Xenon Pharmaceuticals Inc.
Form 10-Q
May 12, 2015

UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 10 Q

x QUARTERLY REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934
For the quarterly period ended March 31, 2015

OR

o TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934
For the transition period from to

Commission file number: 001-36687

XENON PHARMACEUTICALS INC.

(Exact name of registrant as specified in its charter)

Canada	98-0661854
(State or other jurisdiction of incorporation or organization)	(I.R.S. Employer Identification Number)

200-3650 Gilmore Way

Burnaby, British Columbia V5G 4W8

Canada

(Address of principal executive offices)

(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 x No ¨

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate Web site, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files). Yes x No ¨

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, 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 x (Do not check if a smaller reporting company) Smaller reporting company ¨

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

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 May 11, 2015 was 14,228,536

XENON PHARMACEUTICALS INC.

QUARTERLY REPORT ON FORM 10-Q

FOR THE QUARTER ENDED MARCH 31, 2015

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PART I. FINANCIAL INFORMATION

Item 1. Financial Statements

XENON PHARMACEUTICALS INC.

Balance Sheets

(Unaudited)

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

	March 31, 2015	December 31, 2014
Assets		
Current assets:		
Cash and cash equivalents	$65,917	$72,026
Marketable securities	9,464	12,015
Accounts receivable	1,205	215
Prepaid expenses and other current assets	464	686
	77,050	84,942
Property, plant and equipment, net	2,353	2,476
Total assets	$79,403	$87,418
Liabilities and Shareholders' Equity		
Current liabilities:		
Accounts payable and accrued expenses (note 7)	1,530	2,664
Deferred revenue	8,724	11,622
	10,254	14,286
Deferred revenue, less current portion	—	157
Deferred tenant inducements	180	196
	$10,434	$14,639
Shareholders' equity:		
Common shares, without par value; unlimited shares authorized; issued and outstanding: 14,222,275 (December 31, 2014 - 14,181,333)	147,508	147,157
Additional paid-in capital	30,450	30,346
Accumulated deficit	(107,999)	(103,734)
Accumulated other comprehensive loss	(990)	(990)
	$68,969	$72,779
Total liabilities and shareholders' equity	$79,403	$87,418
Collaboration agreements (note 9)		
Commitments and contingencies (note 10)		

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

XENON PHARMACEUTICALS INC.

Statements of Operations and Comprehensive Income (Loss)

(Unaudited)

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

	Three Months Ended March 31,	
	2015	2014
Revenue:		
Collaboration revenue (note 9)	$4,010	$5,001
Operating expenses:		
Research and development	3,427	2,533
General and administrative	1,789	1,436
	5,216	3,969
Income (loss) from operations	(1,206)	1,032
Other income (expense):		
Interest income	152	141
Foreign exchange gain (loss)	(3,171)	200
Net income (loss)	(4,225)	1,373
Net income attributable to participating securities	—	1,373
Net loss attributable to common shareholders	$(4,225)	$—
Net loss per common share:		
Basic and diluted	$(0.30)	$—
Weighted-average shares outstanding:		
Basic and diluted	14,212,579	1,345,312
Other comprehensive income (loss):		
Foreign currency translation adjustment	—	(909)
Comprehensive income (loss)	$(4,225)	$464

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

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											
r	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
e										13,018	
of											
	(1,151,468)	(2,939)	(994,885)	(8,683)	(4,322,126)	(90,866)	7,725,924	102,488			
et							5,095,000	38,373			
e											
nt											(3,501)
on											
on									760		
							13,365	124	(124)		

of											
ion											
						2,417	25	(12)			
of											
r	—	$—	—	$—	—	$—	14,181,333	$147,157	$30,346	$(103,734)	$(990)
r										(4,225)	
on											
ion									288		
						40,942	351	(184)	(40)		
of											
	—	$—	—	$—	—	$—	14,222,275	$147,508	$30,450	$(107,999)	$(990)(1)

(1) At March 31, 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)

