UNITED STATES SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

Form 10-K

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

For the fiscal year ended December 31, 2014

OR

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

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)

Securities registered pursuant to Section 12(b) of the Act:

Title of Each Class	Name of Each Exchange on Which Registered
Common Stock, $0.001 par value	**The NASDAQ Global Select Market**

Securities registered pursuant to Section 12(g) of the Act: None.

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. YES R NO ☐

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15 (d) of the Act. YES ☐ NO R

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. YES 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 if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K (§229.405 of this chapter) is not contained herein, and will not be contained, to the best of registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K. ☐

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 ☐	Accelerated filer ☐	Non- accelerated filer R	Smaller reporting company ☐
		(Do not check if a 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

The aggregate market value of the voting and non-voting common equity held by non-affiliates of the Company as of June 30, 2014 was approximately $910.6 million, based upon the closing price on The NASDAQ Global Select Market reported for such date. Shares of common stock held by each officer and director and by each person who is known to own 10% or more of the outstanding common stock have been excluded in that such persons may be deemed to be affiliates of the Company. This determination of affiliate status is not necessarily a conclusive determination for other purposes.

As of March 23, 2015, the Company had 35,596,219 shares of common stock issued and outstanding.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant's definitive Proxy Statement relating to its 2015 Annual Meeting of Stockholders, to be held on or about June 18, 2015, are incorporated by reference into Part III of this Annual Report on Form 10-K where indicated. Such Proxy Statement will be filed with the U.S. Securities and Exchange Commission within 120 days after the end of the fiscal year to which this report relates.

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CAUTIONARY NOTE REGARDING FORWARD-LOOKING STATEMENTS

Statements made in this Annual Report on Form 10-K that are not statements of historical information are forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended and Section 21E of the Securities Exchange Act of 1934, as amended, or the Exchange Act. We have made these statements in reliance on the safe harbor provisions of the Private Securities Litigation Reform Act of 1995. These statements are subject to certain risks and uncertainties, which could cause actual results to differ materially from those projected or anticipated. Although we believe our assumptions underlying our forward-looking statements are reasonable as of the date of this report we cannot assure you that the forward-looking statements set out in this report will prove to be accurate. 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 words or other comparable terminology. Some of the factors that could cause our actual results to differ materially from our expectations or beliefs are disclosed in the “Risk Factors” as well as other sections of this report which include, without limitation: our capital resources, commercial market estimates, safety of our product candidates, future development efforts, patent protection, effects of healthcare reform, reliance on third parties, and other risks set forth below. All forward-looking statements speak only as of the date on which they are made and we disclaim any intent or obligation to update forward-looking statements to reflect subsequent developments or actual results. Except as required by law, we assume no obligation to update any forward-looking statements publicly, or to revise any forward-looking statement to reflect events or developments occurring after the date of this report, even if new information becomes available in the future. Thus, you should not assume that our silence over time means that actual events are bearing out as expressed or implied in any such forward-looking statement.

This Annual Report on Form 10-K 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.

PART I

Item 1. *Business*

Overview

We are a clinical-stage biopharmaceutical company 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 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 product candidate pipeline has been either in-licensed from academic institutions or derived from partnerships with other pharmaceutical companies. Our strategy is to acquire and retain global commercialization rights to our products to maximize long-term value, where possible. 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, 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 rare disease drug development and commercialization capabilities. 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 genetic diseases, including Aldurazyme, Naglazyme, Kuvan, and Vimizim (BioMarin); Lumizyme/Myozyme (Sanofi-Genzyme); and asfotase alpha (Enobia; now Alexion).

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, or EU, and select international markets, with the goal of becoming a leading rare disease biotechnology company. The critical components of our business strategy include the following:

