Ultragenyx Pharmaceutical Inc.
Form 10-Q
May 10, 2016

UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

WASHINGTON, DC 20549

FORM 10-Q

(Mark One)

x QUARTERLY REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934.
For the quarterly period ended March 31, 2016

OR

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

Commission File No. 001-36276

ULTRAGENYX PHARMACEUTICAL INC.

(Exact name of registrant as specified in its charter)

Delaware	27-2546083
(State or other jurisdiction of incorporation or organization)	(I.R.S. Employer Identification No.)

60 Leveroni Court, Novato, California	94949
(Address of principal executive offices)	(Zip Code)

(415) 483-8800

(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 and 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 R NO ¨

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate Website, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T (§ 232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files). YES R NO ¨

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

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

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

As of May 4, 2016, the registrant had 39,020,576 shares of common stock issued and outstanding.

ULTRAGENYX PHARMACEUTICAL INC.

FORM 10-Q FOR THE QUARTER ENDED MARCH 31, 2016

INDEX

CAUTIONARY NOTE REGARDING FORWARD-LOOKING STATEMENTS

This Quarterly Report on Form 10-Q contains forward-looking statements that involve risks and uncertainties. We make such forward-looking statements pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995 and other federal securities laws. All statements other than statements of historical facts contained in this Quarterly Report on Form 10-Q are forward-looking statements. In some cases, you can identify forward-looking statements by words such as “anticipate,” “believe,” “contemplate,” “continue,” “could,” “estimate,” “expect,” “intend,” “may,” “plan,” “potential,” “predict,” “project,” “seek,” “should,” “target,” “will,” “would,” or the negative of these w comparable terminology. These forward-looking statements include, but are not limited to, statements about:

- our expectations regarding the timing of commencing our clinical studies and reporting results from same;
- the timing and likelihood of regulatory approvals for our product candidates;
- the potential market opportunities for commercializing our product candidates;
- our expectations regarding the potential market size and the size of the patient populations for our product candidates, if approved for commercial use;
- estimates of our expenses, future revenue, capital requirements, and our needs for additional financing;
- our ability to develop, acquire, and advance product candidates into, and successfully complete, clinical studies;
- the implementation of our business model and strategic plans for our business and product candidates;
- the initiation, timing, progress, and results of future preclinical studies and clinical studies, and our research and development programs;
- the scope of protection we are able to establish and maintain for intellectual property rights covering our product candidates;
- our ability to maintain and establish collaborations or obtain additional funding;
- our ability to maintain and establish relationships with third parties, such as contract research organizations, suppliers, and distributors;
- our financial performance and expansion of our organization;
- our ability to obtain supply of our product candidates;
- developments and projections relating to our competitors and our industry; and
- other risks and uncertainties, including those listed under Part II, Item 1A. Risk Factors.

Any forward-looking statements in this Quarterly Report on Form 10-Q reflect our current views with respect to future events or to our future financial performance and involve known and unknown risks, uncertainties, and other factors that may cause our actual results, performance, or achievements to be materially different from any future results, performance, or achievements expressed or implied by these forward-looking statements. Factors that may cause actual results to differ materially from current expectations include, among other things, those discussed under Part II, Item 1A. Risk Factors and discussed elsewhere in this Quarterly Report on Form 10-Q. Given these uncertainties, you should not place undue reliance on these forward-looking statements. Except as required by law, we assume no obligation to update or revise these forward-looking statements for any reason, even if new information becomes available in the future.

This Quarterly Report on Form 10-Q also contains estimates, projections, and other information concerning our industry, our business, and the markets for certain diseases, including data regarding the estimated size of those markets, and the incidence and prevalence of certain medical conditions. Information that is based on estimates, forecasts, projections, market research, or similar methodologies is inherently subject to uncertainties and actual events or circumstances may differ materially from events and circumstances reflected in this information. Unless otherwise expressly stated, we obtained this industry, business, market, and other data from reports, research surveys, studies, and similar data prepared by market research firms and other third parties, industry, medical and general publications, government data, and similar sources.

1

PART I. FINANCIAL INFORMATION

Item 1. Financial Statements

ULTRAGENYX PHARMACEUTICAL INC.

CONDENSED CONSOLIDATED BALANCE SHEETS

(Unaudited)

(In thousands, except share and per share amounts)

	March 31, 2016	December 31, 2015
Assets		
Current assets:		
Cash and cash equivalents	$70,763	$ 93,569
Short-term investments	341,092	343,428
Restricted cash	1,291	150
Prepaid expenses and other current assets	17,088	13,060
Total current assets	430,234	450,207
Property and equipment, net	13,418	7,373
Restricted cash	2,537	2,135
Long-term investments	75,932	99,259
Other assets	2,063	595
Total assets	$524,184	$ 559,569
Liabilities and Stockholders' Equity		
Current liabilities:		
Accounts payable	$6,012	$ 2,942
Accrued liabilities	23,565	24,784
Deferred rent—current portion	303	192
Total current liabilities	29,880	27,918
Other liabilities	4,480	561
Total liabilities	34,360	28,479
Stockholders' equity:		
Preferred stock — 25,000,000 shares authorized; nil outstanding as of March 31, 2016 and December 31, 2015	—	—
Common stock — 250,000,000 shares authorized; 38,992,346 and 38,882,394 shares issued and outstanding as of March 31, 2016 and December 31, 2015, respectively	39	39
Additional paid-in capital	827,109	816,578
Accumulated other comprehensive income (loss)	92	(868)
Accumulated deficit	(337,416)	(284,659)
Total stockholders' equity	489,824	531,090
Total liabilities and stockholders' equity	$524,184	$ 559,569

See accompanying notes.

2

ULTRAGENYX PHARMACEUTICAL INC.

CONDENSED CONSOLIDATED STATEMENTS OF OPERATIONS

(Unaudited)

(In thousands, except share and per share amounts)

	Three Months Ended March 31,	
	2016	2015
Operating expenses:		
Research and development	$40,415	$17,364
General and administrative	13,207	4,138
Total operating expenses	53,622	21,502
Loss from operations	(53,622)	(21,502)
Other income (expense), net:		
Interest income	984	273
Other expense, net	(119)	(150)
Total other income (expense), net	865	123
Net loss	$(52,757)	$(21,379)
Net loss per share, basic and diluted	$(1.35)	$(0.63)
Shares used in computing net loss per share, basic and diluted	38,970,151	34,008,830

See accompanying notes.

ULTRAGENYX PHARMACEUTICAL INC.

CONDENSED CONSOLIDATED STATEMENTS OF COMPREHENSIVE LOSS

(Unaudited)

(In thousands)

	Three Months Ended March 31,	
	2016	2015
Net loss	$(52,757)	$(21,379)
Other comprehensive income:		
Unrealized gain (loss) on available-for-sale securities	960	80
Total comprehensive loss	$(51,797)	$(21,299)

See accompanying notes.

ULTRAGENYX PHARMACEUTICAL INC.

CONDENSED CONSOLIDATED STATEMENTS OF CASH FLOWS

(Unaudited)

(In thousands)

	Three Months Ended March 31,	
	2016	2015
Operating activities:		
Net loss	$(52,757)	$(21,379)
Adjustments to reconcile net loss to net cash used in operating activities:		
Depreciation and amortization	544	201
Amortization of premium (discount) on investment securities, net	1,828	965
Stock-based compensation	10,217	2,408
Changes in operating assets and liabilities:		
Prepaid expenses and other current assets	(4,028)	(948)
Other assets	(1,468)	(7)
Accounts payable	2,638	437
Accrued liabilities and other liabilities	(1,869)	664
Net cash used in operating activities	(44,895)	(17,659)
Investing activities:		
Purchase of property and equipment	(1,477)	(459)
Purchase of investments	(118,130)	(77,254)
Proceeds from the sale of investments	11,494	12,766
Proceeds from maturities of investments	131,431	62,240
Increase in restricted cash	(1,543)	(1,358)
Net cash provided by (used in) investing activities	21,775	(4,065)
Financing activities:		
Proceeds from issuance of common stock, net	314	175,440
Net cash provided by financing activities	314	175,440
Net increase (decrease) in cash and cash equivalents	(22,806)	153,716
Cash and cash equivalents at beginning of period	93,569	24,324
Cash and cash equivalents at end of period	$70,763	$178,040

See accompanying notes.

5

ULTRAGENYX PHARMACEUTICAL INC.

Notes to Condensed Consolidated Financial Statements

1. Organization

Ultragenyx Pharmaceutical Inc. (the Company) is a biopharmaceutical company and was incorporated in California on April 22, 2010. The Company subsequently reincorporated in the state of Delaware in June 2011.

The Company is focused on the identification, acquisition, development, and commercialization of novel products for the treatment of rare and ultra-rare diseases, with a focus on serious, debilitating metabolic genetic diseases. The Company is currently conducting a Phase 3 study of aceneuramic acid extended-release (Ace-ER) in patients with GNE myopathy, which is also known as hereditary inclusion body myopathy (HIBM), a progressive muscle-wasting disorder; a Phase 3 study of recombinant human beta-glucuronidase (rhGUS) in patients with mucopolysaccharidosis 7, or MPS 7, a rare lysosomal storage disease; a Phase 2 clinical study for UX007 in patients with glucose transporter type-1 deficiency syndrome (Glut1 DS), a brain energy deficiency; a Phase 2 clinical study of UX007 in patients severely affected by long-chain fatty acid oxidation disorders (LC-FAOD), a genetic disorder in which the body is unable to convert long chain fatty acids into energy; and Phase 2 and Phase 3 studies of KRN23, an antibody targeting fibroblast growth factor 23, or FGF23, in patients with X-linked hypophosphatemia (XLH) and tumor-induced osteomalacia (TIO), both rare diseases that impair bone mineralization. The Company operates as one reportable segment.

2. Summary of Significant Accounting Policies

Basis of Presentation

The accompanying unaudited condensed consolidated financial statements include the amounts of the Company and our wholly-owned subsidiaries and have been prepared in accordance with U.S. general accepted accounting principles (GAAP) for interim financial information and in accordance with the instructions to Form 10-Q and Rule 10-01 of Regulation S-X. Accordingly, they do not include all of the information and footnotes required by GAAP for complete financial statements. The unaudited interim consolidated financial statements have been prepared on the same basis as the annual financial statements. In the opinion of management, the accompanying unaudited condensed consolidated financial statements reflect all adjustments (consisting only of normal recurring adjustments) considered necessary for a fair presentation. These financial statements should be read in conjunction with the audited financial statements and notes thereto for the preceding fiscal year contained in the Company’s Annual Report on Form 10-K filed on February 26, 2016 with the United States Securities and Exchange Commission (SEC).

The results of operations for the three months ended March 31, 2016 are not necessarily indicative of the results to be expected for the year ending December 31, 2016. The condensed balance sheet as of December 31, 2015 has been derived from audited financial statements at that date but does not include all of the information required by GAAP for complete financial statements.

Use of Estimates

The preparation of condensed consolidated financial statements in conformity with GAAP requires management to make estimates and assumptions that affect the reported amounts of assets and liabilities, disclosure of contingent liabilities, and the reported amounts of expenses in the condensed consolidated financial statements and the accompanying notes. Management bases its estimates on historical experience and on various other market-specific and relevant assumptions that management believes to be reasonable under the circumstances. Actual results could

differ from those estimates.

Recently Issued Accounting Pronouncements

In February 2016, the FASB issued ASU No. 2016-02, Leases (Topic 842), which requires an entity that is a lessee to recognize the assets and liabilities arising from leases on the balance sheet. This guidance also requires disclosures about the amount, timing, and uncertainty of cash flows arising from leases. This guidance is effective for annual reporting periods beginning after December 15, 2018, and interim periods within those annual periods, using a modified retrospective approach, and early adoption is permitted. The Company is evaluating the effect that this guidance will have on its Consolidated Financial Statements and related disclosures.

In March 2016, the FASB issued ASU No. 2016-09, Compensation — Stock Compensation (Topic 718): Improvements to Employee Share-Based Payment Accounting, which simplifies several aspects of the accounting for employee share-based payments, including income tax consequences, application of award forfeitures to expense, classification on the statement of cash flows, and classification of awards as either equity or liabilities. This guidance is effective for annual reporting periods beginning after December 15, 2016, and interim periods within those annual periods. The Company is evaluating the effect that this guidance will have on its Consolidated Financial Statements and related disclosures.

3. Fair Value Measurements

Financial assets and liabilities are recorded at fair value. The carrying amount of certain financial instruments, including cash and cash equivalents, accounts payable, and accrued liabilities approximate fair value due to their relatively short maturities. Assets and liabilities recorded at fair value on a recurring basis in the condensed consolidated balance sheets are categorized based upon the level of judgment associated with the inputs used to measure their fair values. Fair value is defined as the exchange price that would be received for an asset or the exit price that would be paid to transfer a liability in the principal or most advantageous market for the asset or liability in an orderly transaction between market participants on the measurement date. The authoritative guidance on fair value measurements establishes a three-tier fair value hierarchy for disclosure of fair value measurements as follows:

Level 1—Inputs are unadjusted, quoted prices in active markets for identical assets or liabilities at the measurement date;

Level 2—Inputs are observable, unadjusted quoted prices in active markets for similar assets or liabilities, unadjusted quoted prices for identical or similar assets or liabilities in markets that are not active, or other inputs that are observable or can be corroborated by observable market data for substantially the full term of the related assets or liabilities; and

Level 3—Unobservable inputs that are significant to the measurement of the fair value of the assets or liabilities that are supported by little or no market data.

The following tables set forth the fair value of the Company's financial assets remeasured on a recurring basis based on the three-tier fair value hierarchy (in thousands):

	March 31, 2016			
	Level 1	Level 2	Level 3	Total
Financial Assets:				
Money market funds	$44,133	$—	$ —	$44,133
Corporate bonds	—	318,215	—	318,215
Asset-backed securities	—	38,998	—	38,998
U.S. Government Treasury and agency securities	13,979	47,598	—	61,577
Commercial paper	—	9,985	—	9,985
Total financial assets	$58,112	$414,796	$ —	$472,908

	December 31, 2015			
	Level 1	Level 2	Level 3	Total
Financial Assets:				
Money market funds	$53,254	$—	$ —	$53,254
Corporate bonds	—	370,445	—	370,445
Asset-backed securities	—	29,302	—	29,302
U.S. Government Treasury and agency securities	—	47,452	—	47,452
Commercial paper	—	13,887	—	13,887
Total financial assets	$53,254	$461,086	$ —	$514,340

4. Balance Sheet Components

Cash Equivalents and Investments

The fair values of cash equivalents, short-term investments, and long-term investments classified as available-for-sale securities, consisted of the following (in thousands):

	March 31, 2016			
	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Estimated Fair Value
Money market funds classified as cash equivalents	$44,133	$—	$—	$44,133
Corporate bonds classified as cash equivalents	11,753	—	(2)	11,751
Commercial paper classified as short-term investments	9,985	—	—	9,985
Corporate bonds classified as short-term investments	262,257	121	(94)	262,284
Asset-backed securities classified as short-term investments	29,737	9	(8)	29,738
U.S. Government Treasury and agency securities classified as short-term investments	39,095	4	(14)	39,085
Corporate bonds classified as long-term investments	44,129	78	(27)	44,180
Asset-backed securities classified as long-term investments	9,246	14	—	9,260
U.S. Government Treasury and agency securities classified as long-term investments	22,481	18	(7)	22,492
Total	$472,816	$244	$(152)	$472,908

	December 31, 2015			
	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Estimated Fair Value
Money market funds classified as cash equivalents	$53,254	$—	$—	$53,254
Corporate bonds classified as cash equivalents	18,403	—	(4)	18,399
Commercial paper classified as short-term investments	13,887	—	—	13,887
Corporate bonds classified as short-term investments	282,386	9	(397)	281,998
Asset-backed securities classified as short-term investments	15,019	—	(27)	14,992
U.S. Government Treasury and agency securities classified as short-term investments	32,628	—	(77)	32,551
Corporate bonds classified as long-term investments	70,309	2	(263)	70,048

Asset-backed securities classified as long-term investments	14,337	—	(27)	14,310
U.S. Government Treasury and agency securities classified as long-term investments	14,985	—	(84)	14,901
Total	$515,208	$11	$(879)	$514,340

At March 31, 2016, the remaining contractual maturities of available-for-sale securities were less than three years. There have been no significant realized gains or losses on available-for-sale securities for the periods presented.

