Ultragenyx Pharmaceutical Inc.
Form S-1/A
January 17, 2014
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As filed with the Securities and Exchange Commission on January 17, 2014.

Registration No. 333-192244

UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

Amendment No. 2

to

FORM S-1

REGISTRATION STATEMENT UNDER THE SECURITIES ACT OF 1933

ULTRAGENYX PHARMACEUTICAL INC.

(Exact name of Registrant as specified in its charter)

Delaware	**2834**	**27-2546083**
(State or other jurisdiction of	*(Primary Standard Industrial*	*(I.R.S. Employer*

incorporation or organization) *Classification Code Number)* *Identification Number)*

60 Leveroni Court

Novato, CA 94949

(415) 483-8800

(Address, including zip code, and telephone number, including area code, of Registrant s principal executive offices)

Emil D. Kakkis, M.D., Ph.D.

President and Chief Executive Officer

Ultragenyx Pharmaceutical Inc.

60 Leveroni Court

Novato, CA 94949

(415) 483-8800

(Name, address, including zip code, and telephone number, including area code, of agent for service)

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Approximate date of commencement of proposed sale to the public:

As soon as practicable after the effective date of this Registration Statement.

If any of the securities being registered on this Form are to be offered on a delayed or continuous basis pursuant to Rule 415 under the Securities Act of 1933, check the following box. ¨

If this Form is filed to register additional securities for an offering pursuant to Rule 462(b) under the Securities Act, please check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering. ¨

If this Form is a post-effective amendment filed pursuant to Rule 462(c) under the Securities Act, check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering. ¨

If this Form is a post-effective amendment filed pursuant to Rule 462(d) under the Securities Act, check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering. ¨

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.

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

CALCULATION OF REGISTRATION FEE

Title of each class of securities to be registered	**Amount to be Registered[1]**	**Proposed maximum aggregate offering price per share[2]**	**Proposed maximum aggregate offering price[2]**	**Amount of registration fee[3]**
Common Stock, $0.001 par value per share	5,564,516	$ 17.00	$ 94,596,772	$ 12,185

(1) Includes shares that the underwriters have the option to purchase to cover overallotments, if any.
(2) Estimated solely for the purpose of calculating the amount of the registration fee in accordance with Rule 457(a) under the Securities Act of 1933, as amended.
(3) Registration fees totaling $11,109 were previously paid in connection with the initial filing of this registration statement. The amount paid in connection with this filing for the aggregate registration fee of $12,185, which includes $11,109 previously paid and $1,076 for the additional amount of $8,346,772 of securities included in this amendment to the registration statement, is offset by the $11,109 previously paid.

The Registrant hereby amends this Registration Statement on such date or dates as may be necessary to delay its effective date until the Registrant shall file a further amendment which specifically states that this Registration Statement shall thereafter become effective in accordance with Section 8(a) of the Securities Act of 1933 or until the Registration Statement shall become effective on such date as the Commission, acting pursuant to said Section 8(a), may determine.

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The information in this preliminary prospectus is not complete and may be changed. We may not sell these securities until the registration statement filed with the Securities and Exchange Commission is effective. This prospectus is not an offer to sell these securities, and it is not soliciting an offer to buy these securities in any jurisdiction where the offer or sale is not permitted.

Subject to completion, dated January 17, 2014

Prospectus

4,838,710 shares

Common Stock

This is an initial public offering of common stock by Ultragenyx Pharmaceutical Inc. We are selling 4,838,710 shares of common stock. The initial public offering price is between $14.00 and $17.00 per share.

Prior to this offering, there has been no public market for our common stock. We have applied for listing of our common stock on The NASDAQ Global Market under the symbol RARE .

We are an emerging growth company under applicable Securities and Exchange Commission rules and will be subject to reduced public company reporting requirements.

	Per share	Total
Initial public offering price	$	$
Underwriting discounts and commissions[(1)]	$	$
Proceeds to Ultragenyx Pharmaceutical Inc., before expenses	$	$

(1) See Underwriting for additional disclosure regarding underwriting discounts, commissions and estimated offering expenses.
We have granted the underwriters an option for a period of 30 days to purchase up to 725,806 additional shares of common stock.

Investing in our common stock involves a high degree of risk. See Risk Factors beginning on page 10.

Neither the Securities and Exchange Commission nor any state securities commission has approved or disapproved of these securities or passed on the adequacy or accuracy of this prospectus. Any representation to the contrary is a criminal offense.

The underwriters expect to deliver the shares of common stock to investors on or about , 2014.