	Three Months Ended March 31,	
	2015	2014
Operating activities:		
Net income (loss)	$(4,225)	$1,373
Adjustments to reconcile net income (loss) to net cash used in operating activities:		
Depreciation and amortization	207	175
Stock-based compensation	288	186
Deferred tenant inducements	(16)	(17)
Unrealized foreign exchange loss	3,140	37
Changes in operating assets and liabilities:		
Accounts receivable	(996)	2
Prepaid expenses, and other current assets	220	29
Accounts payable and accrued expenses	(1,110)	(265)
Deferred revenue	(3,055)	(2,362)
Net cash used in operating activities	(5,547)	(842)
Investing activities:		
Purchases of property, plant and equipment	(84)	(480)
Purchase of marketable securities	—	(2,578)
Proceeds from marketable securities	1,575	2,720
Net cash provided by (used in) investing activities	1,491	(338)
Financing activities:		
Deferred financing fees	—	(398)
Proceeds from issuance of common shares	127	5
Net cash provided by (used in) financing activities	127	(393)
Effect of exchange rate changes on cash and cash equivalents	(2,180)	(1,430)
Decrease in cash and cash equivalents	(6,109)	(3,003)
Cash and cash equivalents, beginning of period	72,026	37,950
Cash and cash equivalents, end of period	$65,917	$34,947
Supplemental disclosures:		
Interest received	$121	$125
Supplemental disclosures of non-cash transactions:		

Issuance of common shares on conversion of subscription rights	—	14
Fair value of options exercised on a cashless basis	69	—

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

XENON PHARMACEUTICALS INC.

Notes to Financial Statements

(Unaudited)

(Expressed in thousands of U.S. dollars except numbers of shares)

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.

On October 1, 2014, the Company effected a 1 for 4.86 reverse share split of its common and Series A, B and E redeemable convertible preferred shares. At the time of the consolidation, there were no outstanding Series C and D preferred shares and therefore such series were not included in the consolidation. Accordingly, (i) every 4.86 common shares were combined into one common share, (ii) every 4.86 redeemable Series A, B and E convertible preferred shares were combined into one redeemable convertible preferred share, (iii) the number of common shares into which each outstanding subscription right was exchangeable into common shares were proportionately decreased on a 1 for 4.86 basis, (iv) the number of common shares into which each outstanding option to purchase common shares was exercisable were proportionately decreased on a 1 for 4.86 basis, and (v) the exercise price for each such outstanding option to purchase common shares was proportionately increased on a 1 for 4.86 basis. All of the share numbers, share prices, and exercise prices prior to October 1, 2014 have been adjusted, on a retroactive basis, to reflect this 1 for 4.86 reverse share split.

On November 10, 2014, the Company completed an initial public offering ("IPO") of 4,600,000 of its common shares at a price to the public of $9.00 per share. On November 10, 2014, the Company also completed a private placement, in which the Company issued 495,000 of its common shares to an affiliate of Genentech, Inc. ("Genentech") at a price of $9.00 per share. Immediately prior to the closing of the IPO, all outstanding convertible preferred shares were converted into 7,725,924 common shares and 10,201 outstanding subscription rights were converted into 10,201 common shares. Following the IPO, there were no preferred shares or subscription rights outstanding.

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 month periods ended March 31, 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 change in functional currency described in note 3.

3. Changes in significant accounting policies:

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.

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 as foreign exchange gain (loss).

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 three months ended March 31, 2015 and no net income was attributable to common shareholders for the three months ended March 31, 2014, all stock options were anti-dilutive and were excluded from the diluted weighted average shares outstanding for both periods.

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.

7. Accounts payable and accrued expenses:

Accounts payable and accrued expenses consisted of the following:

	March 31, 2015	December 31, 2014
Trade payables	$632	$ 553
Employee compensation, benefits, and related accruals	384	1,077
Consulting and contracted research	288	774
Professional fees	171	180
Other	55	80
Total	$1,530	$ 2,664

8. Stock option plan:

The following table presents stock option activity for the period:

	Three Months Ended March 31,	
	2015	2014
Outstanding, beginning of period	1,484,218	1,333,099
Granted	346,964	157,231
Exercised[(1)]	(44,656)	(772)
Forfeited and expired	(1,090)	(44,238)
Outstanding, end of period	1,785,436	1,445,320
Exercisable, end of period	1,146,383	999,089

(1) During the three months ended March 31, 2015, 26,910 stock options were exercised for the same number of common shares for cash. In the same period, the Company issued 14,032 common shares for the cashless exercise of 17,746 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 March 31,	
	2015	2014
Average risk-free interest rate	1.71%	1.97%
Average expected term (in years)	6.25	6.20
Expected volatility	75 %	74 %
Expected dividend yield	0.00%	0.00%
Expected forfeiture rate	0.00%	0.00%

The weighted-average fair value of options granted during the three months ended March 31, 2015 was $11.84 (three months ended March 31, 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 months ended March 31, 2015 and 2014:

	Three Months Ended March 31,	
	2015	2014
Teva:		
Recognition of upfront payment	$2,876	$3,025
Research funding	45	80
Genentech:		
Recognition of upfront payment	179	786
Research funding	910	1,110
Total collaboration revenue	$4,010	$5,001

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.