Accrued Liabilities

Accrued liabilities consist of the following (in thousands):

	March 31, 2016	December 31, 2015
Research and clinical study expenses	$13,179	$ 9,764
Payroll and related expenses	5,339	9,423
Other	5,047	5,597
Total accrued liabilities	$23,565	$ 24,784

5. License and Research Agreements

Kyowa Hakko Kirin Collaboration and License Agreement

In August 2013, the Company entered into a collaboration and license agreement with Kyowa Hakko Kirin Co., Ltd. (KHK), which was amended in August 2015. Under the terms of this collaboration and license agreement, the Company and KHK will collaborate on the development and commercialization of certain products containing KRN23, an antibody directed towards FGF23, in the field of orphan diseases in the United States and Canada, or the profit share territory, and in the European Union, Switzerland, and Turkey, or the European territory, and the Company will have the right to develop and commercialize such products in the field of orphan diseases in Mexico and Central and South America, or Latin America. In the field of orphan diseases, and except for ongoing studies being conducted by KHK, the Company will be the lead party for development activities in the profit share territory and in the European territory until the applicable transition date; the Company will also be the lead party for core development activities conducted in Japan and Korea, provided that the core development plan related to Japan and Korea shall be limited to clinical trials mutually agreed to by the Company and KHK. The Company will share the costs for development activities in the profit share territory and the European territory conducted pursuant to the development plan before the applicable transition date equally with KHK, and KHK shall be responsible for 100% of the costs for development activities in Japan and Korea. On the applicable transition date in the profit share territory and the European territory, KHK will become the lead party and be responsible for the costs of the development activities. However, the Company will continue to share the costs of the studies commenced prior to the applicable transition date equally with KHK. The Company has the primary responsibility for conducting certain research and development services. The Company is obligated to provide assistance in accordance with the agreed upon development plan as well as participate on various committees. If KRN23 is approved, the Company and KHK will share commercial responsibilities and profits in the profit share territory until the applicable transition date, KHK will commercialize KRN23 in the European territory, and the Company will develop and commercialize KRN23 in Latin America. KHK will manufacture and supply KRN23 for clinical use globally and will manufacture and supply KRN23 for commercial use in the profit share territory and Latin America.

The Company is accounting for the agreement as a collaboration arrangement as defined in ASC 808, Collaborative Agreements; accordingly, the Company’s expenses were reduced by $4.9 million and $1.5 million for the three months ended March 31, 2016 and 2015, respectively, for its share of the costs as research and development. As of March 31, 2016 and December 31, 2015, the Company had receivables in the amount of $4.9 million and $3.8 million, respectively, for this collaboration arrangement.

6. Stock-Based Awards

2014 Incentive Plan

In 2014, the Company adopted the 2014 Incentive Plan (the 2014 Plan), which became effective upon the closing of the Company’s IPO in February 2014. The 2014 Plan provides for automatic annual increases in shares available for grant, beginning on January 1, 2015 through January 1, 2024. As of March 31, 2016, there were 2,238,250 shares reserved under the 2014 Plan for the future issuance of equity awards. The Company also had 1,380,922 shares reserved for the 2014 Employee Stock Purchase Plan, for which no shares had been issued.

Stock-Based Compensation Expense

The table below sets forth the functional classification of stock-based compensation expense, net of estimated forfeitures, for the periods presented (in thousands):

	Three Months Ended March 31,

	2016	2015
Research and development	$6,575	$1,841
General and administrative	3,642	567
Total stock-based compensation	$10,217	$2,408

7. Net Loss Per Share

Basic net loss per share has been computed by dividing the net loss by the weighted-average number of shares of common stock outstanding during the period. Diluted net loss per share is calculated by dividing net loss by the weighted-average number of shares of common stock and potential dilutive securities outstanding during the period.

The following weighted-average outstanding common stock equivalents were excluded from the computation of diluted net loss per share for the periods presented because including them would have been antidilutive:

	Three Months Ended March 31,	
	2016	2015
Stock options to purchase common stock	3,829,812	2,698,846
Unvested restricted stock units	211,261	33,856
Common stock warrants	149,700	324,351
	4,190,773	3,057,053

Item 2. Management's Discussion and Analysis of Financial Condition and Results of Operations

MANAGEMENT'S DISCUSSION AND ANALYSIS OF

FINANCIAL CONDITION AND RESULTS OF OPERATIONS

The following discussion and analysis of our financial condition and results of operations should be read in conjunction with the accompanying unaudited consolidated financial statements and related notes in Item 1 and with the audited consolidated financial statements and the related notes included in our Annual Report on Form 10-K for the year ended December 31, 2015.

Overview

We are a clinical-stage biopharmaceutical company focused on the identification, acquisition, development, and commercialization of novel products for the treatment of serious rare and ultra-rare diseases, with a focus on serious, debilitating genetic diseases. We target diseases for which the unmet medical need is high, the biology for treatment is clear, and for which there are no currently approved therapies. Since our inception in 2010, we have in-licensed potential treatments for multiple rare genetic disorders. Our strategy, which is predicated upon time- and cost-efficient drug development, allows us to pursue multiple programs in parallel with the goal of delivering safe and effective therapies to patients with the utmost urgency.

Our current clinical-stage pipeline consists of two product categories: biologics (including a monoclonal antibody and an enzyme replacement therapy); and small-molecule substrate replacement therapies. Enzymes are proteins that the body uses to process materials needed for normal cellular function, and substrates are the materials upon which enzymes act. When enzymes or substrates are missing, the body is unable to perform its normal cellular functions, often leading to significant clinical disease. Several of our therapies are intended to replace deficient enzymes or substrates.

Our biologics pipeline includes the following product candidates in clinical development for the treatment of three diseases:

- KRN23, or UX023, is an antibody targeting fibroblast growth factor 23, or FGF23, in development for the treatment of X-linked hypophosphatemia, or XLH, a rare genetic disease that impairs bone growth. We are developing KRN23 pursuant to our collaboration with Kyowa Hakko Kirin Co., Ltd., or KHK. KHK has completed one Phase 1 study, one Phase 1/2 study, and one longer-term Phase 1/2 study of KRN23 in adults with XLH. We initiated a Phase 2 pediatric study in July 2014 and a Phase 3 adult study in December 2015.
- KRN23 is also being developed for the treatment of tumor-induced osteomalacia, or TIO. TIO results from typically benign tumors that produce excess levels of FGF23, which can lead to severe hypophosphatemia, osteomalacia, fractures, fatigue, bone and muscle pain, and muscle weakness. We initiated a Phase 2 study of KRN23 in adult inoperable TIO patients in March 2015.
- Recombinant human beta-glucuronidase, or rhGUS or UX003, is an enzyme replacement therapy we are developing for the treatment of mucopolysaccharidosis 7, or MPS 7, a rare lysosomal storage disease that often leads to multi-organ dysfunction, pervasive skeletal disease, and death. We completed enrollment of a Phase 3 clinical study in June 2015.

Our substrate replacement therapy pipeline includes the following product candidates in clinical development for the treatment of three diseases:

- UX007 is a synthetic triglyceride with a specifically designed chemical composition being studied in an open-label Phase 2 study for the treatment of long-chain fatty acid oxidation disorders, or LC-FAOD, from which interim

results were recently reported. LC-FAOD is a set of rare metabolic diseases that prevents the conversion of fat into energy and can cause low blood sugar, muscle rupture, and heart and liver disease. The Company is planning for a Phase 3 study that it expects to initiate in 2017 after discussions with regulatory authorities.

- UX007 is also in a Phase 2 study for the treatment of glucose transporter type-1 deficiency syndrome, or Glut1 DS, a rare metabolic disease of brain energy deficiency that is characterized by seizures, developmental delay, and movement disorder. The Phase 2 study in Glut1 DS patients with seizures continues to enroll patients. A Phase 3 study in the movement disorder phenotype of Glut1 DS is expected to begin in the second half of 2016.
- Aceneuramic acid extended-release, or Ace-ER or UX001, is an extended-release form of aceneuramic acid in a Phase 2 extension study for the treatment of GNE myopathy, a neuromuscular disorder that causes muscle weakness and wasting. We initiated a Phase 3 study in May 2015 and filed a Marketing Authorization Application, or MAA, seeking conditional approval from the European Medicines Agency, or EMA, for the use of Ace-ER in the treatment of GNE myopathy, which was accepted for review in October 2015. The Committee for Orphan Medicinal Products for Human Use (CHMP) opinion on the conditional marketing authorization application is expected in the second half of 2016, and a decision from the European Commission is expected in the first half of 2017.

Clinical Product Candidates

The following table summarizes our current clinical-stage product candidate pipeline:

KRN23 (UX023) for the treatment of XLH

KRN23 is a fully human monoclonal antibody administered via subcutaneous injection that is designed to bind and reduce the biological activity of FGF23 to increase abnormally low phosphate levels in patients with XLH. Patients with XLH have low serum phosphate levels due to excessive phosphate loss into the urine, which is directly caused by the effect on kidney function of excess FGF23 production in bone cells. Low phosphate levels lead to poor bone mineralization and a variety of clinical manifestations, including rickets leading to bowing and other skeletal deformities, short stature, bone pain and fractures, and muscle weakness. There is no approved drug therapy or treatment for the underlying cause of XLH. Most patients are managed using frequently dosed oral phosphate replacement and vitamin D therapy, which can lead to significant side effects. Oral phosphate/vitamin D replacement therapy requires extremely close monitoring due to the potential for excessive phosphate levels and secondary increases in calcium, which can result in severe damage to the kidneys from excess calcium phosphate deposits and other complications. Additionally, some patients are unable to tolerate the regimen due to the chalky stool that results from taking large amounts of oral phosphate or the high frequency of dosing required.

In August 2013, we entered into a collaboration agreement with KHK, as amended in August 2015, to jointly develop and commercialize KRN23. KHK has conducted one Phase 1 study, one Phase 1/2 study, and one longer-term Phase 1/2 study of KRN23 in adults with XLH.

Results from the Phase 1 single-dose study in 38 adult XLH patients were presented at the American Society for Bone and Mineral Research, or ASBMR, Annual Meeting in October 2013 and published in the Journal of Clinical Investigation in February 2014.

Results from a four-month Phase 1/2 study in 28 adult XLH patients and a subsequent twelve-month Phase 1/2 study of KRN23 in 22 patients were presented at the 2014 ICE/ENDO joint meeting of The Endocrine Society and the International Congress on Endocrinology in June 2014 and ASBMR Annual Meeting in September 2014, respectively.

In July 2014, we announced the first patient screened and enrolled in the Phase 2 pediatric study of KRN23 in patients aged 5 to 12 with XLH. The study consists of a 16-week individual dose-titration period followed by a 48-week treatment period, for a total of 64 weeks. Patients were divided into three cohorts of escalating starting dose levels of KRN23 with either monthly or biweekly dosing regimens. At the end of the 16-week dose-titration period, patients were allowed to continue to receive dose increases in order to reach the individually optimized dose of KRN23 on a monthly or biweekly basis for the 48-week treatment period. In late 2014, we completed enrollment of 36 patients. Based on positive 16-week data, we decided to enroll an additional 16 patient cohort with patients who had more severe disease at baseline (based on their Thacher Rickets Severity Scoring System (RSS) knee score >1.5). Patients for the Phase 2 study were enrolled at nine global centers of excellence in XLH. The primary objectives of the study are to identify a dose and dosing regimen and to establish the safety profile of treatment with KRN23 in pediatric XLH patients. We are also assessing preliminary clinical effects of KRN23 treatment on bone health and deformity as measured by radiographic assessments, growth, muscle strength, and motor function, as well as markers of bone health and patient-reported outcomes of pain, disability, and quality of life.

In December 2015, we released interim data through 40 weeks from the first 36 patients in this study. Thirty five of 36 patients had previously been on standard of care (oral phosphate/vitamin D therapy) for an average of 6.6 years (range: 0 - 11.7 years). Patient demographics were well balanced between the biweekly (n=18) and monthly (n=18) dose groups. Rickets were evaluated via two scoring systems – the RSS and the Radiographic Global Impression of Change (RGI-C). A subset of patients (n=18; 9 dosed biweekly and 9 dosed monthly) were pre-specified as having high rickets severity (greater bone disease) if their baseline total RSS scores were > 1.5. For the responder analysis using total RSS, responders were pre-defined as those patients who had baseline total RSS scores > 1.0 and had 1.0 or more reduction at Week 40 which is considered a significant improvement.

Overall, in all patients (n=36), the mean total RSS score decreased from 1.43 at baseline to 1.00 at 40 weeks (-0.43; 30% reduction; p=0.0076), and 61% of the patients (14/23) were responders. In all the high severity patients (n=18), the mean total rickets score decreased from 2.31 at baseline to 1.22 at 40 weeks (-1.08; 47% reduction; p<0.0001), and 72% of these patients were responders (13/18). In patients who were dosed bi-weekly (n=18), the mean total RSS score decreased from 1.53 at baseline to 0.86 at 40 weeks (-0.67 points; 44% reduction; p=0.0126), and 75% of the patients (9/12) were responders. In the high severity patients who were dosed bi-weekly (n=9), the mean total rickets score decreased from 2.44 at baseline to 1.00 at 40 weeks (-1.44 points; 59% reduction; p<0.0001), and 89% of these patients were responders (8/9). In patients who were dosed monthly (n=18), the mean total rickets score decreased from 1.33 at baseline to 1.14 at 40 weeks (-0.19 points; 14% reduction), and 46% of the patients (5/11) were responders. In the high severity patients who were dosed monthly (n=9), the mean total RSS score decreased from 2.17 at baseline to 1.44 at 40 weeks (-0.72; 33% reduction) and 56% of these patients (5/9) were responders.

Overall, all patients (n=36) experienced a mean improvement in RGI-C score of +1.38 (p<0.0001) and those patients who were severe (n=18) experienced a mean improvement of +1.85 (p<0.0001) at 40 weeks. Within the high severity subset, 67% (12/18) experienced substantial healing (score >2). Patients who were dosed bi-weekly (n=18) experienced a mean improvement in RGI-C score of +1.56 (p<0.0001). Those patients with high severity rickets (n=9) experienced a mean improvement of +2.00 (p<0.0001) at 40 weeks (substantial healing) and 89% (8/9) experienced substantial healing (score >2). Patients who were dosed monthly (n=18) experienced a mean improvement in RGI-C score of +1.20. The patients with high severity rickets (n=9) experienced a mean improvement of +1.70 at 40 weeks and 44% (4/9) experienced substantial healing (score >2).

Patients with walking impairment at baseline (defined by < 80% predicted normal walk distance in the six minute walk test, or 6MWT; n=14) achieved a mean increase of 80 meters (an approximate 20% increase from baseline) in the 6MWT at week 40. Both high and low rickets-severity patients with walking impairments at baseline experienced a mean improvement in meters walked at week 40. Functional disability scores were measured with the Pediatric Orthopedic Society North America/Pediatric Outcome Data Collection Instrument (POSNA/PODCI). When evaluating the global score across all five domains in those patients with substantial impairment at baseline (n=15) or with severe rickets at baseline (n=18), a substantial mean improvement was observed of about one standard deviation

or greater in both dose groups. The Pain/Comfort and Sports/Physical Functioning domains were the most affected at baseline and also substantially improved in these severely affected subjects treated in both dose groups.

The most common treatment-related adverse event reported by preferred term was injection site reaction in 39% of patients. All of these reactions were considered mild. All other treatment-related adverse events were considered mild. There was one serious adverse event considered possibly treatment-related. This was a patient with fever and muscle pain who improved without complication and is still in the trial. There have been no deaths or discontinuations from the study for any reason. No clinically meaningful changes were observed in mean serum calcium, urinary calcium and in serum intact parathyroid hormone. None of the patients had serum phosphorus levels above the upper limit of normal at any time point. No clinically significant changes were observed in renal ultrasounds pre- and post-treatment. All patients demonstrated increases in serum phosphorus that were consistent with what had been observed previously reaching the low normal or just below normal range. Across both dose groups there were mean increases in both the renal phosphate reabsorption (TmP/GFR) and in serum 1,25 dihydroxy vitamin D levels through 40 weeks of treatment.

Additional data from the pediatric Phase 2 study are expected in the second half of 2016. We expect to have 40-week data from 52 patients, including rickets scores (RSS and RGI-C), and 64-week data from 36 patients, including height-growth velocity. We and our partner, KHK, plan to file an application near the end of 2016 seeking Conditional Marketing Authorization in the EU based on these data. In addition, we plan to proceed with a pediatric Phase 3 study in mid-2016. The study will utilize RGI-C as the primary endpoint and will include a standard of care reference arm. This study is expected to be required for potential approval in the US and

could also serve as a confirmatory study in the EU if a conditional marketing authorization is granted. The study could be required for approval in the EU if we do not receive conditional marketing authorization.