J.P. Morgan **Morgan Stanley**

Cowen and Company

Canaccord Genuity

, 2014

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We have not authorized anyone to provide you with information other than that contained in this prospectus or in any free writing prospectus prepared by or on behalf of us or to which we have referred you. We take no responsibility for, and can provide no assurance as to the reliability of, any other information that others may give to you. We are offering to sell, and seeking offers to buy, shares of our common stock only in jurisdictions where offers and sales are permitted. The information contained in this prospectus is accurate only as of the date of this prospectus, regardless of the time of delivery of this prospectus or any sale of our common stock. Our business, financial condition, results of operations, and prospects may have changed since that date.

No action is being taken in any jurisdiction outside the United States to permit a public offering of our common stock or possession or distribution of this prospectus in that jurisdiction. Persons who come into possession of this prospectus in jurisdictions outside the United States are required to inform themselves about and to observe any restrictions as to this offering and the distribution of this prospectus applicable to that jurisdiction.

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PROSPECTUS SUMMARY

The items in the following summary are described in more detail later in this prospectus. This summary provides an overview of selected information and does not contain all of the information you should consider before buying our common stock. Therefore, you should read the entire prospectus carefully, especially the Risk Factors section beginning on page 10 and our financial statements and the related notes appearing at the end of this prospectus, before deciding to invest in our common stock. In this prospectus, unless the context otherwise requires, references to the Company, we, us, our, or Ultragenyx refer to Ultragenyx Pharmaceutical Inc.

Overview

We are a development-stage biopharmaceutical company focused on the identification, acquisition, development, and commercialization of novel products for the treatment of rare and ultra-rare diseases, with an initial focus on serious, debilitating metabolic genetic diseases. We focus on diseases for which the unmet medical need is high, the biology for treatment is clear, and for which there are no approved therapies. Since our inception in 2010, we have in-licensed potential treatments for five different diseases that are or we expect will be in Phase 1/2 or Phase 2 clinical studies by early 2014. 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 pipeline consists of two product categories: biologics, including a monoclonal antibody and enzyme replacement therapies; 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.

The following table summarizes our product candidate pipeline:

Our current product candidate pipeline has been either in-licensed from academic institutions or derived from partnerships with other pharmaceutical companies. Where possible, our strategy is to acquire and retain

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global commercialization rights to our products to maximize long-term value. Over time, we intend to build our own commercial organization, which we believe will be of modest size due to the relatively small number of specialists who treat patients with rare and ultra-rare diseases.

The patients we seek to treat have diseases with limited or no treatment options, and we recognize that their lives and well-being are highly dependent upon our efforts to develop new therapies. For this reason, we are passionate about developing these therapies with the utmost urgency and care. We strive to build a company that is faster, better, and smarter about advancing multiple product candidates through approval.

We were founded in April 2010 by our current President and Chief Executive Officer, Dr. Emil Kakkis, M.D., Ph.D., who is the former Chief Medical Officer of BioMarin Pharmaceutical Inc. We have assembled an experienced team with extensive drug development and commercialization capabilities, particularly in the orphan drug area. Dr. Kakkis and the team at Ultragenyx have been previously involved, at other companies, in the development and/or commercialization of many therapies approved or in development for rare metabolic genetic diseases, including Aldurazyme, Naglazyme, Kuvan, and Vimizim (BioMarin); Lumizyme/Myozyme (Sanofi-Genzyme); and asfotase alpha (Enobia; now Alexion). Our investors include, but are not limited to, the following entities, their affiliates or funds advised by them: TPG Biotech, Fidelity Biosciences (Beacon Bioventures), HealthCap, Pappas Ventures, Adage Capital Partners, L.P., Capital Research Global Investors, Columbia Wanger Asset Management, Jennison Associates LLC, BlackRock, Inc., Genzyme Corporation, Shire LLC, and Ramius LLC.

Product Candidates

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 fibroblast growth factor 23, or FGF23, to increase abnormally low phosphate levels in patients with X-linked hypophosphatemia, or 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 skeletal deformity, bone pain, short stature, gross motor impairment, muscle weakness, and lower than normal bone density. There is no approved drug therapy or treatment for the underlying cause of XLH. Most patients are managed using oral phosphate replacement and vitamin D therapy, which is only partially effective at restoring bone physiology and growth and has significant side effects.

In August 2013, we formed a collaboration with Kyowa Hakko Kirin Co., Ltd., or KHK, to jointly develop and commercialize KRN23 for the treatment of XLH. KHK has conducted one Phase 1, one Phase 1/2 study and one Phase 1/2 extension study of KRN23 in adults with XLH. We expect to release data for the Phase 1/2 studies in 2014. Results from the Phase 1 single dose study demonstrated that KRN23 was well tolerated. The data suggest efficacy in increasing serum phosphate levels, while reducing urinary excretion of phosphate. We expect to continue to develop KRN23 in adults with XLH. In addition, we expect to initiate a Phase 2 pediatric study in 2014. Given the high turnover and growth of bone during childhood and the critical role phosphate plays in bone growth, pediatric XLH patients have the highest morbidity and potential for benefit.

rhGUS (UX003) for the treatment of MPS 7

Recombinant human beta-glucuronidase, or rhGUS, is an intravenous, or IV, enzyme replacement therapy for the treatment of mucopolysaccharidosis 7, or 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. There are currently no approved drug therapies for MPS 7.