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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 expr 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;

- 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. uniQure has reported that while Chiesi believes the first patient may receive treatment by mid-2015, the ultimate timing is subject to several factors including the treating physician's decision and relevant patient consent. 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 an additional clinical evaluation of Glybera to be included in a future Biologic License Application, or BLA, submission with the FDA;
- TV-45070 (formerly XEN402), a product candidate with four Phase 2 proof-of-concept clinical trials completed. Our partner Teva is conducting a randomized, double-blind, placebo-controlled Phase 2b clinical trial in osteoarthritis, or OA, of the knee. Results from the trial are expected in the third quarter of 2015. In April 2015, Teva initiated patient enrollment in a 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; and

- Proprietary preclinical programs, including XEN801, a stearoyl 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 mid-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 three months ended March 31, 2015, we recognized revenues, consisting primarily of funding from our collaborators of approximately $4.0 million. This compared to $5.0 million for the three months ended March 31, 2014.

Though our revenue from our collaboration and license agreements has 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 $4.2 million for the three months ended March 31, 2015 and had an accumulated deficit of $108.0 million as of March 31, 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.

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 months ended March 31, 2015 and 2014 (in thousands):

	Three Months Ended March 31,	
	2015	2014
Teva:		
Recognition of upfront payment	$2,876	$3,025
Research funding	45	80
Genentech:		
Recognition of upfront payment	179	786
Research funding	910	1,110
Total collaboration revenue	$4,010	$5,001

Through March 31, 2015, we had recognized upfront fees and milestone payments totaling CAD$1.1 million, pursuant to our sublicense and research agreement with uniQure. We are eligible to receive certain additional milestone payments of less than CAD$1.0 million for Glybera and for each subsequent product, if any, developed pursuant to the agreement.

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 March 31, 2015 and December 31, 2014 (in thousands):

	March 31, 2015	December 31, 2014
Teva	$ 8,021	$ 10,897
Genentech	703	882
Total deferred revenue	$ 8,724	$ 11,779

We expect such deferred revenue remaining as of March 31, 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 months ended March 31, 2015 and 2014 (in thousands):

	Three Months Ended March 31,	
	2015	2014
Research and development	$3,427	$2,533
General and administrative	1,789	1,436
Total operating expenses	$5,216	$3,969

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, related benefits and share-based compensation 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 the IPO, 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 build our commercial infrastructure for the potential option for co-promotion of TV-45070 in the U.S., if and when regulatory approval is received.

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 months ended March 31, 2015, net foreign exchange losses comprise 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 three months ended March 31, 2015, we had the following changes in our critical accounting policies:

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 as foreign exchange gain (loss).

There have been no other significant and material changes in our critical accounting policies during the three months ended March 31, 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 AnnualReport 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 Months Ended March 31, 2015 and 2014

The following table summarizes the results of our operations for the three months ended March 31, 2015 and 2014 together with changes in those items (in thousands):

	Three Months Ended March 31,		Change 2015 vs. 2014 Increase/(Decrease)
	2015	2014	
Collaboration revenue	$ 4,010	$ 5,001	$ (991)
Research and development expenses	3,427	2,533	894
General and administrative expenses	1,789	1,436	353
Other:			
Interest income	152	141	11
Foreign exchange gain (loss)	(3,171)	200	(3,371)
Net income (loss)	$ (4,225)	$ 1,373	$ (5,598)

Revenue

We recognized revenue of $4.0 million for the three months ended March 31, 2015 compared to $5.0 million for the three months ended March 31, 2014, a decrease of $1.0 million. In the comparative period, $0.8 million was recognized relating to the upfront payment from the December 2011 collaborative development and license agreement with Genentech. No such amounts were recognized in the current quarter as the upfront payment was fully recognized by December 2014. This decrease was partially offset by recognition of $0.2 million of an upfront payment received from Genentech for the pain genetics collaboration entered into in March 2014. The remaining decrease was due to less FTE funding from both 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 months ended March 31, 2015 and 2014 together with changes in those items (in thousands):