We are also continuing to develop KRN23 in adults with XLH. We have initiated a long-term, open-label Phase 2b extension study of KRN23 in adult XLH patients who had previously participated in the studies conducted by KHK. In December 2015, we initiated a Phase 3 study of KRN23 for the treatment of adults with XLH. The Phase 3 study is an international, randomized, double-blind, placebo-controlled clinical study that will assess the efficacy and safety of monthly KRN23 at 24 weeks in approximately 120 adult XLH patients. The primary endpoint of the study will be serum phosphorus levels through 24 weeks, and the key secondary endpoint is the Brief Pain Inventory Question 3 (pain at its worst in the last 24 hours) at Week 24. Other secondary endpoints include patient reported outcomes assessing skeletal pain, stiffness, fatigue, motor function, and quality of life in these patients. A 48-week open-label bone quality study in approximately ten adult XLH patients evaluating the potential impact of KRN23 on the underlying osteomalacia via bone biopsy is currently enrolling patients.

KRN23 (UX023) for the treatment of TIO

We are also developing KRN23 for the treatment of TIO. TIO results from typically benign tumors that produce excess levels of FGF23, which can lead to severe hypophosphatemia, osteomalacia, bone fractures, fatigue, bone and muscle pain, and muscle weakness. There are cases in which resection of the tumor is not feasible or recurrence of the tumor occurs after resection. In patients for whom the tumor is inoperable, the current standard of care consists of oral phosphate and/or vitamin D replacement. The efficacy of this treatment is often limited, as it does not treat the underlying disease and its benefits must be balanced with monitoring for potential risks such as nephrocalcinosis, hypercalciuria, and hyperparathyroidism. We are enrolling patients in an open-label, proof of concept Phase 2 clinical study.

This Phase 2 study evaluates safety and efficacy in approximately 15 adult inoperable patients. The primary objectives of the study are to establish the dose and assess the safety profile of treatment with KRN23 in adults with TIO. Patients receive subcutaneous injections of KRN23 once every four weeks for 48 weeks. All patients begin treatment with KRN23 at a starting dose of 0.3 mg/kg. Doses are then titrated in an effort to achieve a target fasting serum phosphorus range of 2.5 to 4.0 mg/dL. After completing the initial 48-week treatment period of the study, patients may continue into a planned treatment extension period in which they would receive KRN23 treatment for up to an additional 96 weeks. The co-primary endpoints include: the proportion of patients achieving mean peak serum phosphorus levels above the lower limit of normal (LLN; 2.5 mg/dL), as averaged between baseline and week 24; and the percent change from baseline in excess osteoid after 48 weeks of treatment. Preliminary clinical effects of KRN23 treatment are evaluated by radiographic assessments, muscle strength, walking ability, and patient-reported measures of pain, disability, and quality of life. Markers of bone health and changes in serum phosphorus and other biochemical measures are also followed.

In April 2016 we released interim data from the first eight patients in this study. Before KRN23 treatment and after washout with any oral phosphate treatment, the mean serum phosphorus level was 1.7 mg/dL, below the lower limit of normal of 2.5 mg/dL. After KRN23 treatment began, six of the eight patients achieved normalization of their serum phosphorus levels. The dose continues to be titrated up in one of the two patients whose serum phosphorus levels increased but had not yet entered the normal range. Renal phosphate reabsorption (TmP/GFR) and serum 1,25 dihydroxy vitamin D levels also increased in seven of the eight patients. One of these patients did not demonstrate an improvement in these markers. Overall, the improvement in serum phosphorus and other bone mineral metabolism measures observed in this study to date is generally consistent with what has been observed in studies of KRN23 in pediatric and adult patients with XLH. Of the eight patients enrolled, the two patients who completed 24 weeks of treatment showed an improvement in bone mineral density, and one of these two patients showed early evidence of fracture resolution, determined via bone scan.

There have been no serious adverse events. Treatment-emergent adverse events were observed in seven patients. Treatment-emergent adverse events occurring in two or more patients were primarily musculoskeletal disorders including pain in extremity, arthralgia, and musculoskeletal pain consistent with the symptoms typically seen in patients with TIO and epidermal nevus syndrome (ENS). Two of the eight patients had treatment-related adverse events that were possibly/probably related, including Vitamin D deficiency and rash, both of which were mild in grade. No injection site reactions were observed. Two subjects reported symptoms suggestive of worsening pre-existing restless leg syndrome.

No clinically meaningful changes were observed in mean serum calcium, urinary calcium and in serum intact parathyroid hormone. One patient had serum phosphorus levels above the upper limit of normal at three weeks of treatment that returned to the normal range by week four after dose reduction, and has remained in the normal range. Additional bone data is expected in the second half of 2016.

rhGUS (UX003) for the treatment of MPS 7

rhGUS is an intravenous, or IV, enzyme replacement therapy for the treatment of MPS 7, also known as Sly Syndrome. Patients with MPS 7 suffer from severe cellular and organ dysfunction that typically leads to death in the teens or early adulthood. MPS 7 is caused by a deficiency of the lysosomal enzyme beta-glucuronidase, which is required for the breakdown of certain complex carbohydrates known as glycosaminoglycans, or GAGs. The inability to properly break down GAGs leads to their accumulation in many tissues, resulting in a serious multi-system disease. Patients with MPS 7 may have abnormal coarsened facial features, enlargement of the liver and spleen, airway obstruction, lung disease, cardiovascular complications, joint stiffness, short stature, and a skeletal disease known as dysostosis multiplex. In addition, many patients experience progressive lung problems as a result of airway obstruction and mucous production, often leading to sleep apnea and pulmonary insufficiency, and eventually requiring tracheostomy. There are currently no approved drug therapies for MPS 7.

We licensed exclusive worldwide rights to rhGUS-related know-how and cell lines from Saint Louis University in November 2010. We have conducted preclinical studies to support the chronic IV administration of rhGUS. Administration of rhGUS resulted in substantial distribution of enzyme, as well as reduction in tissue pathology in a wide variety of tissues, including the liver, spleen, lung, heart, kidney, muscle, bone, and brain. No adverse toxicology related to rhGUS was noted in these studies.

In December 2013, we initiated an open-label, Phase 1/2 study in the United Kingdom to evaluate the safety, tolerability, efficacy, and dose of IV administration of rhGUS every other week in three patients with MPS 7. Results from the 12-week analysis evaluating 2 mg/kg of rhGUS every other week were presented in September 2014 at the Society for the Study of Inborn Errors of Metabolism, or SSIEM, Annual Symposium and showed a decline in urinary glycosaminoglycans, or GAG excretion of approximately 40-50% from baseline. After the initial 12 weeks, the study entered a dose-exploration phase in which patients were treated with a lower and then higher dose of rhGUS. The 36-week results, which were presented in February 2015 at the Annual WORLD Symposium, showed a greater change in urinary GAG excretion at the higher 4 mg/kg dose of rhGUS, with a mean urinary GAG reduction of approximately 60%.

Sustained decreases in liver size were observed in the two patients who had enlarged livers at baseline, and an improvement in pulmonary function was observed in the one patient who was able to perform the evaluations. Improvements were also observed in the MPS Health Assessment Questionnaire measure of functional capabilities and in the Physician Global Impression of Change scale of overall health status in this open-label study.

No serious adverse events or infusion-associated reactions were observed in the study. The most common adverse events were consistent with the symptoms of MPS 7 or related to intravenous administration of the investigational therapy, including respiratory disorders, infections, and arthralgia.

We initiated a Phase 3 global, randomized, placebo-controlled, blind-start clinical study in December 2014. The Phase 3 study is assessing the efficacy and safety of rhGUS in 12 patients between five and 35 years of age. Patients are randomized to one of four groups. One cohort begins rhGUS therapy immediately, while the other three start on placebo and cross over to rhGUS at different predefined time points in a blinded manner. This study design generates treatment data from all 12 patients. Based on data from the Phase 1/2 study, patients will be dosed with 4 mg/kg of rhGUS every other week for up to a total of 48 weeks, and all groups will receive a minimum of 24 weeks of treatment with rhGUS. The Phase 3 study fully enrolled in June 2015, and data are expected in mid-2016.

The primary objective of the study is to determine the efficacy of rhGUS as determined by the percent reduction in urinary GAG excretion after 24 weeks of treatment. The Phase 3 study is also evaluating as secondary endpoints the safety and tolerability of rhGUS, pulmonary function, walking, stair climb, shoulder flexion, fine and gross motor function, hepatosplenomegaly, cardiac size and function, visual acuity, patient and caregiver assessment of most significant clinical problems, global impressions of change, a multi-domain responder index, and other endpoints.

We have obtained positive feedback from the United States Food and Drug Administration, or FDA, and the EMA regarding the design of the Phase 3 study. The FDA stated that their evaluation of the pivotal Phase 3 study will be based on the totality of the data on a patient-by-patient basis and advised against the declaration of a primary endpoint. The EMA has agreed that approval under exceptional circumstances could be possible based upon a single positive placebo-controlled pivotal study in approximately 12 patients using urinary GAG levels as a surrogate primary endpoint, provided the data was strongly supportive of a favorable benefit/risk ratio. The EMA requested that some evidence or trend in improvement in clinical endpoints be observed to support the primary endpoint, but recognized that a statistically significant result on clinical endpoints was unlikely given the small number of patients expected to be enrolled in the study.

In August 2015 we initiated a study of rhGUS in MPS 7 patients under the age of five years, including potentially younger infants born with hydrops fetalis. These hydropic infants can die within a few months to one year of birth, but enzyme replacement therapy might be able to reduce GAG storage and improve health in these patients. The Phase 2 open-label study will assess the safety, tolerability, and efficacy of rhGUS in up to seven pediatric patients under five years old.

We are also supplying rhGUS to investigators who are treating patients under emergency investigational new drug, or eIND, applications and other expanded access programs. Results following 24 weeks of treatment of the first eIND patient were announced in September 2014 and published in Molecular Genetics and Metabolism in February 2015.

UX007 for the treatment of LC-FAOD

We are developing UX007 for oral administration intended as a substrate replacement therapy for patients with LC-FAOD. UX007 is a purified, pharmaceutical-grade form of triheptanoin, a specially designed synthetic triglyceride compound, created via a multi-step chemical process. UX007 is a medium odd-chain triglyceride of seven-carbon fatty acids designed to provide substrate replacement for fatty acid metabolism and restore production of energy. Patients with LC-FAOD have a deficiency that impairs the ability to produce energy from fat, which can lead to depletion of glucose in the body, and severe liver, muscle, and heart disease, as well as death. There are currently no approved drugs or treatments specifically for LC-FAOD. The current standard of care for LC-FAOD includes diligent prevention of fasting combined with the use of low-fat/high-carbohydrate diets, carnitine supplementation in some cases, and medium even-chain triglyceride oil supplementation. Despite treatment with the current standard of care, many patients continue to suffer significant morbidity and mortality.

We licensed certain intellectual property rights for triheptanoin from Baylor Research Institute in August 2012. Triheptanoin has been studied clinically for over a decade in more than a hundred human subjects affected by a variety of diseases. Multiple investigator-sponsored open-label studies suggest clinical improvements with triheptanoin treatment, even for patients who were on standard of care. We presented data at the International Conference of Inborn Errors of Metabolism, or ICIEM, in August 2013 from a retrospective medical record review study assessing the clinical outcome of triheptanoin treatment on LC-FAOD subjects who had been participating in a compassionate use program at the University of Pittsburgh Medical Center. The data showed that treatment with triheptanoin appeared to reduce the frequency and severity of hospitalizations previously experienced by these patients for disease-related causes, including muscle rupture, hypoglycemia, and cardiomyopathy. A reduction in mean total hospital days per year from 17.55 to 5.40 (69%; p = 0.0242) was observed after transitioning from standard of care to triheptanoin therapy. These results are clinically important but are derived from a retrospective medical review, and not from a prospective randomized controlled study.

In September 2015, case reports from five infants with moderate or severe cardiomyopathy due to LC-FAOD were presented at the SSIEM Annual Symposium. While on the standard of care medium-chain triglyceride, or MCT, oil, the patients were hospitalized with heart failure that required cardiac support and, in some cases, resuscitation. The patients discontinued MCT oil and then began to receive triheptanoin on an expanded access basis. In patients with known ejection fraction, or EF, values before and after treatment (n=4) the mean EF prior to treatment with triheptanoin was 32% (range: 21% to 44%) and after treatment at last assessment was 66% (range: 55% to 71%). The most common adverse events were gastrointestinal distress, including loose stools. One patient discontinued treatment after approximately 14 weeks due to gastrointestinal symptoms. No other significant tolerance issues or treatment-related adverse events were reported. Four of the patients continue to receive triheptanoin. These data are from an expanded access program and are based on open-label uncontrolled treatment, which limits definitive conclusions about efficacy and safety.

In October 2015, we reported interim data on the acute effects of UX007 that was being evaluated in a Phase 2 study in LC-FAOD patients. The study was single-arm open-label and evaluated 29 pediatric and adult patients across three main symptom groups (musculoskeletal, liver/hypoglycemia, and cardiac). Patients needed to have moderate to severe FAOD with significant disease in at least one of these domains or a frequent medical events history in order to enroll. The study began with a four-week run-in period to assess baseline data while on the standard of care therapy including MCT oil, if applicable. Patients on MCT oil then discontinued it and UX007 was titrated to a target dose of 25-35% of total daily caloric intake. Patients were followed to evaluate the effects of UX007 treatment over 24 weeks on several endpoints, including cycle ergometry performance, 12-minute walk test, liver disease/hypoglycemia, cardiac disease, and quality of life. The 24-week analysis mainly evaluated the acute effects of UX007 on the musculoskeletal aspects of the disease. Patients who opted to continue will be treated for a total of 78 weeks, and rates of major medical events, such as rhabdomyolysis, hypoglycemia and cardiac events, will be monitored and compared to rates for the two years prior to treatment with UX007. The study planned to evaluate the safety and tolerability of UX007 and to determine both the appropriate patient population as well as endpoints for evaluation in a Phase 3 study. The majority

of patients enrolled presented with musculoskeletal disease compared to a limited number who presented with liver and cardiac symptoms. Patients spanned a wide age range from ten months to 58 years old. Prior to initiating treatment with UX007, 27 of the 29 patients were on the standard of care MCT oil therapy. Following discontinuation of MCT oil therapy, the average dose of UX007 through 24 weeks was 30% of total daily caloric intake.

Improvements were observed in both measures of exercise tolerance (cycle ergometry and 12 minute walk test) in musculoskeletal patients who performed the tests. The three areas of evaluation with cycle ergometry included workload (measured in watts produced at a fixed heart rate), respiratory exchange ratio, or RER, a measure of energy supply, and duration of cycling. Patients showed improvements in both workload and duration and no change in RER. At week 24, seven patients (who qualified by age and performed the test at baseline) produced a mean 60% increase in watts over baseline representing a mean increase of +446.8 watts (median: +127.5; min, max: -388, +2438). The mean duration was increased in 3 patients who did not complete all 40 minutes at baseline. Eight qualified patients demonstrated a mean 28% increase of +188 meters (median: 93.5; min, max: -80, +880) at week 18 in the 12-minute walk test. These patients also experienced an improvement in the mean energy expenditure index (a ratio of heart rate per meter walked). The data on the 12 minute walk test and cycle ergometry together support an improvement in muscle function and exercise efficiency in a small number of patients that would need to be confirmed in larger controlled studies. Patients with liver/hypoglycemia and cardiac disease were limited, 3 and 2 respectively, but they qualified for entry due to frequent history of events and will contribute to the event rate measurement over 78 weeks.

Overall, major medical events appeared to decrease in the 25 patients who completed the 24 weeks of treatment when compared to the reported event rate in these patients approximately 18 months prior to treatment with UX007. These data are preliminary and

require significantly more time for proper evaluation at the 78 week time-point. The major medical event rate aggregates events related to hypoglycemia, rhabdomyolysis, and cardiomyopathy.

Improvements in patient-reported quality of life scores (SF-12) were observed in adult patients, but no difference was seen in parent-reported scores (SF-10) for pediatric patients. The Peabody Developmental Motor Score (PDMS-2) and the Pediatric Disability Inventory (PEDI-CAT), also showed no impairment in the overall patient population at baseline and no change after 24 weeks.

