.

The Sarbanes-Oxley Act requires, among other things, that we assess the effectiveness of our internal control over financial reporting annually and the effectiveness of our disclosure controls and procedures quarterly. In particular, commencing with our second Annual Report on Form 10-K, Section 404 of the Sarbanes-Oxley Act, or Section 404, will require us to perform system and process evaluation and testing of our internal control over financial reporting to allow management to report on, and our independent registered public accounting firm potentially to attest to, the effectiveness of our internal control over financial reporting. As an “emerging growth company” we expect to avail ourselves of the exemption from the requirement that our independent registered public accounting firm attest to the effectiveness of our internal control over financial reporting under Section 404. However, we may no longer avail ourselves of this exemption when we cease to be an “emerging growth company.” When our independent registered public accounting firm is required to undertake an assessment of our internal control over financial reporting, the cost of our compliance with Section 404 will correspondingly increase. Our compliance with applicable provisions of Section 404 will require that we incur substantial accounting expense and expend significant management time on compliance-related issues as we implement additional corporate governance practices and comply with reporting requirements. Moreover, if we are not able to comply with the requirements of Section 404 applicable to us in a timely manner, or if we or our independent registered public accounting firm identifies deficiencies in our internal control over financial reporting that are deemed to be material weaknesses, the market price of

our common shares could decline and we could be subject to sanctions or investigations by the SEC or other regulatory authorities, which would require additional financial and management resources.

Furthermore, investor perceptions of our company may suffer if deficiencies are found, and this could cause a decline in the market price of our common shares. Irrespective of compliance with Section 404, any failure of our internal control over financial reporting could have a material adverse effect on our stated operating results and harm our reputation. If we are unable to implement these requirements effectively or efficiently, it could harm our operations, financial reporting, or financial results and could result in an adverse opinion on our internal controls from our independent registered public accounting firm.

We are an “emerging growth company,” and any decision on our part to comply only with certain reduced reporting and disclosure requirements applicable to emerging growth companies could make our common shares less attractive to investors.

We are an “emerging growth company,” as defined in the Jumpstart Our Business Startups Act of 2012, or the JOBS Act. For as long as we continue to be an “emerging growth company,” we may choose to take advantage of exemptions from various reporting requirements applicable to other public companies that are not “emerging growth companies,” including, but not limited to, not being required to have our independent registered public accounting firm audit our internal control over financial reporting under Section 404, reduced disclosure obligations regarding executive compensation in our periodic reports and proxy statements and exemptions from the requirements of holding a nonbinding advisory vote on executive compensation and shareholder approval of any golden parachute payments not previously approved. We could be an “emerging growth company” for up to five years following the completion of our initial public offering, although, if we have more than \$1.0 billion in annual revenue, if the market value of our common shares held by non-affiliates exceeds \$700 million as of June 30 of any year, or we issue more than \$1.0 billion of non-convertible debt over a three-year period before the end of that five-year period, we would cease to be an “emerging growth company” as of the following December 31. Investors could find our common shares less attractive if we choose to rely on these exemptions. If some investors find our common shares less attractive as a result of any choices to reduce future disclosure, there may be a less active trading market for our common shares and our share price may be more volatile.

As an “emerging growth company,” the JOBS Act allows us to delay adoption of new or revised accounting pronouncements applicable to public companies until such pronouncements are made applicable to private companies. However, we previously decided to “opt out” of such extended transition period, and as a result, we will comply with new or revised accounting standards on the relevant dates on which adoption of such standards is required for non-emerging growth companies. Section 107 of the JOBS Act provides that our decision to opt out of the extended transition period for complying with new or revised accounting standards is irrevocable.

If we fail to maintain an effective system of internal control over financial reporting, we may not be able to accurately report our financial results or prevent fraud. As a result, shareholders could lose confidence in our financial and other public reporting, which would harm our business and the trading price of our common shares.

Effective internal controls over financial reporting are necessary for us to provide reliable financial reports and, together with adequate disclosure controls and procedures, are designed to prevent fraud. Any failure to implement required new or improved controls, or difficulties encountered in their implementation could cause us to fail to meet our reporting obligations. In addition, any testing by us conducted in connection with Section 404 or any subsequent



testing by our independent registered public accounting firm, may reveal deficiencies in our internal controls over financial reporting that are deemed to be material weaknesses or that may require prospective or retroactive changes to our financial statements or identify other areas for further attention or improvement. Inferior internal controls could also cause investors to lose confidence in our reported financial information, which could have a negative effect on the trading price of our common shares.