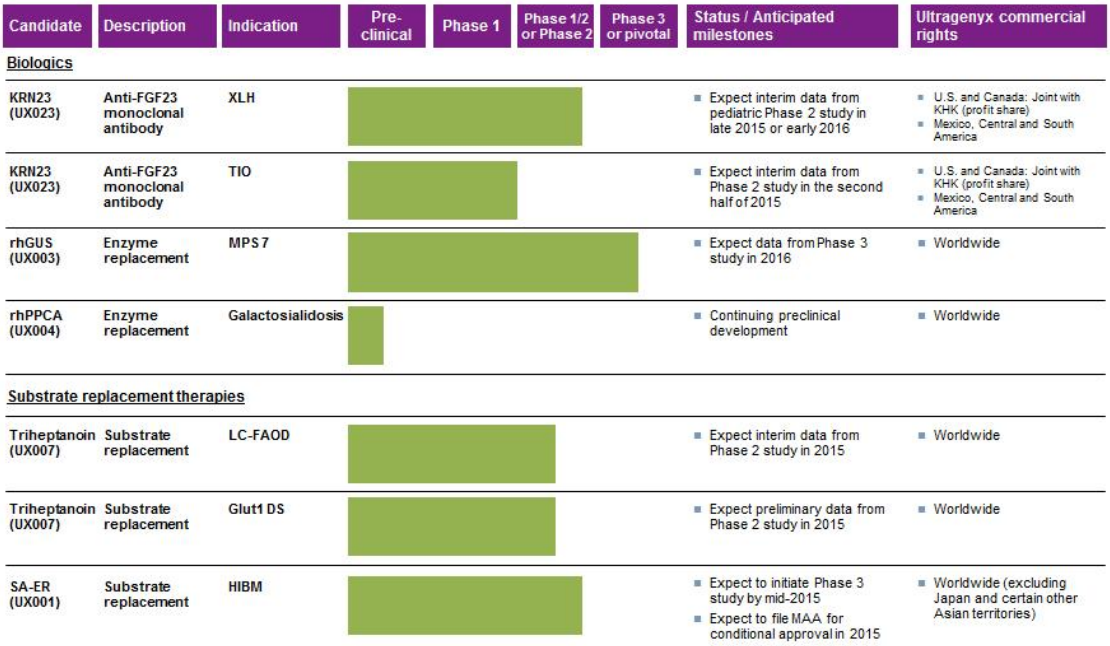
- ***Focus on rare and ultra-rare diseases with significant unmet medical need.*** There are numerous rare and ultra-rare genetic diseases that currently have no approved drug therapy and for which no therapies are currently in development. Patients suffering from these diseases often have a high unmet medical need with significant morbidity and/or mortality. We are focused on developing and commercializing therapies for multiple such indications with the utmost urgency.
- ***Focus on diseases and therapies with clear mechanisms of action.*** We also focus on diseases that have biology and root causes that are well understood. For example, several of our product candidates are replacement therapies for a single deficient enzyme or substrate in the body. We believe that developing drugs that directly impact known disease pathways will increase the probability of success of our development programs.
- ***Leverage our experience and relationships to in-license promising product candidates.*** Our management team has strong relationships with key opinion leaders in the genetic field, as well as a history of success in the development and commercialization of therapies for rare and ultra-rare genetic diseases. Accordingly, we enjoy unique access to many in-licensing opportunities. All of our current product candidates are in-licensed from academic institutions or derived from partnerships with other pharmaceutical companies. We believe these parties have agreed to license product candidates to us because they are confident in our drug development capabilities and experience in bringing rare disease therapies to market.
- ***Develop and commercialize multiple product candidates in parallel.*** Clinical studies for rare and ultra-rare diseases can often be smaller, fewer in number, and less expensive than those for larger market indications. Development of multiple programs in the genetics field also generates organizational efficiencies and economies of scale. As a result of these efficiencies, we can feasibly develop multiple clinical-stage product candidates in parallel, resulting in a more diversified portfolio that provides multiple opportunities to create value.
- ***Focus on excellent and rapid clinical and regulatory execution.*** We believe that building a successful and sustainable rare disease-focused company requires very specific expertise in the areas of patient identification, clinical study design and conduct, and regulatory strategy. We have assembled a team with a successful track record in managing global clinical development activities in an efficient manner, and with multinational experience in obtaining regulatory approvals for rare disease products.

- ***Seek to retain global commercialization rights to product candidates.*** We intend to seek and retain global commercialization rights to our product candidates whenever possible to maximize the potential value of our product portfolio. Our plan is to establish our own commercial organization in major pharmaceutical markets and develop a network of third-party distributors in smaller markets. We believe this commercial organization can be modest and targeted due to the relatively small number of specialists who typically treat patients with the diseases to be addressed by our product candidates. As a result, we do not expect that we will require pharmaceutical partners for commercialization of our product candidates, although we may consider partnering for certain territories or indications or for other strategic purposes.

Product Candidates

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 current product candidate pipeline:



Candidate	Description	Indication	Pre-clinical	Phase 1	Phase 1/2 or Phase 2	Phase 3 or pivotal	Status / Anticipated milestones	Ultragenyx commercial rights
Biologics								
KRN23 (UX023)	Anti-FGF23 monoclonal antibody	XLH					▪ Expect interim data from pediatric Phase 2 study in late 2015 or early 2016	▪ U.S. and Canada: Joint with KHK (profit share) ▪ Mexico, Central and South America
KRN23 (UX023)	Anti-FGF23 monoclonal antibody	TIO					▪ Expect interim data from Phase 2 study in the second half of 2015	▪ U.S. and Canada: Joint with KHK (profit share) ▪ Mexico, Central and South America
rhGUS (UX003)	Enzyme replacement	MPS 7					▪ Expect data from Phase 3 study in 2016	▪ Worldwide
rhPPCA (UX004)	Enzyme replacement	Galactosialidosis					▪ Continuing preclinical development	▪ Worldwide
Substrate replacement therapies								
Triheptanoin (UX007)	Substrate replacement	LC-FAOD					▪ Expect interim data from Phase 2 study in 2015	▪ Worldwide
Triheptanoin (UX007)	Substrate replacement	Glut1 DS					▪ Expect preliminary data from Phase 2 study in 2015	▪ Worldwide
SA-ER (UX001)	Substrate replacement	HIBM					▪ Expect to initiate Phase 3 study by mid-2015 ▪ Expect to file MAA for conditional approval in 2015	▪ Worldwide (excluding Japan and certain other Asian territories)

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 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 Kyowa Hakko Kirin Co., Ltd., or KHK, to jointly develop and commercialize KRN23 for the treatment of XLH. 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. The data demonstrated that KRN23 was well tolerated and increased serum phosphate, or phosphorus. Corresponding changes were observed in renal tubular reabsorption of phosphate. Increases in vitamin D were also observed, suggesting improved intestinal absorption of both phosphate and calcium. Importantly, from a safety perspective, changes were not observed in serum calcium.