Four of the 29 enrolled patients discontinued prior to 24 weeks. One patient discontinued due to diarrhea in week 1, which resolved within a few days of discontinuation, and three patients withdrew consent (weeks 1, 8, 8) for reasons not attributed to treatment with UX007. All other patients opted to continue treatment in the extension phase of the study. There have been no deaths. One serious related adverse event of moderate gastroenteritis with vomiting was considered treatment-related. A viral infection was suspected, but the investigator could not rule out cause by UX007 given the proximity to dosing. That patient continues to be treated in the study and maintained dosing throughout the event, which has now resolved. Overall, 18 patients (62%) had treatment-related adverse events, most of which were mild-to-moderate in nature. The most common treatment-related adverse events were diarrhea, abdominal/gastrointestinal pain, and vomiting. Some gastrointestinal events were managed by adjusting dosing or dosing with food. The most common adverse events, including those not deemed treatment-related, were viral infections, gastrointestinal disorders, rhabdomyolysis, fever, and headache.

78-week data, including a comparison of major medical event rates approximately 18 months before and after UX007 treatment, are expected in the second half of 2016.

We are planning to initiate a Phase 3 study in LC-FAOD patients in 2017 based on the interim Phase 2 data. We intend to provide further details after completing discussions with the regulatory authorities. The Phase 3 trial design and endpoints continue to be optimized prior to discussion with regulators. Further details are expected to be provided after discussions with regulatory authorities.

UX007 for the treatment of Glut1 DS

We are also developing UX007 for patients with Glut1 DS. Glut1 DS is caused by a mutation affecting the gene that codes for Glut1, which is a protein that transports glucose from the blood into the brain. Because glucose is the primary source of energy for the brain, Glut1 DS results in a chronic state of brain energy deficiency and is characterized by seizures, developmental delay, and movement disorder. There are currently no approved drugs specific to Glut1 DS. The current standard of care for Glut1 DS is the ketogenic diet, an extreme high-fat (70-80% of daily calories as fat)/low-carbohydrate diet, which generates ketone bodies as an alternative energy source to glucose, and one or more antiepileptic drugs. The ketogenic diet can be effective in reducing seizures but compliance can be difficult, and the effectiveness of the diet in the treatment of developmental delay and movement disorders has not been confirmed. In addition, ketogenic diet can lead to side effects including renal stones. In general, Glut1 DS patients are considered relatively refractory to antiepileptic drugs with only approximately 8% achieving seizure control on antiepileptic drugs alone. There are currently no antiepileptic drugs approved specifically for patients with Glut1 DS.

UX007 is intended as a substrate replacement therapy to provide an alternative source of energy to the brain in Glut1 DS patients. There are open-label investigator-sponsored clinical studies ongoing, and there is one publication presenting data on absence seizure reduction and improved developmental function in some Glut1 DS subjects taking UX007.

In March 2014, we initiated a Phase 2 global, randomized, double-blind, placebo-controlled, parallel-group clinical study that plans to enroll up to 40 patients who are currently not fully compliant with ketogenic diet and continue to have seizures. The primary efficacy objective is the reduction in frequency of seizures compared to placebo following

a 6-week baseline period and subsequent 8-week placebo-controlled treatment period. Other efficacy objectives include cognitive function and movement disorder. The blinded treatment period will be followed by an open-label extension period in which patients will be treated with UX007 through week 52. In order to accelerate enrollment, we amended the enrollment criteria to also include patients with only absence seizures. The study will target enrollment of up to 40 patients with data expected in the second half of 2016.

In April 2015, positive data from an investigator-sponsored study of UX007 for the treatment of movement disorders associated with Glut1 DS were presented at the American Academy of Neurology Annual Meeting. The data showed a statistically significant 90% reduction in movement disorder events after treatment with UX007 (p=0.028) and a statistically significant increase in events after withdrawal from treatment with UX007 (p=0.043). Based on these study results, in November 2015 we announced an update to our development plan for UX007 in Glut1 DS patients. We now plan to initiate a Phase 3 study in approximately 40 Glut1 DS patients with the movement disorder phenotype in the second half of 2016. The study is intended to be a randomized, double-blind, placebo-controlled, double cross-over study. The study is designed to assess the impact of UX007 on movement disorder events as recorded by a patient diary. In recent interactions with the FDA, they have raised questions about the clinical meaningfulness of Glut1 DS movement disorder events. Therefore, we are currently working on further substantiating the clinical meaningfulness of Glut1 DS movement disorder events prior to finalizing the study design.

If the data are positive, the two studies are intended to support a new drug application, or NDA, filing for the treatment of Glut1 DS.

Ace-ER (UX001) for the treatment of GNE myopathy

We are developing Ace-ER, which is an extended-release, oral formulation of sialic acid for the treatment of GNE myopathy, which is also known as hereditary inclusion body myopathy, or HIBM. GNE myopathy is characterized by severe progressive muscular myopathy, or disease in which muscle fibers do not function properly, with onset typically in the late teens or twenties. Patients with GNE myopathy have a genetic defect in the gene coding for a particular enzyme that is involved in the first step in the biosynthesis of sialic acid. Therefore, GNE myopathy patients have a sialic acid deficiency, which interferes with muscle function, leading to myopathy and atrophy. Patients typically lose major muscle function within ten to 20 years of diagnosis. There is no approved drug therapy for GNE myopathy.

Ace-ER is intended as a potential substrate replacement therapy designed to address sialic acid deficiency and restore muscle function in GNE myopathy patients. We have conducted a Phase 2 randomized, double-blind, placebo-controlled study of Ace-ER in 47 GNE myopathy patients. Data from this study were presented at the American Academy of Neurology Annual Meeting in April 2014. Patients in the study were initially randomized to receive placebo, three grams, or six grams of Ace-ER per day. After 24 weeks, placebo patients crossed over to either three grams or six grams total daily dose, for an additional 24 weeks. The final analysis compared change at week 48 from baseline for the combined groups at six grams versus three grams of Ace-ER. Assessments included pharmacokinetics, composites of upper extremity and lower extremity muscle strength as measured by dynamometry, other clinical endpoints, patient reported outcomes, and safety.

At 24 weeks, assessments of upper extremity composite of muscle strength showed a statistically significant difference in the six-gram group compared to placebo (+2.33 kg; 5.5% relative difference from baseline; p=0.040). At 48 weeks, a statistically significant difference between the combined six-gram group and the combined three-gram group was observed (+3.44 kg; 8.5% relative difference from baseline; p=0.0033). Patients with less advanced disease (able to walk more than 200 meters at baseline), a predefined subset, showed a more pronounced difference (+4.69 kg; 9.6% relative difference from baseline; p=0.00055). The lower extremity composite showed a similar pattern of response but did not show a statistically significant difference between the dose groups. None of the groups showed a significant decline in the lower extremity composite during the treatment period. A positive trend was seen in patient-reported outcomes of functional activity consistent with the potential clinical meaningfulness of the muscle strength assessment. Ace-ER appeared to be well tolerated with no serious adverse events observed to date in either dose group, and no dose-dependent treatment-emergent adverse events were identified. Most adverse events were mild to moderate and the most commonly reported adverse events were gastrointestinal in nature and pain related to muscle biopsy procedures.

We continued to treat these patients in an extension study evaluating an increased daily dosage of sialic acid based on the dose dependence observed at weeks 24 and 48. Interim data from the extension study were presented at the International Congress of the World Muscle Society, or WMS, in October 2014. In the first part of the extension study, all 46 patients who completed the 48-week Phase 2 study crossed over to six grams for a variable period of time that was on average 24 weeks. In the second part of the extension study, all 46 patients and 13 treatment-naïve patients received 12 grams of Ace-ER for 24 weeks. The results presented at WMS included the 49 out of 59 patients who had 24 weeks of data at the higher dose. While the 12-gram data did not suggest any clinically meaningful advantage over six grams, the 12-gram data do provide additional data that supported clinical activity with Ace-ER treatment. The higher dose appeared to be generally safe and well tolerated with no drug-related serious adverse events, but the rate of mild to moderate gastrointestinal adverse events did appear to be greater with this dose. Throughout the approximately two-year study period, treatment with Ace-ER appeared to slow the progression of upper extremity disease when compared to the 24-week placebo group extrapolated out to two years.

We initiated a randomized, double-blind, placebo-controlled 48-week pivotal Phase 3 study of Ace-ER in approximately 80 patients with GNE myopathy in May 2015. The FDA agreed with the Phase 3 study design, including the primary endpoint of a composite of upper extremity muscle strength, with supportive secondary

endpoint data from a patient-reported outcome, both of which were studied in the Phase 2 study. Data from the Phase 3 study are expected in 2017.

In October 2015 we announced the filing and acceptance for review of an MAA seeking conditional approval from the EMA based on our Phase 2 study results for the use of six grams per day of Ace-ER tablets in the treatment of GNE myopathy. The CHMP opinion on the conditional marketing authorization is expected in the second half of 2016 and a decision from the European Commission is expected in the first half of 2017.

Preclinical Pipeline

rhPPCA (UX004) for the treatment of galactosialidosis

Recombinant human protective protein cathepsin-A, or rhPPCA, which we in-licensed from St. Jude Children's Research Hospital in September 2012, is in preclinical development as an enzyme replacement therapy for galactosialidosis, a rare lysosomal storage disease for which there are no currently approved drug therapies. Similar to MPS patients, patients with galactosialidosis present with both soft tissue storage in the liver, spleen, and other tissues, as well as connective tissue (bone and cartilage) related disease. As with MPS 7, an enzyme deficiency results in accumulation of substrates in the lysosomes, causing skeletal and organ dysfunction, and death. We are continuing preclinical development of rhPPCA with plans to file an investigational new drug application, or IND, in 2017.

Collaboration with Arcturus Therapeutics, Inc. for mRNA therapeutics

We signed a research collaboration and license agreement with Arcturus Therapeutics, Inc. to develop mRNA therapeutics for select rare disease targets in October 2015. The Arcturus collaboration may help us address a wider range of rare diseases than possible with current approaches. As part of the collaboration, Arcturus will utilize its UNA Oligomer™ chemistry and LUNAR™ nanoparticle delivery platform to initially design and optimize mRNA therapeutics for two targets selected by us; we also have the option to add up to eight additional targets during the collaborative research period.

Other preclinical programs

We continue to work on other compounds in various preclinical stages of development.

Financial Operations Overview

We are considered a clinical-stage company and have only a limited operating history. To date, we have invested substantially all of our efforts and financial resources to identifying, acquiring, and developing our product candidates, including conducting clinical studies and providing general and administrative support for these operations. To date, we have funded our operations primarily from the sale of equity securities.

We have never been profitable and have incurred net losses in each year since inception. Our net losses were $52.8 million and $21.4 million for the three months ended March 31, 2016 and 2015, respectively. Substantially all of our net losses have resulted from costs incurred in connection with our research and development programs and from general and administrative costs associated with our operations.

Revenue

To date, we have not generated any revenue. We do not expect to receive any significant revenue until we obtain regulatory approval for any product candidates that we develop and commercialize them or enter into collaborative agreements with third parties through which we could generate revenue.

Research and Development Expenses

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

- expenses incurred under agreements with clinical study sites that conduct research and development activities on our behalf;
- expenses incurred under license agreements with third parties;
- employee and consultant-related expenses, which include salaries, benefits, travel, and stock-based compensation;
- laboratory and vendor expenses related to the execution of preclinical, non-clinical, and clinical studies;
- the cost of acquiring, developing, and manufacturing clinical study materials; and
- facilities, depreciation, and other expenses, which include direct and allocated expenses for rent and maintenance of facilities, insurance, and other supply costs.

We expense all research and development costs in the periods in which they are incurred. Costs for certain development activities are recognized based on an evaluation of the progress to completion of specific tasks using information and data provided to us by our vendors and clinical sites. Nonrefundable advance payments for goods or services to be received in future periods for use in research and development activities are deferred and capitalized. The capitalized amounts are then expensed as the related goods are delivered and the services are performed.

The largest component of our total operating expenses has historically been our investment in research and development activities, including the clinical development of our product candidates. We allocate research and development salaries, benefits, stock-based compensation, and indirect costs to our product candidates on a program-specific basis, and we include these costs in the program-specific expenses. We expect our research and development expenses will increase in absolute dollars in future periods as we continue to invest in research and development activities related to developing our product candidates, and as programs advance into later stages of development and we enter into larger clinical studies. The process of conducting the necessary clinical research to obtain FDA approval is costly and time consuming and the successful development of our product candidates is highly uncertain. As a result, we are unable to determine the duration and completion costs of our research and development projects or when and to what extent, if any, we will generate revenue from the commercialization and sale of any of our product candidates.

General and Administrative Expenses

General and administrative expenses consist primarily of personnel costs, allocated facilities costs, and other expenses for outside professional services, including legal, human resources, audit, and accounting services. Personnel costs consist of salaries, benefits, and stock-based compensation. We expect that our general and administrative expenses will increase in the future to support continued research and development activities, preparation for potential commercialization of our product candidates, and as a result of operating as a public company, including expenses related to compliance with the rules and regulations of the Securities and Exchange Commission, or SEC, and those of any national securities exchange on which our securities are traded, additional insurance expenses, investor relations activities, and other administration and professional services.

Interest income

Interest income consists of interest earned on our cash, cash equivalents, and investments.

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 condensed consolidated financial statements, which have been prepared in accordance with GAAP. The preparation of these condensed consolidated financial statements requires us to make estimates and assumptions that affect the reported amounts of assets and liabilities and the disclosure of contingent assets and liabilities at the date of the financial statements, as well as the reported expenses incurred during the reporting periods. Our estimates are based on our historical experience and on 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 readily apparent from other sources. Actual results may differ from these estimates under different assumptions or conditions. There have been no significant and material changes in our critical accounting policies during the three months ended March 31, 2016, as compared to those disclosed in "Management's Discussion and Analysis of Financial Condition and Results of Operations-Critical Accounting Policies and Significant Judgments and Estimates" in our in our most recent Annual Report on Form 10-K filed with the SEC.

Results of Operations

Comparison of the three months ended March 31, 2016 to the three months ended March 31, 2015:

Research and Development Expenses (dollars in thousands)

	Three Months Ended March 31,		Dollar	%
	2016	2015	Change	Change
Development candidate:				
KRN23 (XLH)	$6,454	$1,870	$4,584	245%
KRN23 (TIO)	289	195	94	48%
rhGUS	7,085	3,400	3,685	108%
UX007 (LC-FAOD)	6,056	2,466	3,590	146%
UX007 (Glut 1 DS)	3,063	1,634	1,429	87%
Ace-ER	7,797	4,511	3,286	73%
Other research costs and preclinical costs	9,671	3,288	6,383	194%
Total research and development expenses	$40,415	$17,364	$23,051	133%

Research and development expenses increased $23.1 million for the three months ended March 31, 2016, compared to the same period in 2015. The increase in research and development expenses above is primarily due to:

- for KRN23 (XLH), an increase of $4.6 million related to the continued development of our clinical program, the enrollment of our Phase 3 adult study, and other development planning and regulatory activities, net of KHK reimbursement;
- for KRN23 (TIO), an increase of $0.1 million related to the continued development of our adult TIO study and other development planning and regulatory activities, net of KHK reimbursement;
- for rhGUS, an increase of $3.7 million related to our Phase 3 clinical program and increases in manufacturing-related and quality activities;
- for UX007 (LC-FAOD), an increase of $3.6 million related to clinical manufacturing, the continued development of our clinical program, and support of investigator-sponsored studies across multiple diseases;
- for UX007 (Glut1 DS), an increase of $1.4 million related to the continued development of our clinical program, including patient identification;

- for Ace-ER, an increase of $3.3 million related to the enrollment of our Phase 3 study, and manufacturing, quality, and regulatory activities for this program; and
- an increase of $6.4 million in other research and development costs including expenses in support of our clinical product candidate pipeline, expenses related to our research stage programs and research collaborations, and certain cost allocations, including stock compensation.

We expect our research and development expenses to increase in the future as we advance our product candidates through clinical development. The timing and amount of expenses incurred will depend largely upon the outcomes of current or future clinical studies for our product candidates as well as the related regulatory requirements, manufacturing costs and any costs associated with the advancement of our preclinical programs.