We will be required to disclose changes made in our internal controls and procedures on a quarterly basis and our management will be required to assess the effectiveness of these controls annually. However, for as long as we are an “emerging growth company” under the JOBS Act, our independent registered public accounting firm will not be required to attest to the effectiveness of our internal controls over financial reporting pursuant to Section 404. We could be an “emerging growth company” for up to five years from the completion of our initial public offering. An independent assessment of the effectiveness of our internal controls could detect problems that our management’s assessment might not. In addition, our management and independent registered public accounting firm did not perform an evaluation of our internal control over financial reporting as of December 31, 2014, December 31, 2013 or December 31, 2012, in accordance with the provisions of the Sarbanes-Oxley Act. Had we and our independent registered public accounting firm performed such an evaluation, control deficiencies may have been identified by management or our independent registered public accounting firm, and those control deficiencies could have also represented one or more material weaknesses. Undetected material weaknesses in our internal controls could lead to financial statement restatements and require us to incur the expense of remediation.

Future sales and issuances of our common shares or rights to purchase common shares, including pursuant to our equity incentive plans, could cause you to incur dilution and could cause our share price to fall.

As of June 30, 2015, options to purchase 1,746,303 of our common shares with a weighted-average exercise price of \$6.77 per common share were outstanding. The exercise of any of these options would result in dilution to current shareholders. Further, because we will need to raise additional capital to fund our clinical development programs, we may in the future sell substantial amounts of common shares or securities convertible into or exchangeable for common shares. Pursuant to our equity incentive plan(s), our compensation committee (or a subset thereof) is authorized to grant equity-based incentive awards to our employees, directors and consultants. Future option grants and issuances of common shares under our share-based compensation plans may have an adverse effect on the market price of our common shares.

These future issuances of common shares or common share-related securities, together with the exercise of outstanding options and any additional common shares issued in connection with acquisitions, if any, may result in further dilution to our existing shareholders, and new investors could gain rights, preferences and privileges senior to those of holders of our common shares.

Our management team will have broad discretion to use the net proceeds from our initial public offering and the concurrent private placement and its investment of these proceeds may not yield a favorable return. They may invest the proceeds of our initial public offering and the concurrent private placement in ways with which investors disagree.

Our management team will have broad discretion in the application of the net proceeds from our November 2014 initial public offering and the concurrent private placement and could spend or invest the proceeds in ways with which our shareholders disagree. Accordingly, investors will need to rely on our management team's judgment with respect to the use of these proceeds. These uses may not yield a favorable return to our shareholders. We intend to use the proceeds from the offering to: (1) fund preclinical and early clinical development of our DS and XEN801 programs; (2) to fund genetic research and drug discovery activities using our Extreme Genetics discovery platform; and (3) for working capital and other general corporate purposes. We may also use a portion of the net proceeds in connection with any exercise of co-development or co-promotion rights under our strategic alliances; however, no such rights are currently exercisable. In addition, we may also use a portion of the net proceeds to acquire, license and invest in complementary products, technologies or businesses; however, we currently have no agreements or commitments to complete any such transaction. These uses may not yield a favorable return to our shareholders.

We cannot specify with certainty all of the particular uses for the net proceeds received from our November 2014 initial public offering and the concurrent private placement. In addition, the amount, allocation and timing of our actual expenditures will depend upon numerous factors, including milestone payments received from our collaborations and royalties received on sale of our approved product and any future approved product. Accordingly, we will have broad discretion in using these proceeds. Until the net proceeds are used, they may be placed in investments that do not produce significant income or that may lose value.

We are at risk of securities class action litigation.

In the past, securities class action litigation has often been brought against a company following a decline in the market price of its securities. This risk is especially relevant for us because biotechnology companies have experienced significant stock price volatility in recent years. If we face such litigation, it could result in substantial

costs and a diversion of management's attention and resources, which could harm our business.

We do not anticipate paying any cash dividends on our common shares in the foreseeable future.

We do not currently intend to pay any cash dividends on our common shares in the foreseeable future. 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 shares may be investors' sole source of gain for the foreseeable future.

NASDAQ may delist our securities from its exchange, which could limit investors' ability to make transactions in our securities and subject us to additional trading restrictions.