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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. In December 2013 we initiated an open-label, Phase 1/2 study to evaluate the safety, tolerability, efficacy, and dose of IV administration every other week of rhGUS in four to five patients with MPS 7 who are between five and 30 years of age. The initial 12-week treatment period will be followed by a dose-titration period and a long-term extension study. We expect to receive interim data from this study in 2014. If results from the initial 12-week treatment period from this study are supportive, we plan to initiate a pivotal Phase 3 study enrolling at least 12 patients.

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 plan to continue preclinical development of rhPPCA during 2014.

Triheptanoin (UX007) for the treatment of LC-FAOD

We are developing triheptanoin for oral liquid administration intended as a substrate replacement therapy for patients with long-chain fatty acid oxidation disorders, or LC-FAOD. Triheptanoin is a medium-chain triglyceride of three 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 all 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-chain triglyceride, or MCT, oil supplementation. Despite treatment with the current standard of care, many patients continue to suffer significant morbidity and mortality.

Triheptanoin has been studied clinically for 13 years in approximately 130 human subjects affected by a variety of diseases, including 65 patients with LC-FAOD. Multiple investigator-sponsored open-label studies suggest clinical improvements with triheptanoin treatment, even for patients who were on standard of care. We recently completed a retrospective medical record review study to assess the clinical outcome of triheptanoin treatment on LC-FAOD subjects who have 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.

We licensed certain intellectual property rights relating to triheptanoin from Baylor Research Institute in September 2012. Triheptanoin is in an ongoing investigator-sponsored Phase 2 study for the treatment of LC-FAOD. We plan to initiate a prospective open-label Phase 2 study of triheptanoin treatment in approximately 30 severely affected LC-FAOD patients in early 2014. The effects of treatment on clinical and physiologic disease will be assessed in three areas: skeletal myopathy, liver disease, and cardiac disease. A principal goal of the study is to determine the appropriate clinical endpoints and patient population for testing in potential later-stage pivotal studies.

Triheptanoin (UX007) for the treatment of Glut1 DS

We are also developing triheptanoin for patients with glucose transporter type-1 deficiency syndrome, or Glut1 DS. Glut1 DS is caused by a mutation affecting the gene that codes for Glut1, which is a protein that

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transports glucose from blood into the brain. Because glucose is the primary source of energy for the brain, Glut1 DS results in a chronic state of energy deficiency in the brain 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. The ketogenic diet is difficult to comply with and has demonstrated limited effectiveness in the treatment of developmental delay and movement disorder.

Triheptanoin is intended as a substrate replacement therapy to provide an alternative source of energy to the brain in Glut1 DS patients. Although an open-label investigator-sponsored clinical study is ongoing and the results have not yet been reported, there are anecdotal reports of benefit in terms of reduced seizures and improved development rate in some Glut1 DS subjects taking triheptanoin. We are planning to initiate a clinical development program to study the effects of triheptanoin in Glut1 DS in the first half of 2014. We anticipate that the program will initially consist of a Phase 2 adaptive, randomized, double-blind, placebo-controlled, parallel-group study of at least 30 patients between three and 17 years of age inclusive who are currently not on, or not fully compliant with, ketogenic diet.

SA-ER (UX001) for the treatment of HIBM

We are developing an extended-release, oral formulation of sialic acid, or SA-ER, for the treatment of hereditary inclusion body myopathy, or HIBM, which is also known as GNE myopathy. HIBM 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 HIBM 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, HIBM patients have a sialic acid deficiency, which interferes with muscle function, leading to myopathy and atrophy. Patients typically become wheelchair bound within ten to 20 years from onset. There is no approved drug therapy for HIBM.

SA-ER is intended as a substrate replacement therapy designed to address sialic acid deficiency and restore muscle function in HIBM patients. We have conducted a Phase 2 randomized, double-blind, placebo-controlled study of SA-ER in 46 HIBM patients. Top-line results after 48 weeks of treatment showed a modest increase in upper extremity muscle strength composite at the higher dose and a statistically significant difference versus the decline observed at the lower dose. A positive trend was seen in a patient-reported outcome of functional activity. The results were consistent with the 24-week analysis. SA-ER appears to be well tolerated with no serious adverse events observed to date in either dose group. We plan to continue to treat these patients in an extension study with an increased dosage of sialic acid based on the dose dependence observed at weeks 24 and 48. We anticipate that data from the extension study should be available in late 2014.