General and Administrative Expenses (dollars in thousands)

	Three Months Ended March 31,		Dollar	%
	2016	2015	Change	Change
General and administrative	$13,207	$4,138	$9,069	219 %

General and administrative expenses increased $9.1 million for the three months ended March 31, 2016 compared to the same period in 2015. The increase in general and administrative expenses was primarily due to increases in commercial planning costs, professional services costs, stock-based compensation, and personnel costs resulting from an increase in employees in support of our activities.

We expect general and administrative expenses to increase to support our organizational growth, the costs of being a public company, and for our expected staged build out of our commercial organization over the next several years related to multiple late-stage product candidates.

Interest Income (dollars in thousands)

	Three Months Ended March 31,		Dollar	%
	2016	2015	Change	Change
Interest income	$984	$273	$ 711	260 %

Interest income increased $0.7 million for the three months ended March 31, 2016 compared to the same period in 2015, primarily due to funds invested from our underwritten public offering in July 2015 and increased yield on our investment portfolio.

Other Expense, net (dollars in thousands)

	Three Months	Dollar	%

	Ended March 31,			
	2016	2015	Change	Change
Other expense, net	$119	$150	$ (31)	-21%

Liquidity and Capital Resources

Since our inception, we have funded our operations primarily with $103.9 million in net proceeds from the sale of convertible preferred stock, $121.7 million in net proceeds from the sale of common stock in our IPO and $521.4 million in net proceeds from the sale of common stock in our underwritten public offerings. As of March 31, 2016, we had $487.8 million in available cash, cash equivalents, and investments. We do not presently have material sources of liquidity other than cash, cash equivalents, and investments. Our cash, cash equivalents, and investments are held in a variety of interest-bearing accounts, corporate debt securities, U.S. government securities, and money market accounts. Cash in excess of immediate requirements is invested with a view toward liquidity and capital preservation, and we seek to minimize the potential effects of concentration and credit risk.

The following table summarizes our cash flows for the periods indicated (in thousands):

	Three Months Ended March 31,	
	2016	2015
Cash used in operating activities	$(44,895)	$(17,659)
Cash provided by (used in) investing activities	21,775	(4,065)
Cash provided by financing activities	314	175,440
Net increase in cash and cash equivalents	$(22,806)	$153,716

Cash Used in Operating Activities

Our primary use of cash is to fund operating expenses, which consist primarily of research and development expenditures. Due to our significant research and development expenditures, we have generated significant operating losses since our inception. Cash used to fund operating expenses is affected by the timing of when we pay these expenses, as reflected in the change in our outstanding accounts payable and accrued expenses.

Cash used in operating activities for the three months ended March 31, 2016 was $44.9 million and reflected a net loss of $52.8 million, offset by non-cash charges of $0.5 million for depreciation and amortization, $1.8 million for the amortization of premium paid on purchased investments, and $10.2 million for stock-based compensation. Cash used in operating activities also reflected a $4.0 million increase in prepaid expenses and other current assets primarily due to an increase in prepaids and other current assets for contract research organization, or CRO, other prepaid clinical costs, and prepaid subscriptions which were partially offset by a decrease in interest receivables. There was also a $1.5 million increase in other assets primarily due to prepaid leasehold improvements, equipment and office furniture, a $2.6 million increase in accounts payable primarily due to higher collaboration and research costs, and a $1.9 million decrease in accrued expenses and other liabilities as a result of the payment of employee bonuses, offset by an increase in clinical study, manufacturing, and related costs as we continued to increase our research and development activities.

Cash used in operating activities for the three months ended March 31, 2015 was $17.7 million and reflected a net loss of $21.4 million, offset by non-cash charges of $0.2 million for depreciation and amortization, $1.0 million for the amortization of premium paid on purchased short-term investments, and $2.4 million for stock-based compensation. Cash used in operating activities also reflected a $0.9 million increase in prepaid expenses and other current assets primarily due to an increase in CRO, other prepaid clinical costs, and prepaid insurance expenses, a $0.4 million increase in accounts payable primarily due to higher clinical study and related costs and an increase in professional fees, and a $0.7 million increase in accrued expenses and other liabilities as a result of an increase in clinical study, manufacturing, and related costs as we continued to increase our research and development activities offset by a decrease in employee bonuses.

Cash Provided by or Used in Investing Activities

Cash provided by investing activities for the three months ended March 31, 2016 was $21.8 million and related to purchases of investments of $118.1 million, purchases of property and equipment of $1.5 million and an increase of $1.5 million in restricted cash for the expansion of the space under our current lease agreement, offset by proceeds from maturities of investments of $131.4 million and the sale of investments of $11.5 million.

Cash used in investing activities for the three months ended March 31, 2015 was $4.1 million and related to purchases of short-term investments of $77.3 million, purchases of property and equipment of $0.5 million and an increase of $1.4 million in restricted cash for the expansion of the space under our current lease agreement, offset by proceeds from maturities of short-term investments of $62.2 million and the sale of investments of $12.8 million.

Cash Flows Provided by Financing Activities

Cash provided by financing activities for the three months ended March 31, 2016 was $0.3 million and was comprised of proceeds from the issuance of common stock from the exercise of stock options.

Cash provided by financing activities for the three months ended March 31, 2015 was $175.4 million and was comprised of proceeds from the issuance of common stock from our underwritten public offering and the exercise of stock options and warrants.

Funding Requirements

We anticipate that we will continue to generate losses for the foreseeable future, and we expect the losses to increase as we continue the development of, and seek regulatory approvals for, our product candidates, and begin to commercialize any approved products. We will likely require additional capital to fund our operations and complete our ongoing and planned clinical studies, and funding may not be available to us on acceptable terms or at all. We expect to satisfy future cash needs through existing capital balances or, if necessary, through equity or debt financings, or strategic collaborations. If we are unable to raise additional capital in sufficient amounts or on terms acceptable to us, we may be required to delay, limit, reduce the scope of, or terminate one or more of our clinical studies, research and development programs, future commercialization efforts, or grant rights to develop and market product candidates that we would otherwise prefer to develop and market ourselves.

Our future funding requirements will depend on many factors, including the following:

- the scope, rate of progress, results and cost of our clinical studies, nonclinical testing, and other related activities;
- the cost of manufacturing clinical supplies, and establishing commercial supplies, of our product candidates and any products that we may develop;
- the number and characteristics of product candidates that we pursue;
- the cost, timing, and outcomes of regulatory approvals;

- the cost and timing of establishing commercial infrastructure, and distribution capabilities; and
- the terms and timing of any collaborative, licensing, and other arrangements that we may establish, including any required upfront milestone and royalty payments thereunder.

We may seek to raise any necessary additional capital through some combination of public or private equity offerings, debt financings, collaborations, strategic alliances, licensing arrangements, and other marketing and distribution arrangements. To the extent that we raise additional capital through marketing and distribution arrangements or other collaborations and strategic alliances or licensing arrangements with third parties, we may have to relinquish valuable rights to our product candidates, future revenue streams, research programs, or product candidates or grant licenses on terms that may not be favorable to us. If we do raise additional capital through public or private equity offerings, the ownership interest of our existing stockholders will be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect our stockholders' rights. If we raise additional capital through debt financing, we may be subject to covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, making capital expenditures or declaring dividends.

Off-Balance Sheet Arrangements

Since our inception in April 2010, we have not engaged in any off-balance sheet arrangements, as defined in the rules and regulations of the SEC.

Item 3. Quantitative and Qualitative Disclosures About Market Risk

Our exposure to market risk for changes in interest rates relates primarily to interest earned on our cash equivalents and investments. The primary objective of our investment activities is to preserve our capital to fund operations. A secondary objective is to maximize income from our investments without assuming significant risk. Our investment policy provides for investments in low-risk, investment-grade debt instruments. As of March 31, 2016, we had cash, cash equivalents, and investments totaling $487.8 million which includes bank deposits, money market funds, asset-backed securities, and investment-grade corporate bonds which are subject to default, changes in credit rating, and changes in market value. The securities in our investment portfolio are classified as available for sale and are subject to interest rate risk and will decrease in value if market interest rates increase. A hypothetical 100 basis point shift change in interest rates during any of the periods presented would not have had a material impact on our financial statements. To date, we have not experienced a loss of principal on any of our investments.

We face foreign exchange risk as a result of entering into transactions denominated in currencies other than U.S. dollars. Due to the uncertain timing of expected payments in foreign currencies, we do not utilize any forward exchange contracts. All foreign transactions settle on the applicable spot exchange basis at the time such payments are made. An adverse movement in foreign exchange rates could have a material effect on payments made to foreign suppliers and for license agreements. A hypothetical 100 basis point shift change in foreign exchange rates during any of the periods presented would not have had a material impact on our financial statements.

Item 4. Controls and Procedures

Evaluation of Disclosure Controls and Procedures

We carried out an evaluation, under the supervision and with the participation of our management, including our Chief Executive Officer and our Chief Financial Officer, of the effectiveness of our "disclosure controls and procedures" as of the end of the period covered by this report, pursuant to Rules 13a-15(b) and 15d-15(b) under the Exchange Act of 1934, as amended, or the Exchange Act. In connection with that evaluation, our Chief Executive Officer and our Chief Financial Officer concluded that our disclosure controls and procedures were effective and designed to provide reasonable assurance that the information required to be disclosed is recorded, processed, summarized, and reported within the time periods specified in the SEC rules and forms as of March 31, 2016. For the purpose of this review, disclosure controls and procedures means controls and procedures designed to ensure that information required to be

disclosed by us in the reports that we file or submit is recorded, processed, summarized, and reported within the time periods specified in the SEC's rules and forms. These disclosure controls and procedures include, without limitation, controls and procedures designed to ensure that information required to be disclosed by us in the reports that we file or submit is accumulated and communicated to management, including our principal executive officer and principal financial officer, as appropriate to allow timely decisions regarding required disclosure. In designing and evaluating the disclosure controls and procedures, our management recognized that any controls and procedures, no matter how well designed and operated, can provide only reasonable assurance of achieving the desired control objectives, and our management necessarily was required to apply its judgment in evaluating the cost-benefit relationship of possible controls and procedures.

Changes in Internal Control over Financial Reporting

There have been no changes in our internal control over financial reporting (as defined in Rules 13a-15(f) and 15d-15(f) under the Exchange Act) during our first fiscal quarter ended March 31, 2016, that has materially affected, or is reasonably likely to materially affect our internal control over financial reporting.

PART II. OTHER INFORMATION

Item 1. Legal Proceedings

We are not currently a party to any material legal proceedings. We may, however, in the ordinary course of business face various claims brought by third parties and we may, from time to time, make claims or take legal actions to assert our rights, including intellectual property rights as well as claims relating to employment matters and the safety or efficacy of our products. Any of these claims could subject us to costly litigation and, while we generally believe that we have adequate insurance to cover many different types of liabilities, our insurance carriers may deny coverage, may be inadequately capitalized to pay on valid claims, or our policy limits may be inadequate to fully satisfy any damage awards or settlements. If this were to happen, the payment of any such awards could have a material adverse effect on our consolidated operations, cash flows and financial position. Additionally, any such claims, whether or not successful, could damage our reputation and business.

Item 1A. Risk Factors

Investing in our common stock involves a high degree of risk. You should carefully consider the following risks, together with all the other information in this report, including our financial statements and notes thereto, before deciding to invest in our common stock. If any of the following risks actually materializes, our operating results, financial condition and liquidity could be materially adversely affected. As a result, the trading price of our common stock could decline and you could lose part or all of your investment.

Risks Related to Our Financial Condition and Capital Requirements

We are a clinical-stage company and have a limited operating history on which to assess our business, 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 biopharmaceutical company with a limited operating history. We have incurred net losses in each year since our inception in April 2010, including net losses of $52.8 million and $21.4 million for the three months ended March 31, 2016 and 2015, respectively.

We have devoted substantially all of our financial resources to identifying, acquiring, and developing our product candidates, including conducting clinical studies, developing manufacturing processes, manufacturing product candidates for clinical studies, and providing general and administrative support for these operations. To date, we have financed our operations primarily through the sale of equity securities. The amount of our future net losses will depend, in part, on the rate of our future expenditures and our ability to obtain funding through equity or debt financings, strategic collaborations, or grants. Biopharmaceutical product development is a highly speculative undertaking and involves a substantial degree of risk. Our product candidates are in clinical development and we may never have a product candidate approved for commercialization. If we obtain regulatory approval to market a product candidate, our future revenue will depend upon the size of any markets in which our product candidates may receive approval, and our ability to achieve sufficient market acceptance, pricing, reimbursement, and adequate market share for our product candidates in those markets. However, even if we obtain adequate market share for our product candidates, because the potential markets in which our product candidates may ultimately receive regulatory approval are very small, and our expenses may be greater than expected, we may never become profitable despite obtaining such market share and acceptance of our products.

We expect to continue to incur significant expenses and increasing operating losses for the foreseeable future. We anticipate that our expenses will increase substantially if and as we:

- continue our research and nonclinical and clinical development of our product candidates;
- expand the scope of our current clinical studies for our product candidates;
- advance our programs into more expensive clinical studies;
- initiate additional nonclinical, clinical, or other studies for our product candidates;
- pursue preclinical and clinical development for additional indications for existing product candidates;
- change or add additional manufacturers or suppliers;
- seek regulatory and marketing approvals for our product candidates that successfully complete clinical studies;
- establish a marketing and distribution infrastructure and field force to commercialize any products for which we may obtain marketing approval;
- seek to identify, assess, license, acquire, and/or develop other product candidates, technologies, and/or businesses;
- make milestone or other payments under any license agreements;
- seek to maintain, protect, and expand our intellectual property portfolio;
- seek to attract and retain skilled personnel;

- create additional infrastructure, including facilities and systems, to support the growth of our operations, our product development, and our planned future commercialization efforts; and
- experience any delays or encounter issues with any of the above, including but not limited to failed studies, complex results, safety issues, inspection outcomes, or other regulatory challenges that require longer follow-up of existing studies, additional major studies, or additional supportive studies in order to pursue marketing approval.

Further, the net losses we incur may fluctuate significantly from quarter to quarter and year to year, such that a period-to-period comparison of our results of operations may not be a good indication of our future performance.

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

We have no products approved for commercialization and have never generated any revenue. Our ability to generate significant revenue and achieve profitability depends on our ability, alone or with strategic collaboration partners, to successfully complete the development of, and obtain the regulatory and marketing approvals necessary to commercialize one or more of our product candidates. We do not anticipate generating significant revenue from product sales in the near future. Our ability to generate substantial future revenue from product sales, including named patient sales, depends heavily on our success in many areas, including but not limited to:

- completing research and nonclinical and clinical development of our product candidates;
- obtaining regulatory and marketing approvals for product candidates for which we complete clinical studies;
- developing a sustainable and scalable manufacturing process for any approved product candidates and establishing and maintaining supply and manufacturing relationships with third parties that can conduct the processes and provide adequate (in amount and quality) product supply to support clinical development and the market demand for our product candidates, if approved;
- launching and commercializing product candidates for which we obtain regulatory and marketing approval, either directly or with a collaborator or distributor;
- obtaining market acceptance of our product candidates as viable treatment options;
- obtaining adequate reimbursement and pricing for our product candidates;
- our ability to sell our product candidates on a named patient basis or through an equivalent mechanism and the amount of revenue generated from such sales;
- addressing any competing technological and market developments;
- identifying, assessing, licensing, acquiring, and/or developing new product candidates, technologies, and/or businesses;
- negotiating favorable terms in any collaboration, licensing, or other arrangements into which we may enter;
- maintaining, protecting, and expanding our portfolio of intellectual property rights, including patents, trade secrets, and know-how; and
- attracting, hiring, and retaining qualified personnel.

Even if one or more of the product candidates that we develop is approved for commercial sale, we anticipate incurring significant costs associated with commercializing any approved product candidate. Our expenses could increase beyond expectations if we are required by the FDA, the EMA, or other regulatory agencies, domestic or foreign, to change our manufacturing processes or assays, or to perform clinical, nonclinical, or other types of studies in addition to those that we currently anticipate. In cases where we are successful in obtaining regulatory approvals to market one or more of our product candidates, our revenue will be dependent, in part, upon the size of the markets in the territories for which we gain regulatory approval, the accepted price for the product, the ability to get reimbursement at any price, and whether we own the commercial rights for that territory. If the number of our addressable rare disease patients is not as significant as we estimate, the indication approved by regulatory authorities is narrower than we expect, or the reasonably accepted population for treatment is narrowed by competition, physician choice or treatment guidelines, we may not generate significant revenue from sales of such products, even if approved. For example, the development of KRN23, rhGUS, and UX007 for pediatric use is an important part of our current business strategy; if we are unable to obtain regulatory approval for the desired age ranges, our business may suffer.