No serious adverse events were reported in the Phase 1 study. There did not appear to be a relationship between the incidence and types of adverse events and the dose administered following a single dose of study drug.

Results from a Phase 1/2 study with up to four escalating doses from 0.05 mg/kg to 0.6 mg/kg in 28 adult XLH patients were presented at the 2014 ICE/ENDO joint meeting of The Endocrine Society and the International Congress on Endocrinology in June 2014. The data demonstrated that repeat doses of KRN23 over four months led to an increase in serum phosphate in 100% of patients, with approximately 89% of patients reaching the low end of the normal range. Peak mean serum phosphorus increased to 3.03 ± 0.42 mg/dL after the fourth dose, which is an approximate 60% increase from the mean of 1.89 ± 0.33 mg/dL at baseline. Comparable increases were observed in mean renal tubular reabsorption of phosphate and mean serum vitamin D levels.

Increases in bone remodeling markers of bone formation and bone resorption were also observed in this Phase 1/2 study. The increase in P1NP (procollagen type I N propeptide) from baseline was statistically significant ($p<0.05$) after all doses and the increase in osteocalcin was statistically significant ($p<0.05$) after the fourth dose. These data support the concept that KRN23's impact on improving phosphate metabolism will improve bone remodeling, a critical part of creating strong, and properly-formed bones.

Increases in quality of life and disability measures were also observed and we intend to objectively evaluate these in a future randomized controlled study.

Data from the long-term Phase 1/2 study to evaluate KRN23 treatment for an additional 12 doses in 22 adult patients with XLH were presented at the ASBMR Annual Meeting in September 2014. Data from the long-term study demonstrated that the increases in serum phosphate levels, renal tubular reabsorption of phosphate, and serum vitamin D levels observed in the initial four-month Phase 1/2 study were generally sustained during the 12-month extension. All patients continued to demonstrate increases in serum phosphate levels, and 53-86% of subjects in the extension study had serum phosphate levels that reached the normal range after each dose. The mean increases in markers of bone remodeling observed in the prior Phase 1/2 study were also generally sustained.

KRN23 was generally safe and well tolerated over the cumulative treatment period. The most common treatment-related adverse events were injection site reaction, arthralgia, diarrhea, restless legs syndrome, injection site erythema, injection site pain, upper abdominal pain, headache, and decreased neutrophil count (both cases of low neutrophil counts were also observed at baseline and were not associated with any significant infections). Serious adverse events were reported in three subjects but were all considered unrelated to KRN23. One patient discontinued treatment due to nephrolithiasis and one patient discontinued due to restless legs syndrome. There were no clinically significant changes in parathyroid hormone, renal ultrasound or cardiac CT. Serum calcium levels did not change significantly, and mild hypercalcemia was observed intermittently in two subjects. Urinary calcium was not increased, and three subjects had only transient hypercalciuria. No anti-KRN23 antibodies were observed.

In July 2014, we announced the first patient screened and enrolled in the Phase 2 pediatric study of KRN23 in patients with XLH. In late 2014, we completed enrollment of 36 prepubertal patients. 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 will also assess 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.

The study consists of a 16-week individual dose-titration period followed by a 48-week treatment period. The goal of the dose-titration period is to identify the individualized dose of KRN23 required to achieve stable serum phosphorus levels in the target range. Patients will be 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 will receive their individually-optimized dose of KRN23 on a monthly or biweekly basis for the 48-week treatment period. Phosphate control and safety data from the 16-week dose-titration period are expected to be released in the first half of 2015. Additional data, including radiographic assessments, through 40 weeks of treatment are to be available in late 2015 or early 2016.

Depending on the results of our Phase 2 pediatric study, we intend to conduct a Phase 3 pediatric study. In our meeting with the United States Food and Drug Administration, or FDA, the FDA agreed that blinded radiographic assessments of changes in bone abnormalities, i.e. rickets and bowing, and changes in growth may be used as primary endpoint measures in a potential Phase 3 study in pediatric patients. The FDA also indicated that a Phase 3 study in pediatric patients could be open-label, but recommended inclusion of a standard of care control arm for comparison on a non-inferiority basis. We expect that the final design of a pediatric Phase 3 study would be determined once sufficient safety and efficacy data are available and after further consultation with the FDA.

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 in a shorter timeframe. This is consistent with third-party data regarding enzyme replacement therapy in hypophosphatasia, which is another genetic bone disease with poor bone mineralization related to phosphate metabolism caused by a different, unrelated mechanism. We expect to continue to develop KRN23 in adults with XLH and also plan to initiate an adult Phase 2b study in the second half of 2015 that will be conducted in parallel with our Phase 3 pediatric study.

KRN23 (UX023) for the treatment of TIO

KRN23 is also intended 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, 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, dose-finding Phase 2 clinical study. Data from the Phase 2 study is expected in late 2015.

This Phase 2 study will evaluate safety and efficacy in approximately six adult inoperable patients. The primary objectives of the study are to establish the dose, and safety profile of treatment with KRN23 in TIO patients. Preliminary clinical effects of KRN23 treatment will be 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 will also be followed.