Our Strategy

Our strategy is to identify, acquire, develop, and commercialize novel products for the treatment of rare and ultra-rare diseases in the United States, the European Union, and select international markets, with the goal of becoming a leading rare disease company. The critical components of our business strategy include the following:

- Focus on rare and ultra-rare diseases with significant unmet medical need;
- Focus on diseases and therapies with clear mechanisms of action;
- Leverage our experience and relationships to in-license promising product candidates;
- Develop and commercialize multiple product candidates in parallel;
- Focus on excellent and rapid clinical and regulatory execution; and

Seek to retain global commercialization rights to product candidates.

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Risks Associated with Our Business

Our ability to implement our business strategy is subject to numerous risks that you should be aware of before making an investment decision. These risks are described more fully in the section entitled Risk Factors immediately following this prospectus summary. These risks include, among others:

- We are a development-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;
- Even if this offering is successful, we expect that we will need to raise additional funding before we can expect to become profitable from sales of our products;
- We are heavily dependent upon the success of our product candidates, which are in the early stages of clinical development, and we cannot provide any assurance that any of our product candidates will receive regulatory approval;
- Because the target patient populations of our product candidates are small, we must be able to successfully identify patients and acquire a significant market share to achieve profitability and growth;
- The insurance coverage and reimbursement status of newly-approved orphan products is uncertain and failure to obtain or maintain adequate coverage and reimbursement for our product candidates could limit our ability to market those products and decrease our ability to generate revenue;
- If we are unable to obtain and maintain effective intellectual property rights for our technologies, product candidates, or any future product candidates, we may not be able to compete effectively in our markets; and
- Our future success depends in part upon our ability to retain our Founder, President, and Chief Executive Officer and to attract, retain, and motivate other qualified personnel.

Our Corporate Information

We were founded in April 2010 as a California corporation, and we reincorporated as a Delaware corporation in June 2011. Our principal executive offices are located at 60 Leveroni Court, Novato, CA 94949, and our telephone number is (415) 483-8800. Our web site address is www.ultragenyx.com. The information on, or that can be accessed through, our web site is not part of this prospectus. We have included our web site address as an inactive textual reference only.

We have filed trademark applications with the U.S. Patent and Trademark Office for the marks Ultragenyx and Ultragenyx Pharmaceutical, and we are developing commercial names for our product candidates. This prospectus also contains trademarks of others, including Aldurazyme®, Naglazyme®, Kuvan®, Vimizim, Lumizyme®, Myozyme® and asfotase alpha. We do not intend our use or display of other companies trade names or trademarks to imply a relationship with, or endorsement or sponsorship of us by, any other companies.

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THE OFFERING

Common stock offered by us	4,838,710 shares
Common stock to be outstanding after this offering	28,140,212 shares (or 28,866,018 shares if the underwriters exercise their option to purchase additional shares in full)
Underwriters option to purchase additional shares	725,806 shares
Use of proceeds	We estimate that the net proceeds from this offering will be approximately $66.8 million, or approximately $77.2 million if the underwriters exercise their option to purchase additional shares in full, at an assumed initial public offering price of $15.50 per share, the midpoint of the price range set forth on the cover of this prospectus, after deducting the estimated underwriting discounts and commissions and estimated offering expenses payable by us. We intend to use the net proceeds from this offering, together with our existing cash, cash equivalents, and marketable securities to advance our ongoing clinical programs for KRN23, rhGUS, triheptanoin in both LC-FAOD and Glut1 DS, and SA-ER, to pay a cash dividend to holders of our preferred stock payable upon conversion of the shares to common stock, and any remaining proceeds for preclinical research, working capital, and other general corporate purposes. See Use of Proceeds.
Risk factors	You should read the Risk Factors section of this prospectus for a discussion of factors to consider carefully before deciding to invest in shares of our common stock.
Directed share program	At our request, the underwriters have reserved up to 241,935 shares of our common stock offered by this prospectus for sale, at the initial public offering price, to our directors and officers and certain employees and other parties related to us. Shares purchased by our directors and officers will be subject to the 180-day lock-up restriction described in the Underwriting section of this prospectus. The number of shares of common stock available for sale to the general public will be reduced to the extent these individuals purchase such reserved shares. Any reserved shares that are not so purchased will be offered by the underwriters to the general public on the same basis as the other shares offered by this prospectus.
Proposed NASDAQ Global Market symbol	RARE

The number of shares of common stock to be outstanding after this offering is based on 3,703,016 shares of common stock outstanding as of September 30, 2013 and 19,598,486 additional shares of our common stock issuable upon conversion of all of our outstanding shares of preferred stock upon closing of this offering.