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

We are currently advancing our KRN23, rhGUS, UX007, and Ace-ER product candidates through clinical development and our other product candidate, rhPPCA, as well as our other early stage research projects, through preclinical development. Developing our product candidates is expensive, and we expect our research and development expenses to increase substantially in connection with our ongoing activities, particularly as we advance our product candidates through clinical studies and potential global commercialization.

As of March 31, 2016, our available cash, cash equivalents, and investments were $487.8 million. We will likely require additional capital to obtain regulatory approval for, and to commercialize all of our product candidates. In addition, our operating plans may change as a result of many factors that may currently be unknown to us, and we may need to seek additional funds sooner than planned. Our future funding requirements will depend on many factors, including but not limited to:

- the scope, rate of progress, results, and cost of our clinical studies, nonclinical testing, and other related activities;
- the cost of manufacturing clinical supplies, and establishing commercial supplies, of our product candidates and any products that we may develop;
- the number and characteristics of product candidates that we pursue;
- the cost, timing, and outcomes of regulatory approvals;
- the cost and timing of establishing field forces, marketing, and distribution capabilities; and
- the terms and timing of any collaborative, licensing, acquisition, and other arrangements that we may establish, including any required milestone, royalty, and other payments thereunder.

Any additional fundraising efforts may divert our management's attention from their day-to-day activities, which may adversely affect our ability to develop and commercialize our product candidates. In addition, we cannot guarantee that future financing will be available in sufficient amounts or on terms acceptable to us, if at all. Moreover, the terms of any financing may adversely affect the holdings or the rights of our stockholders 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 stockholders. The incurrence of indebtedness could result in increased fixed payment obligations and we may be required to agree to certain restrictive covenants, such as 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 collaborative partnerships or other arrangements and we may be required to relinquish rights to some of our technologies or product candidates or otherwise agree to terms unfavorable to us, any of which may have a material adverse effect on our business, operating results, and prospects. Even if we believe we have sufficient funds for our current or future operating plans, we may seek additional capital if market conditions are favorable or if we have specific strategic considerations.

If we are unable to obtain funding on a timely basis, we may be required to significantly curtail, delay, or discontinue one or more of our research or development programs or the commercialization of any product candidates or be unable to expand our operations or otherwise capitalize on our business opportunities, as desired, which could materially affect our business, financial condition, and results of operations.

Risks Related to the Discovery and Development of Our Product Candidates

We are heavily dependent on the success of our product candidates, some of which are in the early stages of clinical development, which is a lengthy and expensive process with uncertain outcomes and the potential for substantial delays. We cannot give any assurance that any of our product candidates will receive regulatory approval, which is necessary before they can be commercialized.

Before obtaining marketing approval from regulatory authorities for the sale of our product candidates, we must conduct extensive clinical studies to demonstrate the safety and efficacy of the product candidates in humans. To date, we have invested substantially all of our efforts and financial resources to identifying, acquiring, and developing our product candidates, including conducting clinical studies and providing general and administrative support for these operations. We cannot be certain that any clinical studies will be conducted as planned or completed on schedule, if at all. Our inability to successfully complete nonclinical and clinical development could result in additional costs to us and negatively impact our ability to generate revenue. Our future success is dependent on our ability to successfully develop, obtain regulatory approval for, and then successfully commercialize one or more product candidates. We currently generate no revenue from sales of any drugs, and we may never be able to develop or commercialize a marketable drug. We cannot be certain that any of our product candidates will be successful in clinical studies or

receive regulatory approval. Further, our product candidates may not receive regulatory approval even if they are successful in some clinical studies. If we do not receive regulatory approvals for our product candidates, we may not be able to continue our operations.

Each of our product candidates is in development and will require additional clinical development, management of nonclinical, clinical, and manufacturing activities, regulatory approval, obtaining adequate manufacturing supply, building of a commercial organization, significant marketing efforts, and reimbursement before we generate any significant revenue from commercial product sales. We currently have multiple programs that are in clinical studies. Three of our product candidates have advanced into pivotal studies, but such studies may not result in approval. For Ace-ER, we filed for conditional marketing authorization in the EU on the basis of results from our Phase 2 study, which study was originally designed to serve as a hypothesis-generating exploratory study and not as a pivotal study. Additionally, the study had a small sample size, did not have a primary endpoint and had a pre-specified unblinding that occurred halfway during the treatment period. Accordingly, the data from this Phase 2 study are not as comprehensive or robust as data that are typically generated from a pivotal Phase 3 study. Although conditional marketing authorization initially allows for approval without providing comprehensive clinical data, marketing approval applications based on smaller and less definitive studies may entail a higher risk for rejection than the standard approval pathway. Additionally, our filing for conditional marketing authorization for Ace-ER represents our first application for regulatory approval of an investigational drug. In the course of interacting with the EMA on this filing, certain findings and observations have been made, including but not limited to safety and efficacy and deficiencies in our clinical processes and procedures, which we are in the process of addressing. However, there can be no assurance that our responses to these issues will be adequate such that we will be able to secure approval with the current filing or within projected time periods. Even if we obtain conditional approval, it may be withdrawn under certain circumstances. In addition, confirmatory clinical studies would be required and could fail to demonstrate sufficient safety and efficacy to obtain full approval. We also currently plan to file for conditional marketing authorization for KRN23 for XLH in the EU based on Phase 1/2 and Phase 2 data. This filing would face similar hurdles.

Some of our product candidates are in the early-stage translational research phases of development. Such early-stage programs will require substantial investment to reach clinical studies and regulatory approval, and the risk of failure for them may be higher than with our clinical-stage product candidates. For example, our collaboration with Arcturus focuses on an advanced but less established technology platform that will require significant effort and investment. A failure in that collaboration or our other early-stage programs may negatively affect our operational results.

We generally plan to seek regulatory approval to commercialize our product candidates in the United States, the EU, and in additional foreign countries where we have commercial rights. To obtain regulatory approval in other countries, we must comply with numerous and varying regulatory requirements of such other countries regarding safety, efficacy, chemistry, manufacturing, and controls, clinical studies, commercial sales, pricing, and distribution of our product candidates. Even if we are successful in obtaining approval in one jurisdiction, we cannot ensure that we will obtain approval in any other jurisdictions. If we are unable to obtain approval for our product candidates in multiple jurisdictions, our revenue and results of operations could be negatively affected.

We cannot be certain that any of our product candidates will be successful in clinical studies or receive regulatory approval. Further, our product candidates may not receive regulatory approval even if they are successful in clinical studies. If we do not receive regulatory approvals for our product candidates, we may not be able to continue our operations.

The regulatory approval processes of the FDA and comparable foreign authorities are lengthy, time consuming, and inherently unpredictable. Even if we achieve positive results in our pre-clinical and clinical studies, if we are ultimately unable to obtain timely regulatory approval for our product candidates, our business will be substantially harmed.

Our future success is dependent on our ability to successfully develop, obtain regulatory approval for, and then successfully commercialize one or more product candidates. We are not permitted to market or promote any of our product candidates before we receive regulatory approval from the FDA or comparable foreign regulatory authorities, and we may never receive such regulatory approval for any of our product candidates. We have not obtained

regulatory approval for any product candidate, and it is possible that none of our existing product candidates or any product candidates we may seek to develop in the future will ever obtain regulatory approval.

To obtain regulatory approval in the United States and other jurisdictions, we must comply with numerous and varying requirements regarding safety, efficacy, chemistry, manufacturing and controls, clinical studies (including good clinical practices), commercial sales, pricing, and distribution of our product candidates. Even if we are successful in obtaining approval in one jurisdiction, we cannot ensure that we will obtain approval in any other jurisdictions. In addition, approval policies, regulations, positions of the regulatory agencies on study design and/or endpoints, or the type and amount of clinical data necessary to gain approval may change during the course of a product candidate's clinical development, which may cause delays in the approval or the decision not to approve an application. Communications with the regulatory agencies during the approval process are also unpredictable; favorable communications early in the process do not ensure that approval will be obtained and unfavorable communications early on do not guarantee that approval will not be obtained. If we are unable to obtain approval for our product candidates in multiple jurisdictions, our revenue and results of operations could be negatively affected. Applications for our product candidates could fail to receive regulatory approval, or could be delayed in receiving regulatory approval, for many reasons, including but not limited to the following:

- the FDA or comparable foreign regulatory authorities may disagree with the design, implementation, or conduct of our clinical studies;
- the FDA or other comparable foreign regulatory authorities may change their guidance or requirements for a development program for a product candidate;
- the population studied in the clinical program may not be sufficiently broad or representative to assure efficacy and safety in the full population for which we seek approval;
- the FDA or comparable foreign regulatory authorities may disagree with our interpretation of data from nonclinical studies or clinical studies;
- the data collected from clinical studies of our product candidates may not be sufficient to support the submission of an NDA, or biologics license application, or BLA, or other submission or to obtain regulatory approval in the United States or elsewhere;
- we may be unable to demonstrate to the FDA or comparable foreign regulatory authorities that a product candidate's risk-benefit ratio for its proposed indication is acceptable;
- the FDA or comparable foreign regulatory authorities may fail to approve the manufacturing processes, test procedures and specifications, or facilities of third-party manufacturers with which we contract for clinical and commercial supplies;
- as a condition of marketing authorization in the EU, an agreed upon Pediatric Investigational Plan (PIP) detailing the designs and completion timelines for nonclinical and clinical studies is required. If the nonclinical or clinical development does not comply with the agreed upon PIP, marketing authorization could be denied or significantly delayed; and
- the approval policies or regulations of the FDA or comparable foreign regulatory authorities may significantly change in a manner rendering our clinical data insufficient for approval.

Furthermore, the disease states we are evaluating often will not have clear regulatory paths for approval and/or do not have validated outcome measures. In these circumstances, we work closely with the regulatory authorities to define the approval path and may have to qualify outcome measures as part of our development programs. For example, for patients with XLH there is no available regulatory precedent for what is needed to obtain approval to treat this disease and there are no validated patient-reported outcome measures that are specific to this disease. Additionally, many of the disease states we are targeting are highly heterogeneous in nature, which may impact our ability to determine the treatment benefit of our potential therapies. For example, patients with FAOD, Glut1 DS, and MPS 7 have a highly heterogeneous disease course, which may impact our ability to determine the true treatment benefit of our product candidates in these patients.

This lengthy and uncertain approval process, as well as the unpredictability of the clinical and nonclinical studies, may result in our failing to obtain regulatory approval to market any of our product candidates, or being delayed in obtaining regulatory approval, which would significantly harm our business, results of operations, and prospects.

Clinical drug development involves a lengthy and expensive process with uncertain outcomes and the potential for substantial delays, and the results of earlier studies may not be predictive of future study results.

Before obtaining marketing approval from regulatory authorities for the sale of our product candidates, we must conduct extensive clinical studies to demonstrate the safety and efficacy of the product candidates in humans. Clinical testing is expensive, time consuming, and uncertain as to outcome. We cannot guarantee that any clinical studies will be conducted as planned or completed on schedule, if at all. A failure of one or more clinical studies can occur at any stage of testing, and our future clinical studies may not be successful. Product candidates that have shown promising results in early-stage clinical studies may still suffer significant setbacks in subsequent clinical studies. For example, the safety or efficacy results generated to date in clinical studies for KRN23, rhGUS, UX007, and Ace-ER do not ensure that later clinical studies will demonstrate similar results. Results from investigator-sponsored studies or compassionate-use studies may not be confirmed in company-sponsored studies or may negatively impact the prospects for our programs. Additionally, given the nature of the rare diseases we are seeking to treat, we often have to devise newly-defined endpoints to be tested in our studies, which can lead to some subjectivity in interpreting study results and could result in regulatory agencies not agreeing with the validity of our endpoints, or our interpretation of

the clinical data, and therefore denying approval. Given the illness of the subjects in our studies and the nature of their rare diseases, we may also be required or choose to conduct certain studies on an open-label basis. Additionally, we have in the past, and may in the future elect to review interim clinical data at multiple time points during the studies, which could introduce bias into the study results and potentially result in denial of approval.

In the biopharmaceutical industry, there is a high failure rate for drugs and biologics proceeding through clinical studies, and product candidates in later stages of clinical studies may fail to show the desired safety and efficacy despite having progressed through nonclinical studies and initial clinical studies. A number of companies in the biopharmaceutical industry have suffered significant setbacks in advanced clinical studies due to lack of efficacy or adverse safety profiles, notwithstanding promising results in earlier studies.

Scenarios that may prevent successful or timely completion of clinical development include but are not limited to:

- our inability to generate sufficient preclinical, toxicology, or other in vivo or in vitro data to support the initiation or continuation of human clinical studies or filings for regulatory approval;
- delays or failures in reaching a consensus with regulatory agencies on study design;
- delays in reaching agreement on acceptable terms with prospective contract research organizations (or CROs), clinical study sites, and other clinical trial-related vendors;
- delays in obtaining required Institutional Review Board, or IRB, approval at each clinical study site;
- changes in clinical study design or development strategy resulting in delays related to obtaining approvals from IRBs and/or regulatory agencies to proceed with clinical studies;
- failure to gain approval from regulatory authorities or IRBs to conduct clinical studies in certain countries;
- imposition of a clinical hold by regulatory agencies after review of an IND application or amendment, another equivalent application or amendment, or an inspection of our clinical study operations or study sites;
- delays in recruiting suitable patients to participate in our clinical studies;
- difficulty collaborating with patient groups and investigators;
- failure by our CROs, other third parties, or us to adhere to clinical study requirements;
- failure to perform in accordance with the FDA's good clinical practices requirements or applicable regulatory guidelines in other countries;
- delays in patients' completion of studies or their returns for post-treatment follow-up;
- patients dropping out of a study;
- occurrence of adverse events associated with the product candidate that are viewed to outweigh its potential benefits;
- changes in regulatory requirements and guidance that require amending or submitting new clinical protocols;
- the cost of clinical studies of our drug candidates being greater than we anticipate;
- clinical studies of our drug candidates producing negative or inconclusive results, which may result in us deciding, or regulators requiring us, to conduct additional clinical or nonclinical studies or to abandon drug development programs;
- competing clinical studies of potential alternative product candidates or investigator-sponsored studies of our product candidates; and
- delays in manufacturing, testing, releasing, validating, or importing/exporting sufficient stable quantities of our product candidates for use in clinical studies or the inability to do any of the foregoing.

Any inability to successfully complete nonclinical and clinical development could result in additional costs to us or negatively impact our ability to generate revenue. In addition, if we make manufacturing or formulation changes to our product candidates, such as our plan to manufacture a combination extended release and immediate release version of sialic acid, or new formulations of UX007, we may need to conduct additional studies to bridge our modified product candidates to earlier approved versions. Clinical study delays could also shorten any periods during which our products have patent protection and may allow our competitors to bring products to market before we do, which could negatively impact our ability to obtain orphan exclusivity and to successfully commercialize our product candidates and may harm our business and results of operations.

We may find it difficult to enroll patients in our clinical studies given the limited number of patients who have the diseases for which our product candidates are being studied. Difficulty in enrolling patients could delay or prevent clinical studies of our product candidates.

Identifying and qualifying patients to participate in clinical studies of our product candidates is critical to our success. The timing of our clinical studies depends in part on the speed at which we can recruit patients to participate in testing our product candidates, and we may experience delays in our clinical studies if we encounter difficulties in enrollment.

Each of the conditions for which we plan to evaluate our current product candidates is a rare genetic disease. Accordingly, there are limited patient pools from which to draw for clinical studies. For our current product candidates:

- we estimate that several thousand patients in the United States suffer from XLH, for which KRN23 is being studied;
- we estimate that several hundred patients in the United States suffer from TIO, for which KRN23 is being studied;
- we estimate that up to approximately 200 patients in the developed world may suffer from MPS 7, for which rhGUS is being studied;
- we estimate that several thousand patients in the United States suffer from LC-FAOD, for which UX007 is being studied;

- we estimate that several thousand patients in the United States suffer from Glut1 DS, for which UX007 is being studied; and
- we estimate that approximately 2,000 patients in the developed world suffer from GNE myopathy, for which Ace-ER is being studied.