The study will consist of a 16-week individual dose-titration period followed by a 32-week treatment period. The goal of the dose-titration period is to identify the individualized dose of KRN23 required to achieve stable serum phosphorus levels in the target range. Patients will receive subcutaneous injections of KRN23 once every four weeks.

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. 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 every other week of rhGUS 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 (SSIEM) Annual Symposium and showed a decline in urinary glycosaminoglycans (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 will assess 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 trial 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. Data from the Phase 3 study is expected in the first half of 2016.

The primary objective of the study is to determine the efficacy of rhGUS as determined by the reduction in urinary GAG excretion after 24 weeks of treatment. The Phase 3 study will also evaluate 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.

Agreement has been reached with both the FDA and the European Medicines Agency, or EMA, on the Phase 3 study design. 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 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 addition to the above development plan, we intend to study MPS 7 patients under the age of five years, including potentially younger infants born with hydrops fetalis. Currently, these infants can die within a few months to one year, but enzyme replacement therapy might be able to reduce GAG storage and improve health and survival in these patients.

We are also supplying rhGUS to investigators who are treating patients under emergency investigational new drug, or eIND, applications. 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. The results indicated that a decline in urinary GAG excretion of 50-70% and a sustained reduction in the size of the enlarged liver and spleen were observed at a dose of 2 mg/kg. The data also showed improved pulmonary function based on reduced carbon dioxide retention. No serious adverse events or infusion-associated reactions were observed through 12 infusions.

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.

Triheptanoin (UX007) for the treatment of LC-FAOD

We are developing triheptanoin for oral administration intended as a substrate replacement therapy for patients with long-chain fatty acid oxidation disorders, or LC-FAOD. Triheptanoin 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, or MCT, 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 (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. These results are clinically important but are derived from a retrospective medical review, and not from a prospective randomized controlled study.

Triheptanoin is currently being evaluated in a prospective, interventional, open-label Phase 2 study in approximately 30 severely affected LC-FAOD patients. The principal goals of the study are to determine the appropriate clinical endpoints and patient population for testing in potential later-stage pivotal studies. Prior to initiating treatment with triheptanoin, subjects will continue current therapy for four weeks to establish their baseline condition. Triheptanoin will then be titrated to an expected target dose of 25-35% of total daily caloric intake via oral administration, while ensuring tolerability. The study will assess the impact of triheptanoin on several endpoints, including cycle ergometer performance, 12-minute walk test, muscle strength, creatine kinase levels, hypoglycemia, liver size, cardiac disease, and major medical events. The patients will be followed to evaluate the effects of triheptanoin treatment on acute clinical pathophysiology associated with LC-FAOD over 24 weeks, then may continue treatment for an additional 54 weeks for observation of major medical events. The study is fully enrolled, and we expect interim data to be available in the second half of 2015.

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 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 diet has demonstrated limited effectiveness in the treatment of developmental delay and movement disorders. 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.

Triheptanoin 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 triheptanoin.

In March 2014, we initiated a Phase 2 global, randomized, double-blind, placebo-controlled, parallel-group clinical trial that may 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 triheptanoin through week 52. Based on recently published results and in order to accelerate enrollment, we have amended the enrollment criteria to also include patients with only absence seizures. We expect to release interim data from this study in the second half of 2015. We are exploring additional studies in patients with additional disease manifestations and diet regimens based on investigator feedback.

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 lose major muscle function within ten to 20 years of diagnosis. There is no approved drug therapy for HIBM.

SA-ER is intended as a potential 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 47 HIBM 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 SA-ER per day. After 24 weeks, placebo patients crossed over to either three grams or six grams total daily dose, on a blinded basis, 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 SA-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. SA-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 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 SA-ER for 24 weeks. The results presented at WMS include 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 SA-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. Over the entire approximate two-year study, treatment with SA-ER appeared to slow the progression of upper extremity disease when compared to the 24-week placebo group extrapolated out to two years.

We recently completed an End-of-Phase 2 meeting with the FDA regarding a potential randomized placebo-controlled 48-week single pivotal study of SA-ER in HIBM patients. The FDA agreed with the proposed 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. We plan to initiate the Phase 3 trial, which we anticipate will include approximately 80 patients, during the second half of 2015.

Based on Scientific Advice recently received from the EMA's Committee for Medicinal Products for Human Use, we intend to file in the second half of 2015 an MAA seeking conditional approval from the EMA for the use of six grams per day of SA-ER tablets in the treatment of HIBM for stabilization or slowing of decline in upper extremity muscle strength.

Competition

The commercialization of new drugs is competitive, and we may face worldwide competition from individual investigators, major pharmaceutical companies, specialty pharmaceutical companies, biotechnology companies, nutraceutical companies, and ultimately biosimilar and generic companies. Our competitors may develop or market therapies that are more effective, safer, or less costly than any that may be commercialized by us, or may obtain regulatory approval for their therapies more rapidly than we may obtain approval for ours.

The acquisition or licensing of pharmaceutical products is also very competitive, and a number of more established companies, which have acknowledged strategies to license or acquire products, may have competitive advantages as may other emerging companies taking similar or different approaches to product acquisitions. These established companies may have a competitive advantage over us due to their size, cash flows, and institutional experience.