The number of shares of our common stock to be outstanding after this offering excludes the following:

1,526,772 shares of common stock issuable upon the exercise of outstanding stock options as of September 30, 2013 having a weighted-average exercise price of $0.86 per share;

327,853 shares of common stock issuable upon the exercise of outstanding warrants as of September 30, 2013 having a weighted-average exercise price of $3.241 per share;

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1,565,352 shares of common stock reserved for issuance pursuant to future equity awards under our 2011 Equity Incentive Plan, as amended, as of September 30, 2013, which will become available for issuance under our 2014 Incentive Plan after the completion of this offering;

2,250,000 shares of common stock reserved for issuance (including the above-referenced shares reserved for issuance under our 2011 Equity Incentive Plan, as amended) pursuant to future equity awards under our 2014 Incentive Plan, as well as any future increases in the number of shares of our common stock reserved for future issuance under this plan, which will become effective immediately prior to the completion of this offering; and

600,000 shares of common stock reserved for future issuance under our 2014 Employee Stock Purchase Plan, or 2014 ESPP, as well as any future increases in the number of shares of our common stock reserved for future issuance under the 2014 ESPP, which will become effective immediately prior to the completion of this offering.

Except as otherwise indicated, all information contained in this prospectus:

reflects a 1-for-3.1345 reverse stock split of our common stock that we effected on January 17, 2014;

reflects the conversion of all of our outstanding shares of preferred stock into an aggregate of 19,598,486 shares of common stock immediately prior to the completion of this offering;

assumes the effectiveness of our amended and restated certificate of incorporation and amended and restated by-laws immediately prior to the completion of this offering;

assumes that the underwriters do not exercise their option to purchase additional shares; and

assumes no exercise of outstanding options or warrants after September 30, 2013.

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SUMMARY FINANCIAL DATA

The following table summarizes our statements of operations and balance sheet data. We have derived the following statements of operations data for the years ended December 31, 2011 and 2012 from our audited financial statements appearing elsewhere in this prospectus. The statements of operations data for the nine months ended September 30, 2012 and 2013 and the balance sheet data as of September 30, 2013 are derived from our unaudited financial statements appearing elsewhere in this prospectus. In our opinion, these unaudited financial statements have been prepared on a basis consistent with our audited financial statements and contain all adjustments, consisting only of normal and recurring adjustments, necessary for a fair presentation of such financial data. You should read this data together with our financial statements and related notes appearing elsewhere in this prospectus and the information under the captions Selected Financial Data and Management s Discussion and Analysis of Financial Condition and Results of Operations. Our historical results are not necessarily indicative of our future results, and our operating results for the nine-month period ended September 30, 2013 are not necessarily indicative of the results that may be expected for the year ended December 31, 2013 or any other interim periods or any future year or period.

	Year Ended December 31,		Nine Months Ended September 30,	
	2011	2012	2012	2013
	(In thousands, except share and per share amounts)		(unaudited)	
Statements of Operations Data:				
Operating expenses:				
Research and development	$ 4,717	$ 12,641	$ 8,866	$ 19,625
General and administrative	1,844	3,344	2,441	3,130
Total operating expenses	6,561	15,985	11,307	22,755
Loss from operations	(6,561)	(15,985)	(11,307)	(22,755)
Interest income	4	1		157
Interest expense	(270)			
Other expense	(22)	(350)	(97)	(1,155)
Net loss	$ (6,849)	$ (16,334)	$ (11,404)	$ (23,753)
Net loss attributable to common stockholders [1]	$ (7,466)	$ (19,561)	$ (12,749)	$ (31,624)
Net loss per share attributable to common stockholders, basic and diluted	$ (4.62)	$ (14.20)	$ (12.35)	$ (9.70)
Shares used to compute net loss per share attributable to common stockholders, basic and diluted	1,617,384	1,377,207	1,032,159	3,260,484
Pro forma net loss per share attributable to common stockholders, basic and diluted (unaudited) [1]		$ (2.02)		$ (1.16)
Shares used to compute pro forma net loss per share attributable to common stockholders, basic and diluted (unaudited) [1]		9,999,398		23,126,389

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	As of September 30, 2013		
	Actual	Pro Forma[2] (unaudited) (in thousands)	Pro Forma as Adjusted[3][4]
Balance Sheet Data:			
Cash, cash equivalents and marketable securities	$ 63,657	$ 63,657	$ 126,262
Working capital	61,067	56,922	123,672
Total assets	68,592	68,592	131,197
Convertible preferred stock warrant liability	1,596		
Convertible preferred stock	118,002		
Deficit accumulated during the development stage	(56,846)	(56,846)	(56,846)
Total stockholders (deficit) equity	(56,848)	58,605	125,355

(1) See Notes 2 and 14 to our audited financial statements and Note 8 of our unaudited financial statements included elsewhere in this prospectus for an explanation of the calculations of our basic and diluted net loss per share attributable to common stockholders and pro forma net loss per share attributable to common stockholders.