In addition to the rarity of these diseases, the eligibility criteria of our clinical studies will further limit the pool of available study participants as we will require that patients have specific characteristics that we can measure or to assure their disease is either severe enough or not too advanced to include them in a study. For example, the UX007 Glut1 DS Phase 2 study requires a certain minimum baseline rate of generalized tonic-clonic seizures or the presence of absence seizures at baseline. Additionally, the process of finding and diagnosing patients may prove costly. We also may not be able to identify, recruit, and enroll a sufficient number of patients to complete our clinical studies because of the perceived risks and benefits of the product candidate under study, the proximity and availability of clinical study sites for prospective patients, and the patient referral practices of physicians. The availability and efficacy of competing therapies and clinical studies can also adversely impact enrollment. For example, our Phase 2 UX007 Glut1 DS study is enrolling patients who are not currently on or compliant with the ketogenic diet. However, the ketogenic diet is the standard of care and considered effective in seizure control. If patients are unwilling to participate in our studies for any reason, the timeline for recruiting patients, conducting studies, and obtaining regulatory approval of potential products may be delayed, the commercial prospects of our product candidates will be harmed, and our ability to generate product revenue from any of these product candidates could be delayed or prevented. In addition, any delays in completing our clinical studies will increase our costs, slow down our product candidate development and approval process, and jeopardize our ability to commence product sales and generate revenue. 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 studies may also ultimately lead to the denial of regulatory approval of our product candidates.

If we do not achieve our projected development goals in the timeframes we announce and expect, the commercialization of our products may be delayed and the credibility of our management may be adversely affected and, as a result, our stock price may decline.

For planning purposes, we estimate the timing of the accomplishment of various scientific, clinical, regulatory and other product development goals, which we sometimes refer to as milestones. These milestones may include the commencement or completion of scientific studies and clinical trials, the submission of regulatory filings, and the potential approval of such regulatory filings. We periodically make public announcements about the expected timing of some of these milestones. All of these milestones are based on a variety of assumptions, but the actual timing of these milestones can vary dramatically compared to our estimates, in many cases for reasons beyond our control. If we do not meet these milestones as publicly announced, the commercialization of our products may be delayed and the credibility of our management may be adversely affected and, as a result, our stock price may decline.

Our product candidates may cause undesirable side effects or have other properties that could delay or prevent their regulatory approval, limit the commercial profile of an approved label, or result in significant negative consequences following marketing approval, if any.

Undesirable side effects caused by our product candidates could cause us or regulatory authorities to interrupt, delay, or halt clinical studies or further development, and could result in a more restrictive label or the delay or denial of regulatory approval by the FDA or other comparable foreign authorities. Some of our product candidates are in the early stages of development and the safety profile has not been established. For example, in the completed Phase 1 study, four-month Phase 1/2 study, and long-term twelve-month Phase 1/2 study, adult patients treated with KRN23 have experienced drug-related side effects including injection site reaction, arthralgia, diarrhea, restless legs syndrome, injection site erythema, injection site pain, upper abdominal pain, headache, and decreased neutrophil count. Most of these adverse events were mild and no treatment-related serious adverse events have been observed. In interim Phase 2 data in pediatric patients, the most common treatment related adverse event by preferred term was injection site reaction. There were no deaths and there was one serious adverse event of fever and muscle pain in a patient that was considered possibly treatment related. Patients treated with triheptanoin have experienced drug-related side effects such as cramping, diarrhea, and loose stools. In addition, over 14 years of treatment experience in approximately 130 human subjects, including greater than 60 with LC-FAOD, we are aware of three serious adverse events that were classified as possibly related to triheptanoin treatment (muscle cell rupture and elevated creatine kinase reported for two subjects and myoglobinuria in one subject); however, these serious adverse events can be considered typical of the underlying disease. In interim data from our Phase 2 study there were no deaths but there was one treatment related serious adverse event of moderate gastroenteritis with vomiting. The most common treatment-related adverse events were diarrhea, abdominal/gastrointestinal pain, and vomiting. While we have not completed our own clinical studies for UX007, there may be other side effects associated with its use that we discover. Additionally, patients treated with Ace-ER have experienced drug-related side effects including mild gastrointestinal discomfort. Enzyme replacement therapies have been associated with infusion-associated reactions due to a developing allergy to the product, which can cause rashes, pain, significant clinical disease, or even death. Our rhGUS and rhPPCA product candidates may also cause these or similar side effects as further development proceeds. Results of our studies or investigator-sponsored trials could reveal a high and unacceptable severity and prevalence of these or other side effects. In such an event, our studies could be suspended or terminated, and the FDA or comparable foreign regulatory authorities could order us to cease further development of or deny or withdraw approval of our product candidates for any or all targeted indications.

Drug-related side effects could affect patient recruitment and the ability of enrolled patients to complete the study. Such side effects could also result in potential product liability claims. We currently carry product liability insurance in the amount of $10.0 million per incident and $10.0 million in the aggregate, and we are required to maintain product liability insurance pursuant to certain of our agreements. We believe our product liability insurance coverage is sufficient in light of our current clinical programs; however, we may not be able to maintain insurance coverage at a reasonable cost or in sufficient amounts to protect us against losses due to liability, or losses may exceed the amount of insurance that we carry. A product liability claim or series of claims brought against us could cause our stock price to decline and, if judgments exceed our insurance coverage, could adversely affect our results of operations and business. In addition, regardless of merit or eventual outcome, product liability claims may result in impairment of our business reputation, withdrawal of clinical study participants, costs due to related litigation, distraction of management’s attention from our primary business, initiation of investigations by regulators, substantial monetary awards to patients or other claimants, the inability to commercialize our product candidates, and decreased demand for our product candidates, if approved for commercial sale.

Additionally, if one or more of our product candidates receives marketing approval, and we or others later identify undesirable side effects caused by such products, a number of potentially significant negative consequences could result, including but not limited to:

- regulatory authorities may withdraw approvals of such product;

- regulatory authorities may require additional warnings on the product's label or restrict the product's approved use;
- we may be required to create a Risk Evaluation and Mitigation Strategy, or REMS, plan, which could include a medication guide outlining the risks of such side effects for distribution to patients, restricted distribution, a communication plan for healthcare providers, and/or other elements to assure safe use;
- we could be sued and held liable for harm caused to patients;
- patients and physicians may elect not to use our products, or reimbursement authorities may elect not to reimburse for them; and
- our reputation may suffer.

Any of these events could prevent us from achieving or maintaining market acceptance of the particular product candidate, if approved, and could significantly harm our business, results of operations, and prospects.

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

If our product candidates are approved, they will be subject to ongoing regulatory requirements for manufacturing, labeling, packaging, storage, distribution, advertising, promotion, sampling, record-keeping, conduct of post-marketing studies, and submission of safety, efficacy, and other post-market information, including both federal and state requirements in the United States and requirements of comparable foreign regulatory authorities.

Manufacturers and manufacturers' facilities are required to comply with extensive FDA, and comparable foreign regulatory authority, requirements, including ensuring that quality control and manufacturing procedures conform to Good Manufacturing Practices (GMP) regulations. As such, we and our contract manufacturers will be subject to continual review and inspection to assess compliance with GMP and adherence to commitments made in any NDA, BLA, MAA, or other comparable application for approval in another jurisdiction. Accordingly, we and others with whom we work must continue to expend time, money, and effort in all areas of regulatory compliance, including manufacturing, production, and quality control.

Any regulatory approvals that we receive for our product candidates may be subject to limitations on the approved indicated uses for which the product may be marketed or other conditions of approval, or contain requirements for potentially costly post-marketing testing, including Phase IV clinical studies, and surveillance to monitor the safety and efficacy of the product candidate. We could also be asked to conduct post-marketing clinical studies to verify the safety and efficacy of our products in general or in specific patient subsets. If original marketing approval were obtained via the accelerated approval or conditional marketing authorization pathways, we would be required to conduct a successful post-marketing clinical study to confirm clinical benefit for our products. An unsuccessful post-marketing study or failure to complete such a study could result in the withdrawal of marketing approval. We will be required to report certain adverse events and manufacturing problems, if any, to the FDA and comparable foreign regulatory authorities. Any new legislation addressing drug safety issues could result in delays in product development or commercialization, or increased costs to assure compliance. We will have to comply with requirements concerning advertising and promotion for our products. Promotional communications with respect to prescription drugs are subject to a variety of legal and regulatory restrictions and must be consistent with the information in the product's approved label. As such, we may not promote our products for indications or uses for which they do not have approval. The holder of an approved NDA, BLA, MAA, or other comparable application must submit new or supplemental applications and obtain approval for certain changes to the approved product, product labeling, or manufacturing process.

If we fail to comply with applicable regulatory requirements, or there are safety or efficacy problems with a product, a regulatory agency or enforcement authority may, among other things:

- issue warning or notice of violation letters;
- impose civil or criminal penalties;
- suspend or withdraw regulatory approval;
- suspend any of our ongoing clinical studies;
- refuse to approve pending applications or supplements to approved applications submitted by us;
- impose restrictions on our operations, including closing our contract manufacturers' facilities;
- seize or detain products, or require a product recall; or
- require entry into a consent decree.

Any government investigation of alleged violations of law could require us to expend significant time and resources in response, and could generate negative publicity. Any failure to comply with ongoing regulatory requirements may significantly and adversely affect our ability to commercialize and generate revenue from our products. If regulatory sanctions are applied or if regulatory approval is withdrawn, the value of our company and our operating results will be adversely affected.

Changes in methods of treatment of disease could reduce demand for our products and adversely affect revenues.

Even if our drug products are approved, if doctors elect a course of treatment which does not include our drug products, this decision would reduce demand for our drug products and adversely affect revenues. Changes in treatment method can be caused by the introduction of other companies' products or the development of new technologies or surgical procedures which may not directly compete with ours, but which have the effect of changing how doctors decide to treat a disease.

Risks Related to our Reliance on Third Parties

We rely on third parties to conduct our nonclinical and clinical studies and perform other tasks for us. If these third parties do not successfully carry out their contractual duties, meet expected deadlines, or comply with regulatory requirements, we may be exposed to sub-optimal quality and reputational harm, we may not be able to obtain regulatory approval for or commercialize our product candidates, and our business could be substantially harmed.

We have relied upon and plan to continue to rely upon third parties, including CROs and collaborative partners, to analyze, collect, monitor, and manage data for our ongoing nonclinical and clinical programs. We rely on third parties for execution of our nonclinical and clinical studies, and for estimates regarding costs and efforts completed, and we control only certain aspects of their activities. For example, we will rely on our partner Arcturus for the design and optimization of initial product candidates under our messenger RNA collaboration. Nevertheless, we are responsible for ensuring that each of our studies is conducted in accordance with the applicable protocol, legal, regulatory, and scientific standards, and our reliance on the CROs and other third parties does not relieve us of our regulatory responsibilities. We and our CROs and other vendors and partners are required to comply with GMP, Good Clinical Practices (GCP), and Good Laboratory Practices (GLP), which are regulations and guidelines enforced by the FDA, the Competent Authorities of the Member States of the European Economic Area, and comparable foreign regulatory authorities for all of our product candidates in development. Regulatory authorities enforce these regulations through periodic inspections of study sponsors, principal investigators, study sites, and other contractors. If we or any of our CROs or other vendors and partners, including the sites at which clinical studies are conducted, fail to comply with applicable regulations, the data generated in our nonclinical and clinical studies may be deemed unreliable and the FDA, EMA, or comparable foreign regulatory authorities may deny approval and/or require us to perform additional nonclinical and clinical studies before approving our marketing applications, which would delay the approval process. We cannot make assurances that upon inspection by a given regulatory authority, such regulatory authority will determine that any of our clinical studies comply with GCP regulations or that nonclinical studies comply with GLP regulations. In addition, our clinical studies must be conducted with products produced under GMP regulations. If the regulatory authorities determine that we have failed to comply with GLP, GMP, or GCP regulations, they may deny approval of our product candidates and/or we may be required to repeat clinical or nonclinical studies, which would delay the regulatory approval process.

Our CROs and other vendors and partners are not our employees, and except for remedies available to us under our agreements with such third parties, we cannot control whether or not they devote sufficient time and resources to our on-going nonclinical and clinical programs. If our vendors and partners do not successfully carry out their contractual duties or obligations or meet expected deadlines, if they need to be replaced, or if the quality or accuracy of the data they obtain is compromised due to the failure to adhere to our protocols, regulatory requirements, or for other reasons, our clinical studies may be extended, delayed, or terminated, and we may not be able to obtain regulatory approval for or successfully commercialize our product candidates. CROs and other vendors and partners may also generate higher costs than anticipated as a result of changes in scope of work or otherwise. As a result, our results of operations and the commercial prospects for our product candidates would be harmed, our costs could increase, and our ability to generate revenue could be delayed.

If any of our relationships with these third parties terminate, we may not be able to enter into arrangements with alternative vendors or do so on commercially reasonable terms. Switching or adding additional vendors involves additional cost and requires management time and focus. In addition, there is a natural transition period when a new vendor commences work. As a result, delays may occur, which can materially impact our ability to meet our desired clinical development timelines. Though we carefully manage our relationships with our vendors and partners, there can be no assurance that we will not encounter similar challenges or delays in the future or that these delays or challenges will not have a material adverse impact on our business, financial condition, and business prospects.

We also rely on third parties in other ways, including to support our patient identification efforts, to assist our finance and legal departments, and to provide other resources for our business. Use of these third parties could expose us to

sub-optimal quality, missed deadlines, and non-compliance with applicable laws, all of which could result in reputational harm to us and negatively affect our business.

We are dependent on KHK for the clinical and commercial supply of KRN23 for all major markets and for the development and commercialization of KRN23 in certain major markets, and KHK's failure to provide an adequate supply of KRN23 or to commercialize KRN23 in those markets could result in a material adverse effect on our business and operating results.

Under our agreement with KHK, KHK has the sole right to commercialize KRN23 in Europe and, at a specified time, in the United States and Canada subject to a limited promotion right we retained. Our development partnership with KHK may not be successful, and we may not realize the expected benefits from such partnership, due to a number of important factors, including but not limited to the following:

- KHK has no obligation under our agreement to use diligent efforts to commercialize KRN23 in Europe. The timing and amount of any royalty payments we may receive under our agreement will depend on, among other things, the efforts, allocation of resources, and successful commercialization of KRN23 by KHK in Europe. Additionally, if KHK were to decide not to commercialize KRN23 in Europe, and we nevertheless wished to commercialize KRN23 in Europe, we would need to renegotiate with KHK certain terms of our agreement, which we may be unable to do on reasonable terms in a timely manner, or at all;
- the timing and amount of any royalty payments we may receive under our agreement with KHK will depend on, among other things, the efforts, allocation of resources, and successful commercialization of KRN23 by KHK in the United States and Canada under our agreement;
- KHK may change the focus of its commercialization efforts or pursue higher-priority programs;
- KHK may fail to manufacture or supply sufficient drug product of KRN23 in compliance with applicable laws and regulations or otherwise for our development and clinical use, which could result in program delays;
- KHK may fail to manufacture or supply sufficient drug product of KRN23 in compliance with applicable laws and regulations or otherwise for our commercial use, if approved, which could result in lost revenue;
- KHK may elect to develop and commercialize KRN23 indications with a larger market than XLH and at a lower price, thereby reducing the profit margin on sales of KRN23 for any orphan indications, including XLH;
- if KHK were to breach or terminate the agreement with us, we would no longer have any rights to develop or commercialize KRN23 or such rights would be limited to non-terminated countries;
- KHK may terminate its agreement with us, adversely affecting our potential revenue from licensed products; and
- the timing and amounts of expense reimbursement that we may receive are uncertain, and the total expenses for which we are obligated to reimburse KHK may be greater than anticipated.

We rely completely on third parties to manufacture our product candidates. Our business could be harmed if those third parties fail to provide us with sufficient quantities of drug product, or fail to do so at acceptable quality levels or prices.

We do not currently have, nor do we plan to acquire, the infrastructure or capability internally to manufacture our product candidates, and we lack the resources and the capability to manufacture any of our product candidates on a clinical or commercial scale. We rely on our manufacturers to purchase from third-party suppliers the materials necessary to produce our product candidates for our clinical studies. There are a limited number of suppliers for raw materials that we use to manufacture our drugs, placebos, or active controls, and there may be a need to identify alternate suppliers to prevent a possible disruption of the manufacture of the materials necessary to produce our product candidates for our clinical studies, and, if approved, ultimately for commercial sale. We do not have any control over the process or timing of the acquisition of these raw materials by our manufacturers. Although we generally do not begin a clinical study unless we believe we have a sufficient supply of a product candidate to complete such study, any significant delay or discontinuity in the supply of a product candidate, or the raw material components thereof, for an ongoing clinical study due to, among other things, the failure of a manufacturer to provide drug substance or drug product of sufficient quantity or quality, or the need to replace a third-party manufacturer could considerably delay completion of our clinical studies, product testing, and potential regulatory approval of our product candidates, and could also impair named patient sale supply of our product candidates, which could harm our business and results of operations.