With respect to KRN23, although we are not aware of any other products currently in clinical development for the treatment of XLH, it is possible that competitors may produce, develop, and commercialize therapeutics, or utilize other approaches such as gene therapy, to treat XLH. Most pediatric patients with XLH are managed using oral phosphate replacement and/or vitamin D therapy, which is relatively inexpensive and therefore may adversely affect our ability to commercialize KRN23, if approved, in some countries.

With respect to rhGUS and rhPPCA, we are not aware of any other compounds currently in clinical development for MPS 7 or galactosialidosis, but it is possible that other companies may produce, develop, and commercialize compounds that might treat these diseases. Additionally, gene therapy and other therapeutic approaches may emerge for the treatment of lysosomal diseases. Bone marrow or stem cell transplants have also been used in MPS 7 and in other lysosomal storage diseases and represent a potential competing therapy. Stem cell transplants have been effective in treating soft tissue storage and in having an impact on brain disease, but have not to date proven effective in treating bone and connective tissue disease. Typically, enzyme replacement therapy has had an impact on bone and connective tissue disease in other disorders when patients were treated early.

With respect to triheptanoin, there are currently no approved drugs or treatments for patients with LC-FAOD or Glut1 DS. LC-FAOD is commonly treated with diet therapy and MCT, and triheptanoin would compete with MCT. Glut1 DS is commonly treated with ketogenic diet and antiepileptic drugs. Triheptanoin may compete with these approaches, though it may potentially be used in combination. Although we believe that triheptanoin should be considered a drug and will be regulated that way, it is possible that other companies or individuals may attempt to produce triheptanoin for use by LC-FAOD, Glut1 DS, and other patients by attempting to sell the product via a nutritional supplement or medical food pathway. Investigators are testing triheptanoin in clinical studies across multiple indications, including LC-FAOD and Glut1 DS. For example, B. Braun Medical Inc., or B. Braun, has applied for and received orphan drug designation for triheptanoin for the treatment of certain types of LC-FAOD in Europe; however, we are not aware of any ongoing clinical development activities by B. Braun. It is also possible that other companies may produce, develop, and commercialize other medium odd-chain fatty acids, or completely different compounds, to treat LC-FAOD and Glut1 DS. Other companies may also utilize other approaches, such as gene therapy, to treat LC-FAOD and Glut1 DS.

With respect to SA-ER, although there are currently no approved drug therapies for the treatment of HIBM, it is possible that others may develop alternative approaches to the treatment of HIBM, including other metabolites from the sialic acid pathway, prodrugs, other drug therapies, and gene therapy. 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, N-acetyl mannosamine, or ManNAc, for the treatment of HIBM. This program is licensed to New Zealand Pharma, which manufactures ManNAc. The program has completed a Phase 1 clinical study, and an open-label, three-month Phase 2 study is currently enrolling patients.

Many of our competitors have substantially greater financial, technical, and human resources than we have. Additional mergers and acquisitions in the pharmaceutical industry may result in even more resources being concentrated in our competitors. Competition may increase further as a result of advances made in the commercial applicability of technologies and greater availability of capital for investment in these fields. Our success will be based in part on our ability to build and actively manage a portfolio of drugs that addresses unmet medical needs and creates value in patient therapy.

License Agreements

Kyowa Hakko Kirin

In August 2013, we entered into a collaboration and license agreement with Kyowa Hakko Kirin Co., Ltd., or KHK, pursuant to which we 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 EU, Switzerland, and Turkey, or the European territory, and we 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. Under the agreement, we also have a right of first negotiation with KHK to receive a license to develop and commercialize products in any non-diagnostic field, or in the field of orphan drugs outside of the profit share territory, the European territory, and Latin America.

In the field of orphan diseases, and except for studies conducted by KHK, we will be the lead party for development activities in the profit share territory and in the European territory until, with respect to the profit share territory, the fifth anniversary of the first commercial sale in the United States in the first indication and, with respect to the European territory, the date on which marketing approval for a licensed product for the first indication is obtained in the European territory on a country-by-country basis; each such date is referred to herein as the applicable transition date. We will share the costs for development activities in the profit share territory and European territory conducted pursuant to the development plan before the applicable transition date equally with KHK. On the applicable transition date in the relevant territory, KHK will become the lead party and be responsible for these costs. However, we will continue to share the costs of the studies commenced prior to the applicable transition date equally with KHK. While we are the lead development party in the profit share territory, we must use commercially reasonable efforts to conduct development activities in at least one orphan disease indication other than XLH, as mutually agreed upon by KHK and us.

In the profit share territory, KHK will book sales of products and we will have the sole right to promote the products for a specified period of time, with KHK increasingly participating in the promotion of the products until five years from commercial launch, after which KHK will have the sole right to promote the products, subject to a limited promotion right retained by us. In the European territory, KHK will book sales of products and have the sole right to promote and sell the products. In Latin America, we will book sales of products and have the sole right to promote and sell the products.

The profit or loss from commercializing products in the profit share territory until the applicable transition date will be shared between us and KHK on a 50/50 basis. Thereafter, we will be entitled to receive a tiered double-digit revenue share in the mid to high 20% range in the profit share territory, intended to approximate the profit share. We will also be entitled to receive a royalty of up to 10% on net sales in the European territory. In Latin America, we will pay to KHK a low single-digit royalty on net sales. Our and KHK's obligations to pay royalties will continue on a country-by-country basis for so long as we or KHK, as applicable, are selling products in such country.