(2) Pro forma to reflect (i) the conversion of all of our outstanding shares of convertible preferred stock into an aggregate of 19,598,486 shares of our common stock, (ii) the reclassification to additional paid-in capital of our preferred stock warrant liability in connection with the conversion of our outstanding preferred stock warrants into common stock warrants, and (iii) a dividend of $4.1 million payable concurrent with the conversion of our preferred stock to common stock to the holders of our preferred stock, which has been calculated as if the conversion of preferred stock into common stock occurred as of January 17, 2014, in each case, immediately prior to the completion of this offering. Since the dividend represents distributions to existing stockholders to be made from the proceeds of the offering, the pro forma balance sheet data reflects the accrual of the estimated dividend to be paid.

(3) Pro forma as adjusted to further reflect (i) the sale of 4,838,710 shares of common stock in this offering at an assumed initial public offering price of $15.50 per share, the midpoint of the price range set forth on the cover of this prospectus, after deducting the estimated underwriting discounts and commissions and estimated offering expenses payable by us and (ii) the payment of the $4.1 million dividend payable described above.

(4) A $1.00 increase (decrease) in the assumed initial public offering price of $15.50 per share, the midpoint of the price range set forth on the cover of this prospectus, would increase (decrease) each of cash, cash equivalents and marketable securities, working capital, total assets, and total stockholders equity by approximately $4.5 million, assuming that the number of shares offered by us, as set forth on the cover of this prospectus, remains the same and after deducting estimated underwriting discounts and commissions and estimated offering expenses payable by us. A 1,000,000 share increase in the number of shares offered by us would increase each of cash, cash equivalents and marketable securities, working capital, total assets, and total stockholders equity by approximately $14.4 million after deducting estimated underwriting discounts and commissions and any estimated offering expenses payable by us. Conversely, a 1,000,000 share decrease in the number of shares offered by us would decrease each of cash, cash equivalents and marketable securities, working capital, total assets, and total stockholders equity by approximately $14.4 million after deducting estimated underwriting discounts and commissions and any estimated offering expenses payable by us.

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RISK FACTORS

An investment in shares of our common stock involves a high degree of risk. You should carefully consider the following information about these risks, together with the other information appearing elsewhere in this prospectus, including our financial statements and related notes thereto, before deciding to invest in our common stock. The occurrence of any of the following risks could have a material adverse effect on our business, financial condition, results of operations and future growth prospects. In these circumstances, the market price of our common stock could decline, and you may lose all or part of your investment.

Risks Related to Our Financial Condition and Capital Requirements

We are a development-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 development-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 $6.8 million and $16.3 million for the years ended December 31, 2011 and 2012, respectively, and $23.8 million for the nine months ended September 30, 2013. As of September 30, 2013, we had a deficit accumulated during the development stage of $56.8 million.

We have devoted substantially all of our financial resources to identify, acquire, and develop our product candidates, including conducting 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 and convertible promissory notes. 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. We are in the early stages of clinical development for our product candidates, we have not yet commenced pivotal clinical studies for any product candidate and it may be several years, if ever, before we complete pivotal clinical studies and 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 from third-party payors, 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, 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;
- change or add additional manufacturers or suppliers;
- seek regulatory and marketing approvals for our product candidates that successfully complete clinical studies;

establish a sales, marketing, and distribution infrastructure to commercialize any products for which we may obtain marketing approval;

seek to identify, assess, acquire, and/or develop other product candidates;

make milestone or other payments under any license agreements;

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- seek to maintain, protect, and expand our intellectual property portfolio;
- seek to attract and retain skilled personnel;
- create additional infrastructure to support our operations as a public company and our product development and planned future commercialization efforts; and
- experience any delays or encounter issues with any of the above, including but not limited to failed studies, complex results, safety issues, 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 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 revenue from product sales for the foreseeable future. Our ability to generate future revenue from product 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 process and provide adequate (in amount and quality) products 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;
- addressing any competing technological and market developments;
- identifying, assessing, acquiring and/or developing new product candidates;

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 U.S. Food and Drug Administration, or the FDA, the European Medicines Agency, or 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

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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 triheptanoin 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. Additionally, if we are not able to generate revenue from the sale of any approved products, we may never become profitable.

Even if this offering is successful, we expect that we will need to raise additional funding before we can expect to become profitable from sales of our products. 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 operations.

We are currently advancing our KRN23, rhGUS, triheptanoin, and SA-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.

As of September 30, 2013, our cash, cash equivalents and marketable securities were $63.7 million. We expect that our existing cash, cash equivalents and marketable securities, not including the proceeds we receive from this offering, will be sufficient to fund our current operations for at least the next 12 months; however, we expect that we will require additional capital to obtain regulatory approval for, and to commercialize, 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 sales, marketing, and distribution capabilities; and
- the terms and timing of any collaborative, licensing, and other arrangements that we may establish, including any required milestone and royalty payments thereunder.

Any additional fundraising efforts may divert our management from their day-to-day activities, which may adversely affect our ability to develop and commercialize our product candidates. 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 arrangements with collaborative partners or otherwise at an earlier stage than otherwise would be desirable 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.