	Three Months Ended March 31,		Change 2015 vs. 2014 Increase/(Decrease)
	2015	2014	
Teva collaboration (TV-45070) expenses	35	244	$ (209)
Genentech collaboration (GDC-0276) expenses	828	1,232	(404)
Preclinical and discovery program expenses	2,564	1,057	1,507
Total research and development expenses	$ 3,427	$ 2,533	$ 894

Research and development expenses were $3.4 million for the three months ended March 31, 2015 as compared to $2.5 million for the three months ended March 31, 2014. The increase of $0.9 million was primarily attributable to a $1.5 million increase in preclinical and discovery program expenses primarily related to XEN801 entering IND-enabling studies as well as increased spending on our Nav1.6 sodium channel inhibitor program. This increase was 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 months ended March 31, 2015 and 2014 together with changes in those items (in thousands):

	Three Months Ended March 31,		Change 2015 vs. 2014
	2015	2014	Increase/(Decrease)
General and administrative expenses	$ 1,789	$ 1,436	$ 353

General and administrative expenses were $1.8 million for the three months ended March 31, 2015 compared to $1.4 million for the three months ended March 31, 2014. This increase was 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.

Other Income (Expense)

The following table summarizes our other income (expense) for the three months ended March 31, 2015 and 2014 together with changes in those items (in thousands):

	Three Months Ended March 31,		Change 2015 vs. 2014 Increase/(Decrease)
	2015	2014	
Other income (expense):	$ (3,019)	$ 341	$ (3,360)

Other expense was $3.0 million for the three months ended March 31, 2015 as compared to other income of $0.3 million for the three months ended March 31, 2014, a change of $3.4 million, primarily attributable to $3.1 million of unrealized foreign exchange losses arising largely from the translation of $54.5 million of cash and cash equivalents and marketable securities denominated in Canadian dollars to U.S. dollars and an 8% decrease in the value of the Canadian dollar during the 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 March 31, 2015, we had cash and cash equivalents and marketable securities of $75.4 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 a $4.2 million net loss for the three months ended March 31, 2015 and an accumulated deficit of $108.0 million from inception through March 31, 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:

- whether our existing collaborations continue to generate research funding, milestone payments and royalties to us;
- the number and stage of development of future product candidates that we choose to pursue;
- the scope, progress, results and costs of research and development of our future product candidates independently, and conducting preclinical research and clinical studies;
- the timing and costs involved in obtaining regulatory approvals for any future product candidates we develop independently;
- the cost associated with exercising our co-promotion option for TV-45070 in the U.S., should the opportunity arise and we choose to do so;
- the cost of commercialization activities, if any, of any future product candidates we develop independently that are approved for sale, including marketing, sales and distribution costs;
- the cost of manufacturing our future product candidates and any products we successfully commercialize independently;
- our ability to maintain existing collaborations and to establish new collaborations, licensing or other arrangements and the financial terms of such arrangements;
- the costs of 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, or royalties on Glybera, TV-45070, GDC-0276 and our future product candidates, 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 three months ended March 31, 2015 and 2014 (in thousands):

	Three Months Ended March 31,	
	2015	2014
Net cash used in operating activities	$(5,547)	$(842)
Net cash provided by (used in) investing activities	1,491	(338)
Net cash provided by (used in) financing activities	127	(393)

Operating Activities

During the three months ended March 31, 2015, net cash used by operating activities totaled $5.5 million, compared to net cash used in operating activities of $0.8 million for the same period in 2014. The change was driven primarily by a net loss of $4.2 million for the three months ended March 31, 2015, partially offset by an unrealized foreign exchange loss of $3.1 million, and changes in timing of receivables, cash payments of trade payables and timing of revenues.

Investing Activities

During the three months ended March 31, 2015, net cash provided by investing activities totaled $1.5 million, compared to net cash used in investing activities of $0.3 million for the same period in 2014. The change was driven primarily by an increase in net proceeds from the sale of marketable securities and a decrease in the purchase of property, plant and equipment.