KHK will supply all quantities of product for clinical studies. KHK will also supply all quantities of product for commercial sales in the profit share territory and in Latin America. The supply price to us for commercial sales in the profit share territory and in Latin America will be determined based on a fixed double-digit percentage of net sales.

The collaboration and license agreement will continue for as long as products in the field of orphan diseases are sold in the profit share territory, European territory, or Latin America, unless the agreement is terminated in accordance with its terms.

KHK may terminate the agreement in certain countries or territories based upon our failure to meet certain milestones. Specifically, if we do not obtain U.S. or European marketing approval of KRN23 for the treatment of XLH by a certain date, or make a first commercial sale, on a country-by-country basis, in Latin America by certain deadlines, KHK may terminate the agreement only with respect to the applicable territory or country in which the milestone was not timely met. In certain circumstances, we have the right to obtain an extension of the applicable deadline by making a payment to KHK in the low single-digit to low double-digit millions of dollars, depending on the milestone. Also, in the event of the occurrence of certain excusable delays, the deadline for meeting the applicable milestone above is extended to account for the period of the delay. Furthermore, either party may terminate the agreement for the material breach or bankruptcy of the other party. In any event of termination by KHK, unless such termination is the result of KHK's termination for certain types of breach of the agreement by us, we may receive low single-digit to low double-digit royalties on net post-termination sales by KHK in one or more countries or territories, the amount of which varies depending on the timing of, and reason for, such termination. In any event of termination, our rights to KRN23 under the agreement and our obligations to share development costs will cease, and the program will revert to KHK, worldwide if the agreement is terminated as a whole or solely in the terminated countries if the agreement is terminated solely with respect to certain countries.

Saint Louis University

In November 2010, we entered into a license agreement with Saint Louis University, or SLU, wherein SLU granted us certain exclusive rights to intellectual property related to GUS. Under the terms of the license agreement, SLU granted us an exclusive worldwide license to make, have made, use, import, offer for sale, and sell therapeutics related to SLU's beta-glucuronidase product, such as our rhGUS product candidate, for use in the treatment of human diseases. Under this agreement, we agreed to use best efforts to develop and commercialize a licensed product as soon as practicable consistent with sound and reasonable business practices and judgment.

Under the license agreement, we paid SLU an up-front fee of $10,000, which was recorded as a research and development expense. We will make a milestone payment of $100,000 upon approval of a glucuronidase-based enzyme therapy for treatment of MPS 7. Additionally, upon reaching a certain level of cumulative worldwide sales of the product, we will pay to SLU a low single-digit royalty on net sales of the licensed products in any country or region, subject to certain potential deductions. Our obligation to pay royalties to SLU continues on a country-by-country basis until the expiration of the last-to-expire licensed patent covering the product in such country or, in the United States, Japan, and the EU, until the later expiration of any orphan drug exclusivity. We may deduct a portion of the royalty owed if a third-party license is required. We may terminate the agreement for convenience at any time and SLU may terminate the agreement for our material breach, bankruptcy, or challenge of the licensed patents or technology, and SLU may terminate the agreement or render our license non-exclusive if we fail to meet our diligence obligations. Unless terminated as set forth above, this license agreement continues in full force and effect until the latest of expiration of the last patent based on technology licensed under the agreement, at which point our license becomes fully paid.

St. Jude Children's Research Hospital

In September 2012, we entered into a license agreement with St. Jude Children's Research Hospital, or St. Jude, wherein St. Jude granted us certain exclusive rights to intellectual property related to rhPPCA. Under the terms of the license agreement, St. Jude granted us an exclusive license under certain know-how to research, develop, make, use, offer to sell, import, and otherwise commercialize and exploit certain PPCA protein products to treat, prevent, and/or diagnose galactosialidosis and other monogenetic diseases. We agreed to make commercially reasonable efforts to develop and commercialize at least one licensed product.

Under the license agreement, we paid St. Jude an up-front fee of $10,000, which was recorded as research and development expense. Additionally, we will pay to St. Jude a royalty of less than 1% on net sales of these products for so long as such products retain orphan drug exclusivity, on a country-by-country basis. We may terminate the agreement for convenience at any time and St. Jude may terminate the agreement for our material breach of the agreement. Unless terminated for convenience or material breach, as applicable, this license agreement continues in full force and effect, until our royalty obligations expire, at which point our license becomes irrevocable, perpetual, fully paid, and royalty-free.