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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, which are in the early stages of clinical development. We cannot give any assurance that any of our product candidates will receive regulatory approval, which is necessary before they can be commercialized.

To date, we have invested substantially all of our efforts and financial resources to identify, acquire, and develop our product candidates, including conducting clinical studies and providing general and administrative support for these operations. 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.

Each of our product candidates is in the early stages of 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, and significant marketing efforts before we generate any revenue from product sales. We currently have four product candidates in Phase 1/2 or Phase 2 clinical studies. None of our product candidates have advanced into a pivotal study and it may be years before such study is initiated, if at all. 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.

Although certain of our employees have prior experience with submitting marketing applications to the FDA or comparable foreign regulatory authorities, we as a company have not submitted such applications for our product candidates. 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.

We generally plan to seek regulatory approval to commercialize our product candidates in the United States, the European Union, or 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.

The regulatory approval processes of the FDA and comparable foreign authorities are lengthy, time consuming, and inherently unpredictable. If we are ultimately unable to obtain regulatory approval for our product candidates, our business will be substantially harmed.

The time required to obtain approval by the FDA and comparable foreign authorities is unpredictable, typically takes many years following the commencement of clinical studies, and depends upon numerous factors. In addition, approval policies, regulations, or the type and amount of clinical data necessary to gain approval may change during the course of a product candidate s clinical development and may vary among jurisdictions, which may cause delays in the approval or the decision not to approve an application. 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.

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Applications for our product candidates could fail to receive regulatory approval for many reasons, including but not limited to the following:

- the FDA or comparable foreign regulatory authorities may disagree with the design or implementation of our clinical studies;
- the population studied in the clinical program may not be sufficiently broad or representative to assure 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 a new drug application, or 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; 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.

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

Clinical drug development involves a lengthy and expensive process with an uncertain outcome, and results of earlier studies may not be predictive of future study results.

Clinical testing is expensive and can take many years to complete, and its outcome is inherently uncertain. Failure can occur at any time during the clinical study process. The results of preclinical studies and early clinical studies of our product candidates may not be predictive of the results of later-stage clinical studies. Product candidates that have shown promising results in early-stage clinical studies may still suffer significant setbacks in subsequent registration clinical studies. For example, the safety or efficacy results generated to date in clinical studies for KRN23, triheptanoin, and SA-ER do not ensure that later clinical studies will demonstrate similar results. 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 traits despite having progressed through preclinical 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. Moreover, nonclinical and clinical data are often susceptible to varying interpretations and analyses. We do not know whether any Phase 2, Phase 3, or other clinical studies we may conduct will demonstrate consistent or adequate efficacy and safety sufficient to obtain regulatory approval to market our drug candidates.

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.

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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 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 triheptanoin is being studied;
- we estimate that several thousand patients in the United States suffer from Glut1 DS, for which triheptanoin is being studied; and
- we estimate that about 1,200 to 2,000 patients in the developed world suffer from HIBM, for which SA-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. 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 availability and efficacy of competing therapies and clinical studies, the proximity and availability of clinical study sites for prospective patients, and the patient referral practices of physicians. 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.

If we experience delays in the completion of, or termination of, any clinical study of our product candidates, 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.

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

Before obtaining marketing approval from regulatory authorities for the sale of our product candidates, we must conduct extensive clinical 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. Events that may prevent successful or timely completion of clinical development include but are not limited to:

- inability to generate sufficient preclinical, toxicology, or other *in vivo* or *in vitro* data to support the initiation of human clinical studies;
- delays in reaching a consensus with regulatory agencies on study design;

delays in reaching agreement on acceptable terms with prospective contract research organizations, or CROs, and clinical study sites, the terms of which can be subject to extensive negotiation and may vary significantly among different CROs and clinical study sites;

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- delays in obtaining required Institutional Review Board, or IRB, approval at each clinical study site;
- imposition of a clinical hold by regulatory agencies, after review of an investigational new drug, or IND, application or amendment, or 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 having patients complete participation in a study or return 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 studies or abandon drug development programs; 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 impair 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, we may need to conduct additional studies to bridge our modified product candidates to earlier 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 impair our ability to obtain orphan exclusivity and to successfully commercialize our product candidates and may harm our business and results of operations.

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 and could result in a more restrictive label or the delay or denial of regulatory approval by the FDA or other comparable foreign authorities. Patients treated with KRN23 have experienced nausea, headache, elevated serum amylase, and back pain. Most of these adverse events were mild and no serious adverse events have been observed. Only single-dose Phase 1 data for KRN23 has been reported to date and other side effects may result from repeated dosing and/or longer-term exposure. Patients treated with triheptanoin have experienced drug-related side effects such as cramping, diarrhea, and loose stools. In addition, during a 13-year study of approximately 130 human subjects, including 65 with LC-FAOD, three serious adverse events 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. While we have not initiated our own clinical studies for

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triheptanoin, there may be other side effects associated with its use that we discover. Additionally, patients treated with SA-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 when clinical trials are initiated. Results of our studies 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.