34

We are subject to a multitude of manufacturing risks, any of which could substantially increase our costs and limit supply of our product candidates.

The process of manufacturing our product candidates is complex, highly regulated, and subject to several risks, including but not limited to:

- the process of manufacturing our product candidates is extremely susceptible to product loss due to contamination, equipment failure or improper installation or operation of equipment, or vendor or operator error. Even minor deviations from normal manufacturing processes for any of our product candidates could result in reduced production yields, product defects, and other supply disruptions. If microbial, viral, or other contaminations are discovered in our product candidates or in the manufacturing facilities in which our product candidates are made, such manufacturing facilities may need to be closed for an extended period of time to investigate and remedy the contamination; and
- the manufacturing facilities in which our product candidates are made could be adversely affected by equipment failures, labor shortages, raw material shortages, natural disasters, power failures, and numerous other factors.

Any adverse developments affecting manufacturing operations for our product candidates may result in shipment delays, inventory shortages, lot failures, withdrawals or recalls, or other interruptions in the supply of our product candidates. Due to their stage of development, small volume requirements, and infrequency of batch production runs, we carry limited amounts of safety stock for our product candidates. We may also have to take inventory write-offs and incur other charges and expenses for product candidates that fail to meet specifications, undertake costly remediation efforts, or seek more costly manufacturing alternatives.

The drug substance and drug product for most of our product candidates are currently acquired from single-source suppliers. The loss of these suppliers, or their failure to supply us with the necessary drug substance or drug product, could materially and adversely affect our business.

The drug substance and drug product for KRN23 are made by KHK pursuant to our license and collaboration agreement with KHK. The drug substance and drug product for rhGUS are manufactured by Rentschler Biotechnologie GmbH under a development and clinical supply agreement and accompanying purchase orders. The pharmaceutical-grade drug substance for UX007 is manufactured by Cremer Oleo GmbH & Co. KG, or Cremer, pursuant to our supply agreement with Cremer, and the drug product for UX007 is prepared by Haupt Pharma AG and CPM pursuant to purchase orders. The drug substance for Ace-ER is manufactured by Sanyo Fine Co., Ltd. under our license agreement and accompanying purchase orders with Nobelpharma Co., Ltd. and under our clinical supply agreement with Evonik Corporation, and the drug product for Ace-ER is manufactured by Alcami Corporation, or Alcami (formerly known as AAIPharma Services Corp., or AAIPharma), pursuant to our license agreement and accompanying purchase orders with Alcami. We have not currently secured any other suppliers for the drug substance or drug product of our product candidates and, although we believe that there are alternate sources of supply that could satisfy our clinical and commercial requirements, we cannot provide assurance that identifying alternate sources and establishing relationships with such sources would not result in significant delay in the development of our product candidates. Additionally, we may not be able to enter into supply arrangements with alternative suppliers on commercially reasonable terms or at all. A delay in the development of our product candidates or having to enter into a new agreement with a different third-party on less favorable terms than we have with our current suppliers could have a material adverse impact upon on our business.

We and our collaborators and contract manufacturers are subject to significant regulation with respect to manufacturing our product candidates. The manufacturing facilities on which we rely may not continue to meet regulatory requirements or may not be able to meet supply demands.

All entities involved in the preparation of therapeutics for clinical studies or commercial sale, including our existing contract manufacturers for our product candidates, are subject to extensive regulation. Components of a finished therapeutic product approved for commercial sale or used in clinical studies must be manufactured in accordance with GMP. These regulations govern manufacturing processes and procedures (including record keeping) and the implementation and operation of quality systems to control and assure the quality of investigational products and products approved for sale. Poor control of production processes can lead to the introduction of contaminants or to inadvertent changes in the properties or stability of our product candidates that may not be detectable in final product testing. We, our collaborators, or our contract manufacturers must supply all necessary documentation in support of an NDA, BLA, MAA, or other application for regulatory approval, on a timely basis and must adhere to GLP, GMP, and similar regulations enforced by the FDA and other regulatory agencies through their facilities inspection programs. Some of our contract manufacturers have never produced a commercially approved pharmaceutical product and therefore have not obtained the requisite regulatory authority approvals to do so. The facilities and quality systems of some or all of our collaborators and third-party contractors must pass a pre-approval inspection for compliance with the applicable regulations as a condition of regulatory approval of our product candidates or any of our other potential products. In addition, the regulatory authorities may, at any time, audit or inspect a manufacturing facility involved with the preparation of our product candidates or our other potential products or the associated quality systems for compliance with the regulations applicable to the activities being conducted. Although we oversee the contract manufacturers, we cannot control the manufacturing process of, and are substantially dependent on, our contract manufacturing partners for compliance with the regulatory requirements. If these facilities do not pass a pre-approval plant inspection, regulatory approval of the products may not be granted or may be substantially delayed until any violations are corrected to the satisfaction of the regulatory authority, if ever.

The regulatory authorities also may, at any time following approval of a product for sale, audit the manufacturing facilities of our collaborators and third-party contractors. If any such inspection or audit identifies a failure to comply with applicable regulations or if a violation of our product specifications or applicable regulations occurs independent of such an inspection or audit, we or the relevant regulatory authority may require remedial measures that may be costly and/or time consuming for us or a third-party to implement, and that may include the temporary or permanent suspension of a clinical study or commercial sales or the temporary or permanent closure of a facility. Any such remedial measures imposed upon us or third parties with whom we contract could materially harm our business.

If we, our collaborators, or any of our third-party manufacturers fail to maintain regulatory compliance, the FDA or other applicable regulatory authority can impose regulatory sanctions including, among other things, refusal to approve a pending application for a new drug product or biologic product, withdrawal of an approval, or suspension of production. As a result, our business, financial condition, and results of operations may be materially harmed.

Additionally, if supply from one approved manufacturer is interrupted, an alternative manufacturer would need to be qualified through an NDA or BLA supplement or MAA variation, or equivalent foreign regulatory filing, which could result in further delay. The regulatory agencies may also require additional studies if a new manufacturer is relied upon for commercial production. Switching manufacturers may involve substantial costs and is likely to result in a delay in our desired clinical and commercial timelines.

These factors could cause us to incur higher costs and could cause the delay or termination of clinical studies, regulatory submissions, required approvals, or commercialization of our product candidates. Furthermore, if our suppliers fail to meet contractual requirements and we are unable to secure one or more replacement suppliers capable of production at a substantially equivalent cost, our clinical studies may be delayed or we could lose potential revenue.

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

Because we rely on third parties to develop and manufacture our product candidates, we must, at times, share trade secrets with them. We seek to protect our proprietary technology in part by entering into confidentiality agreements and, if applicable, material transfer agreements, collaborative research agreements, consulting agreements, letters of engagement, or other similar agreements with our collaborators, advisors, employees, and consultants prior to beginning research or disclosing proprietary information. These agreements typically limit the rights of the third parties to use or disclose our confidential information, such as trade secrets. Despite the contractual provisions employed when working with third parties, the need to share trade secrets and other confidential information increases the risk that such trade secrets become known by our competitors, are inadvertently incorporated into the technology of others, or are disclosed or used in violation of these agreements. Given that our proprietary position is based, in part, on our know-how and trade secrets, a competitor’s discovery of our trade secrets or other unauthorized use or disclosure would impair our competitive position and may have a material adverse effect on our business.

Risks Related to Commercialization of Our Product Candidates

If the market opportunities for our product candidates are smaller than we believe they are, our revenue may be adversely affected, and our business may suffer. Because the target patient populations of our product candidates are small, and the addressable patient population potentially even smaller, we must be able to successfully identify patients and acquire a significant market share to achieve profitability and growth.

We focus our research and product development on treatments for rare and ultra-rare genetic diseases. Given the small number of patients who have the diseases that we are targeting, it is critical to our ability to grow and become profitable that we continue to successfully identify patients with these rare and ultra-rare genetic diseases. Some of our current clinical programs may be most appropriate for patients with more severe forms of their disease. For instance, our Phase 2 study of UX007 in LC-FAOD enrolled patients with more severe disease. In addition, while adults make up the majority of the XLH patients, they often have less severe disease which may reduce the penetration of KRN23 in the adult population relative to the pediatric population. Given the overall rarity of the diseases we target, it is difficult to project the prevalence of the more severe forms, or the other subsets of patients that may be most suitable to address with our product candidates, which may further limit the addressable patient population to a small subset. 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 our beliefs and estimates. These estimates have been derived from a variety of sources, including the scientific literature, surveys of clinics, patient foundations, or market research, and may prove to be incorrect. Further, new studies may change the estimated incidence or prevalence of these diseases. The number of patients may turn out to be lower than expected. The effort to identify patients with diseases we seek to treat is in early stages, and we cannot accurately predict the number of patients for whom treatment might be possible. Additionally, the potentially addressable patient population for each of our product candidates may be limited or may not be amenable to treatment with our product candidates, and new patients may become increasingly difficult to identify or gain access to, which would adversely affect our results of operations and our business. Further, even if we obtain significant market share for our product candidates, because the potential target populations are very small we may never become or remain profitable nor generate sufficient revenue growth to sustain our business.

We intend to rely on third-party manufacturers to produce our product candidates, but we have not entered into binding agreements with any such manufacturers to support commercialization. Additionally, these manufacturers do not have experience producing our product candidates at commercial levels and may not achieve the necessary regulatory approvals or produce our product candidates at the cost, quality, quantities, locations, and timing needed to support profitable commercialization.

We have not yet secured manufacturing capabilities for commercial quantities of our product candidates. Although we intend to rely on third-party manufacturers for commercialization, we have only entered into agreements with such manufacturers to support our clinical studies. We may be unable to negotiate binding agreements with the manufacturers to support our commercialization activities on commercially reasonable terms.

Manufacturers may not have the experience or ability to produce our product candidates at commercial levels. We may run into technical or scientific issues related to manufacturing or development that we may be unable to resolve in a timely manner or with available funds. We also have not completed all of the characterization and validation activities necessary for commercialization and regulatory approvals. If our manufacturing partners are not able to conduct all such necessary activities in accordance with applicable regulations, our commercialization efforts will be harmed.

Even if our third-party product manufacturers develop an acceptable manufacturing process, if such third-party manufacturers are unable to produce the necessary quantities of our product candidates, are unable to comply with GMP or other pertinent regulatory requirements, or are unable to produce our product candidates within our planned timeframe and cost parameters, the development and sales of our products, if approved, may be materially harmed.

Additionally, the cost to us for the supply of our product candidates manufactured by such third parties may be high and could limit our profitability, even if our third-party product manufacturers develop acceptable manufacturing processes that provide the necessary quantities of our product candidates in a compliant and timely manner. Furthermore, KHK is our sole supplier of commercial quantities of KRN23. The supply price to us for commercial sales of KRN23, which will be determined on a fixed double-digit percentage of net sales, will be higher than the typical cost of goods sold by companies focused on rare diseases.

We face intense competition and rapid technological change and the possibility that our competitors may develop therapies that are similar, more advanced, or more effective than ours, which may adversely affect our financial condition and our ability to successfully commercialize our product candidates.

The biotechnology and pharmaceutical industries are intensely competitive and subject to rapid and significant technological change. We are currently aware of various existing therapies that may compete with our product candidates. For example, XLH is currently treated with oral phosphate and Vitamin D therapy, which may compete with KRN23. Furthermore, B. Braun Medical Inc., or B. Braun, has received orphan drug designation for triheptanoin in Europe for certain LC-FAOD indications and we do not know if B. Braun is planning to initiate clinical development. Triheptanoin is also available in food-grade form, which may compete with our pharmaceutical-grade product. Investigator-sponsored trials evaluating triheptanoin in multiple indications are ongoing. LC-FAOD is currently treated with diet therapy and medium-chain triglyceride oil, which may compete with UX007. Glut1 DS is currently treated primarily with the ketogenic diet and anti-epileptic drugs, which may also compete with UX007. Additionally, we are aware of a

program at the National Institutes of Health that is investigating the use of another metabolite in the sialic acid pathway, ManNAc, for the treatment of GNE myopathy, which could compete with Ace-ER. The intellectual property rights for ManNAc are licensed to Escala Therapeutics, a subsidiary of Fortress Biotech, Inc., which acquired the rights from a company in New Zealand that manufactures ManNAc. Escala has received orphan designation for ManNAc in the United States and Europe for GNEM. ManNAc may have a potential advantage over Ace-ER in that it is not a charged molecule like sialic acid, which might improve ManNac's distribution and uptake. ManNac is also available for purchase from chemical supply and other companies, which may compete with Ace-ER. Gene therapy, gene correction, RNA-based therapies, and other approaches may also emerge for the treatment of any of the disease areas in which we focus.

We have competitors both in the United States and internationally, including major multinational pharmaceutical companies, specialty pharmaceutical companies, and biotechnology companies. Some of the pharmaceutical and biotechnology companies we expect to compete with include Shire, Sanofi, BioMarin, Alexion, and Roche, as well as other companies ranging from startups to large multinational companies. Many of our competitors have substantially greater financial, technical, and other resources, such as larger research and development staff and experienced marketing and manufacturing organizations. Additional mergers and acquisitions in the biotechnology and pharmaceutical industries may result in even more resources being concentrated in our competitors. As a result, these companies may obtain regulatory approval more rapidly than we are able to and may be more effective in selling and marketing their products as well. Smaller or early-stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large, established companies. Competition may increase further as a result of advances in the commercial applicability of technologies and greater availability of capital for investment in these industries. Our competitors may succeed in developing, acquiring, or licensing on an exclusive basis, products that are more effective or less costly than any product candidate that we may develop, or achieve earlier patent protection, regulatory approval, product commercialization, and market penetration than we do. Additionally, technologies developed by our competitors may render our potential product candidates uneconomical or obsolete, and we may not be successful in marketing our product candidates against competitors.

We are currently building an integrated commercial organization. If we are unable to establish sufficient field forces and marketing capabilities or enter into agreements with third parties to market and sell our product candidates, we may be unable to generate any revenue.

Although our employees may have sold other similar products in the past while employed at other companies, we as a company have no experience selling and marketing our product candidates and we currently have minimal marketing and field force capacity. To successfully commercialize any products that may result from our development programs, we will need to develop these capabilities, either on our own or with others. If our product candidates receive regulatory approval, we intend to establish a marketing organization and field forces with technical expertise as well as supporting distribution capabilities to commercialize our product candidates in major markets, which will be expensive, difficult, and time consuming. Any failure or delay in the development of our internal field forces, marketing, and distribution capabilities would adversely impact the commercialization of our products.

Further, given our lack of prior experience in marketing and selling biopharmaceutical products, our initial estimate of the size of the required field force may be materially more or less than the size of the field force actually required to effectively commercialize our product candidates. As such, we may be required to hire large teams to adequately support the commercialization of our product candidates or we may incur excess costs as a result of hiring more commercial personnel than necessary. With respect to certain geographical markets, we may enter into collaborations with other entities to utilize their local marketing and distribution capabilities, but we may be unable to enter into such agreements on favorable terms, if at all. If our future collaborators do not commit sufficient resources to commercialize our future products, if any, and we are unable to develop the necessary marketing capabilities on our own, we will be unable to generate sufficient product revenue to sustain our business. We may be competing with companies that currently have extensive and well-funded marketing and sales operations. Without an internal team or the support of a third-party to perform key commercial functions, we may be unable to compete successfully against

these more established companies.

The commercial success of any current or future product candidate will depend upon the degree of market acceptance by physicians, patients, third-party payors, and others in the medical community.

Even with the requisite approvals from the FDA and comparable foreign regulatory authorities, the commercial success of our product candidates will depend in part on the medical community, patients, and payors accepting our product candidates as medically useful, cost-effective, and safe. Any product that we bring to the market may not gain market acceptance by physicians, patients, payors, and others in the medical community. The degree of market acceptance of any of our product candidates, if approved for commercial sale, will depend on a number of factors, including:

- the efficacy of the product as demonstrated in clinical studies and potential advantages over competing treatments;
- the prevalence and severity of any side effects, including any limitations or warnings contained in a product's approved labeling;