Baylor Research Institute

In August 2012, we entered into a license agreement with Baylor Research Institute, or BRI, whereby we exclusively licensed certain intellectual property related to triheptanoin for North America and paid BRI an up-front fee of $250,000. The license includes patents, patent applications, know-how, and intellectual property related to the composition and formulation of triheptanoin as well as its use in treating a number of orphan diseases, including FAOD. The license grant includes the sole right to develop, manufacture, and commercialize licensed products for all human and animal uses. In June 2013, we exercised our option to license this intellectual property outside of North America and paid BRI the $750,000 fee associated with this option exercise. Under the license agreement, we are obligated to use commercially reasonable efforts to develop and commercialize licensed products in select orphan indications. If we fail to meet our diligence obligations with respect to a specified orphan indication or set of orphan indications, BRI may convert our license to a non-exclusive license with respect to such orphan indication or set of orphan indications until we receive regulatory approval for licensed products in the applicable orphan indication or set of orphan indications. We are also obligated to pay a mid-single digit royalty on net sales to BRI, subject to certain reductions and offsets. Our obligation to pay royalties to BRI continues on a licensed product-by-licensed product and country-by-country basis until the later of the expiration of the first regulatory exclusivity granted with respect to such product in such country or the expiration of the last-to-expire licensed patent claiming such product in such country, in each case in connection with approval in such country for FAOD or an orphan disease covered by our license from BRI. We may make future payments of up to $10.5 million contingent upon attainment of certain development milestones and $7.5 million if certain sales milestones are achieved. We may terminate the agreement for convenience at any time and either we or BRI may terminate the agreement for the material breach or bankruptcy of the other party. If we terminate for BRI’s breach or bankruptcy, our license from BRI will remain in effect, subject to our continued payment of reduced milestones and royalties. Unless terminated for convenience or material breach or bankruptcy, as applicable, this license agreement continues in full force and effect, on a product-by-product and country-by-country basis, until our royalty obligations expire, at which point our license from BRI with respect to such product in such country becomes irrevocable, perpetual, fully paid and royalty-free.

Nobelpharma

In September 2010, we entered into a collaboration and license agreement with Nobelpharma Co., Ltd., or Nobelpharma. Under the terms of the collaboration and license agreement, each party granted the other party a worldwide exclusive license under certain of that party’s intellectual property related to the compound identified as N-acetylneuraminic acid, also known as sialic acid, to develop, manufacture, and commercialize products. Nobelpharma’s licensed territory includes Japan and certain other Asian countries, and our licensed territory includes the rest of the world. The parties conduct development independently, and each party is obligated to make commercially reasonable efforts to file an investigational new drug application, or IND, for licensed products in its territory and, in our case, to obtain patent term extensions and data exclusivity in Europe and North America, and share with the other party all data, documentation, and information that is generated in conducting such activities. Nobelpharma must use commercially reasonable efforts to supply us with the sialic acid drug substance. Either Nobelpharma or we can terminate this supply arrangement for convenience, at which point Nobelpharma would provide technical assistance to allow us to manufacture the sialic acid drug substance ourselves. If we choose to manufacture the sialic acid drug substance, Nobelpharma will have the right to purchase the sialic acid drug substance from us and we will use commercially reasonable efforts to supply Nobelpharma with the sialic acid drug substance.

Under the collaboration and license agreement, we have paid Nobelpharma approximately $110,000 as an upfront fee and approximately $495,000 in development milestone payments and also issued 76,567 shares of common stock to Nobelpharma. We are required to pay Nobelpharma a high single digit royalty on net sales of products in our territory, and Nobelpharma is required to pay us a mid-single digit royalty on net sales in their territory (with the exception of Japan). Each party’s obligation to pay royalties is subject to certain offsets and deductions, and is payable on a product-by-product and country-by-country basis until the expiration of the collaboration and license agreement. In addition, we are obligated to make a future payment to Nobelpharma of ¥200 million (approximately $1.7 million U.S. dollars as of December 31, 2014) based upon achievement of a certain approval milestone. Either party may terminate the agreement for the material breach or bankruptcy of the other party. If either party terminates the agreement, the terminating party’s license will become irrevocable and royalty-free. Unless terminated for material breach or bankruptcy, as applicable, this license agreement continues in full force and effect, on a country-by-country basis, until the date of the first launch of a generic product of the licensed product in a country.

AAIPharma

In March 2011, we entered into a license agreement with AAIPharma Services Corp., or AAIPharma. Under the terms of this license agreement, AAIPharma granted us a fully paid-up, royalty-free, exclusive, perpetual, and irrevocable license to research, develop, make, have made, use, import, offer for sale, and sell products incorporating AAIPharma’s controlled release matrix solid dose oral tablet technology for use in connection with sialic acid for the treatment of HIBM or distal myopathy with rimmed vacuoles. Under the license agreement, we will pay a mid-single digit percentage of any sublicense revenue received by us related to the sublicense of AAIPharma technology. As consideration, we agreed to provide preclinical and clinical data to AAIPharma. AAIPharma is responsible for patent prosecution and maintenance, subject to our right to review and comment on such prosecution and maintenance. We may terminate the agreement for convenience at any time and either party may terminate the agreement for the material breach or bankruptcy of the other party.

HIBM Research Group

In April 2012, we entered into an exclusive license agreement with HIBM Research Group, or HRG, wherein HRG granted us an exclusive, worldwide license to certain intellectual property related to the treatment of HIBM and related conditions using substrate replacement therapy.