Our common shares are listed on NASDAQ under the trading symbol "XENE." Our securities may fail to meet the continued listing requirements to be listed on NASDAQ. If NASDAQ delists our common shares from trading on its exchange, we could face significant material adverse consequences, including:

- significant impairment of the liquidity for our common shares, which may substantially decrease the trading price of our common shares;
- a limited availability of market quotations for our securities;

- a determination that our common shares qualify as a “penny stock” which will require brokers trading in our common shares to adhere to more stringent rules and possibly resulting in a reduced level of trading activity in the secondary trading market for our common shares;
- a limited amount of news and analyst coverage for our company; and
- a decreased ability to issue additional securities or obtain additional financing in the future.

If securities or industry analysts do not publish research reports about our business, or if they issue an adverse opinion about our business, our share price and trading volume could decline.

The trading market for our common shares will be influenced by the research and reports that securities or industry analysts publish about us or our business. If too few securities or industry analysts cover our company, the trading price for our common shares would likely be negatively impacted. If securities and industry analysts who cover us downgrade our common shares or publish inaccurate or unfavorable research about our business, our share price would likely decline. If one or more of these analysts cease coverage of our company or fail to publish reports on us regularly, demand for our common shares could decrease, which might cause our price and trading volume to decline.

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

### Use of Proceeds from Public Offering of Common Shares

On November 4, 2014, our registration statement on Form S-1 (No. 333-198666) was declared effective for our initial public offering, and on November 10, 2014 we completed the initial public offering consisting of 4,600,000 common shares for \$9.00 per share. As a result of the offering, we received total net proceeds of approximately \$34.1 million, after deducting total expenses of \$7.3 million, consisting of underwriting discounts and commissions of \$2.9 million and offering-related expenses of approximately \$4.4 million. No payments for such expenses were made directly or indirectly to (i) any of our officers or directors or their associates, (ii) any persons owning 10% or more of any class of our equity securities, or (iii) any of our affiliates. Jefferies LLC and Wells Fargo Securities, LLC acted as joint book-running managers of the offering and as representatives of the underwriters. Canaccord Genuity Inc. acted as a co-manager for the offering.

There has been no material change in the planned use of proceeds from our initial public offering from that described in the final Prospectus dated November 4, 2014, filed with the SEC pursuant to Rule 424(b)(4).



Item 6. Exhibits

(a) Exhibits.

Exhibit

Number Description

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|-------|---|
| 10.1† | Amendment #4, dated May 13, 2015, to the Collaborative Research and License Agreement, dated December 22, 2011, between Xenon Pharmaceuticals Inc. and Genentech, Inc. together with F. Hoffman-La Roche Ltd, as amended.   |
| 31.1  | Certification of Chief Executive Officer pursuant to Rule 13a-14(a).  |
| 31.2  | Certification of Chief Financial Officer pursuant to Rule 13a-14(a).  |
| 32.1* | Certification of Chief Executive Officer pursuant to 18 U.S.C Section 1350.   |
| 32.2* | Certification of Chief Financial Officer pursuant to 18 U.S.C Section 1350.   |
| 101   | The following financial statements from the Company's Quarterly Report on Form 10-Q for the quarter ended June 30, 2015, formatted in XBRL: (i) Statements of Cash Flows, (ii) Statements of Operations, (iii) Statements of Comprehensive Income (Loss), (iv) Balance Sheets, and (v) Notes to Financial Statements, tagged as blocks of text and including detailed tags. |

Confidential treatment has been requested for portions of this exhibit. These portions are omitted from this Quarterly Report on Form 10-Q and have been filed separately with the Securities and Exchange Commission.

\*The Certifications attached as Exhibits 32.1 and 32.2 that accompany this Quarterly Report on Form 10-Q are not deemed filed with the Securities and Exchange Commission and are not to be incorporated by reference into any filing of Xenon Pharmaceuticals Inc. under the Securities Act of 1933, as amended, or the Securities Exchange Act of 1934, as amended, whether made before or after the date of this Form 10-Q, irrespective of any general incorporation language contained in such filing.



SIGNATURES

Pursuant to the requirements 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: August 13, 2015

XENON PHARMACEUTICALS INC.

By: /s/ Simon Pimstone  
Simon Pimstone  
President and Chief Executive Officer  
(Principal Executive Officer)



EXHIBIT INDEX

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