The drug-related side effects could affect patient recruitment, the ability of enrolled patients to complete the study, or result in potential product liability claims. We currently carry product liability insurance in the amount of $5.0 million in the aggregate, and we are required to maintain product liability insurance pursuant to certain of our license 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. A successful 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 label;
- 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, 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; 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, 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 current Good Manufacturing Practices, or cGMP, regulations. As such, we and our contract manufacturers will be subject to continual review and inspections to assess compliance with cGMP and adherence to commitments made in any NDA, BLA or marketing authorization application, or MAA. 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.

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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 to the conditions of approval, or contain requirements for potentially costly post-marketing testing, including Phase IV clinical trials, and surveillance to monitor the safety and efficacy of the product candidate. We will be required to report certain adverse reactions and production 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, or MAA must submit new or supplemental applications and obtain approval for certain changes to the approved product, product labeling, or manufacturing process. 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 pathway, we could 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.

If a regulatory agency discovers previously unknown problems with a product, such as adverse events of unanticipated severity or frequency, or problems with the facility where the product is manufactured, or disagrees with the promotion, marketing or labeling of a product, such regulatory agency may impose restrictions on that product or us, including requiring withdrawal of the product from the market. If we fail to comply with applicable regulatory requirements, a regulatory agency or enforcement authority may, among other things:

- issue warning 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; or
- seize or detain products, or require a product recall.

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.

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 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-party CROs to monitor and manage data for our ongoing nonclinical and clinical programs. We rely on these parties for execution of our nonclinical and clinical studies, and control only certain aspects of their activities. 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 does not relieve us of our regulatory responsibilities. We and our CROs and other vendors are required to comply with cGMP, current good clinical practices, or cGCP, and Good Laboratory Practices, or

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GLP, which are regulations and guidelines enforced by the FDA, the Competent Authorities of the Member States of the European Economic Area, or EEA, and comparable foreign regulatory authorities for all of our product candidates in clinical 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 vendors 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 require us to perform additional nonclinical and clinical studies before approving our marketing applications. We cannot assure you that upon inspection by a given regulatory authority, such regulatory authority will determine that any of our clinical studies comply with cGCP regulations. In addition, our clinical studies must be conducted with product produced under cGMP regulations. Our failure to comply with these regulations may require us to repeat clinical studies, which would delay the regulatory approval process.

If any of our relationships with these third-party CROs terminate, we may not be able to enter into arrangements with alternative CROs or do so on commercially reasonable terms. In addition, our CROs are not our employees, and except for remedies available to us under our agreements with such CROs, we cannot control whether or not they devote sufficient time and resources to our on-going nonclinical and clinical programs. If CROs 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 may also generate higher costs than anticipated. 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.

Switching or adding additional CROs involves additional cost and requires management time and focus. In addition, there is a natural transition period when a new CRO commences work. As a result, delays occur, which can materially impact our ability to meet our desired clinical development timelines. Though we carefully manage our relationships with our CROs, 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 prospects.

We are dependent on KHK for the development and commercialization of KRN23 in certain major markets, and KHK s failure to commercialize KRN23 in those markets would 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 retained by us. 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 but may be unable to do so 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 for our development and clinical use, which could result in program delays;

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KHK may fail to manufacture or supply sufficient drug product of KRN23 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 impacting 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 nonclinical and clinical drug supplies. 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 nonclinical and clinical drug supplies for use in the conduct of our clinical studies, 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, 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 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, which could harm our business and results of operations.

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, natural disasters, power failures, and numerous other factors.

Although we have not experienced any contaminations, equipment failures, or other similar manufacturing problems, 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

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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 our product candidates are currently acquired from single-source suppliers. The loss of these suppliers, or their failure to supply us with the 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 triheptanoin is manufactured by Cremer Oleo GmbH & Co. KG, or Cremer, pursuant to our supply agreement with Cremer, and the drug product for triheptanoin is prepared by Haupt Pharma AG pursuant to purchase orders. The drug substance for SA-ER is manufactured by Sanyo Fine Co., Ltd. under our license agreement and accompanying purchase orders with Nobelpharma Co., Ltd., and the drug product for SA-ER is manufactured by AAIPharma Services Corp., or AAIPharma, pursuant to our license agreement and accompanying purchase orders with AAIPharma. We do not currently have 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 assure you 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 late-stage clinical studies must be manufactured in accordance with cGMP. 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, or MAA on a timely basis and must adhere to GLP and cGMP regulations enforced by the FDA and other regulatory agencies through their facilities inspection program. 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 completely 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 correcte