Financing Activities

During the three months ended March 31, 2015, net cash provided by financing activities totaled $0.1 million, compared to net cash used in financing activities of $0.4 million for the same period in 2014. Net cash used in financing activities for the three months ended March 31, 2014 consisted primarily of deferred financing costs in connection with our IPO which closed in November 2014 and net cash provided by financing activities for the three months ended March 31, 2015 consisted 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. 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.

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 are choosing 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 primarily 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 primarily 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 March 31, 2015, we held cash and cash equivalents and marketable securities of $54.5 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 $5.5 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 $75.4 million as of March 31, 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 March 31, 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) prior to the filing of this quarterly report. Based on that evaluation, our Chief Executive Officer and our Chief Financial Officer have concluded that, as of the end of the period covered by this quarterly report, our disclosure controls and procedures were, in design and operation, effective.

(b) Changes in internal control over financial reporting. There were no changes in our internal control over financial reporting during the quarter ended March 31, 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 $4.2 million for the three months ended March 31, 2015, $4.3 million for the year ended December 31, 2012, and had an accumulated deficit of $108.0 million as of March 31, 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;

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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, fails 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.

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 three months ended March 31, 2015, we incurred approximately $3.4 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 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 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 changes in foreign currency exchange rates could impact our results of operations.

As of March 31, 2015, approximately 72% 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.

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 June 2013, we paid Isis Pharmaceuticals, Inc., or Isis, an option exercise fee of $2.0 million to obtain an exclusive license to develop, manufacture and commercialize antisense products under our collaboration and license agreement with Isis; however, in the fourth quarter of 2013, we discontinued development of product candidates under this program as the preclinical data did not support the continued advancement of any product candidates.

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.

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^{S447X} 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 is providing 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 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 on a part-time, one-day-a-week basis, 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;
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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.

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 conduct associated preclinical testing and clinical trials, as well as potentially seek additional financing, all of which would have a material adverse effect on our business, growth prospects, operating results, financial condition and results of operations.

We may find it difficult to enroll patients in our clinical studies, including for orphan or niche indications, which could delay or prevent clinical studies of our product candidates.

We may not be able to identify, recruit and enroll a sufficient number of patients, or those with required or desired characteristics to achieve diversity in a study, to complete our clinical studies in a timely manner. Patient enrollment for clinical trials for orphan and niche indications and for more prevalent conditions is affected by factors including:

·severity of the disease under investigation;
·design of the study protocol;
·size of the patient population;
·eligibility criteria for the study in question;
·perceived risks and benefits of the product candidate under study;
·proximity and availability of clinical study sites for prospective patients;
·availability of competing therapies and clinical studies;
·efforts to facilitate timely enrollment in clinical studies; and
·patient referral practices of physicians.

The limited patient populations in orphan and niche indications present significant recruitment challenges for clinical trials. 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. Many of these patients may not be suitable or available for clinical trials. This means that we or our collaborators generally will have to run multi-site and potentially multi-national trials, which can be expensive and require close coordination and supervision. If we experience delays in completing our clinical trials, such delays could result in increased costs, delays in advancing our product development, delays in testing the effectiveness of our technology or termination of the clinical studies altogether.

If we fail to obtain or maintain orphan drug designation or other regulatory exclusivity for some of our product candidates, our competitive position would be harmed.

A product candidate that receives orphan drug designation can benefit from a streamlined regulatory process as well as potential commercial benefits following approval. Currently, this designation provides market exclusivity in the U.S. and the EU for seven years and ten years, respectively, if a product is the first such product approved for such orphan indication. This market exclusivity does not, however, pertain to indications other than those for which the drug was specifically designated in the approval, nor does it prevent other types of drugs from receiving orphan designations or approvals in these same indications. Further, even after an orphan drug is approved, the FDA can subsequently approve a drug with similar chemical structure for the same condition if the FDA concludes that the new drug is clinically superior to the orphan product or a market shortage occurs.

In the EU, orphan exclusivity may be reduced to six years if the drug no longer satisfies the original designation criteria or can be lost altogether if the marketing authorization holder consents to a second orphan drug application or cannot supply enough drug, or when a second applicant demonstrates its drug is “clinically superior” to the original orphan drug. TV-45070 has received both fast track and orphan drug designations for the treatment of 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

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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;

- 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 governmenta