Under the terms of the license agreement, we paid HRG an up-front fee of $25,000, which was recorded as a research and development expense. We will make future payments contingent upon attainment of various development and approval milestones of up to $300,000 in the aggregate. Additionally, we will pay to HRG a royalty of less than 1% of net sales of products, if any. Our obligation to pay royalties to HRG continues on a product-by-product and country-by-country basis until the expiration of the last-to-expire licensed patent claiming such product in such country, or the later expiration of orphan drug exclusivity in certain countries. We are obligated to make commercially reasonable efforts to develop and commercialize a substrate replacement therapy for HIBM. We may terminate the agreement for convenience at any time and either party may terminate the agreement for the material breach or bankruptcy of the other party. We must also terminate the agreement if we terminate our HIBM substrate replacement therapy program. Unless terminated for convenience, for our termination of our HIBM substrate replacement therapy program, or for material breach or bankruptcy, as applicable, this license agreement continues in full force and effect, on a product-by-product and country-by-country basis, until the expiration date of the last-to-expire licensed patent claiming such product in such country, or the later expiration of orphan drug exclusivity in certain countries, at which point our license becomes irrevocable, perpetual, fully paid, and royalty-free.

Patents and Proprietary Rights

The proprietary nature of, and protection for, our product candidates, processes, and know-how are important to our business. Our success depends in part on our ability to protect the proprietary nature of our product candidates, technology, and know-how, to operate without infringing on the proprietary rights of others, and to prevent others from infringing our proprietary rights. We seek patent protection in the United States and internationally for our product candidates and other technology. Our policy is to patent or in-license the technology, inventions and improvements that we consider important to the development of our business. In addition to patent protection, we intend to use other means to protect our proprietary rights, including pursuing marketing or data exclusivity periods, orphan drug status, and similar rights that are available under regulatory provisions in certain countries, including the United States, Europe, Japan, and China. See “U.S. Government Regulation — Orphan Designation and Exclusivity,” “U.S. Government Regulation — Pediatric Studies and Exclusivity,” “U.S. Government Regulation — Patent Term Restoration,” “U.S. Government Regulation — Biosimilars and Exclusivity,” “U.S. Government Regulation — Abbreviated New Drug Applications for Generic Drugs,” “U.S. Government Regulation — Hatch-Waxman Patent Certification and the 30-Month Stay,” and “European Union/Rest of World Government Regulation — Orphan Designation and Exclusivity” below for additional information.

We also rely on trade secrets, know-how, and continuing innovation to develop and maintain our competitive position. We cannot be certain that patents will be granted with respect to any of our pending patent applications or with respect to any patent applications filed by us in the future, nor can we be sure that any of our existing patents or any patents granted to us in the future will be commercially useful in protecting our technology.

We seek regulatory approval for our products in disease areas with high unmet medical need, great market potential, and where we have a proprietary position through patents covering various aspects of our products, such as composition, dosage, formulation, use, and manufacturing process, among others. Our success depends on an intellectual property portfolio that supports our future revenue streams and erects barriers to our competitors. We are maintaining and building our patent portfolio through filing new patent applications, prosecuting existing applications, and licensing and acquiring new patents and patent applications.

Despite these measures, any of our intellectual property and proprietary rights could be challenged, invalidated, circumvented, infringed or misappropriated, or such intellectual property and proprietary rights may not be sufficient to permit us to take advantage of current market trends or otherwise to provide competitive advantages. For more information, please see “Risks Related to our Intellectual Property.”

As of March 9, 2015, we own 1 issued U.S. patent and 11 pending U.S. patent applications as well as corresponding patents and patent applications internationally. In addition, as of March 9, 2015, we have licensed 11 issued U.S. patents and 14 pending U.S. patent applications as well as corresponding foreign patents and applications from third parties, on an exclusive basis. With respect to our issued patents in the United States and Europe, we are also entitled to obtain a patent term extension to extend the patent expiration date. For example, in the United States, we can apply for a patent term extension of up to five years for one of the patents covering a product once the product is approved by the FDA. The exact duration of the extension depends on the time we spend in clinical studies as well as getting a new drug application approval, or NDA, from the FDA. The patent portfolios for our five leading product candidates as of March 9, 2015 are summarized below.

KRN23

We have rights from KHK to patents and patent applications relating to KRN23, a fully human monoclonal antibody against FGF23, and its use for the treatment of XLH and various other hypophosphatemic conditions. Pursuant to this license, we share rights to 20 issued patents, including 3 U.S. patents and 1 pending U.S. application and patents and applications in other jurisdictions covering generic and specific antibodies against FGF23 as well as their use for the treatment of XLH and related conditions. The patent terms for issued patents in the United States are from 2022 to 2029 (without patent term extension). The projected patent term for pending applications in the United States is 2028. We intend to pursue marketing and orphan drug exclusivity periods that are available to us under regulatory provisions in certain countries. KRN23 has received orphan drug designation in the United States and Europe for the treatment of XLH.

rhGUS

We have no issued patents covering rhGUS but we have filed 3 U.S. patent applications directed to compositions with certain characteristics that are useful for the enzyme replacement therapy for the treatment of multi-system lysosomal storage disease. Throughout clinical research and development, we also intend to file patent applications directed to various aspects of the treatment therapy including dosage, regimen, formulation, manufacturing, etc. We intend to pursue marketing and orphan drug exclusivity periods that are available under regulatory provisions in certain countries. rhGUS has received orphan drug designation in both the United States and Europe for the treatment of MPS 7.

rhPPCA

We have no issued patents or patent applications filed for rhPPCA, although it is partially protected by proprietary know-how licensed from St. Jude Children's Hospital. We intend to build a patent portfolio directed to compositions with certain characteristics that are useful for the enzyme replacement therapy for the treatment of autosomal recessive lysosomal storage disease as well as various aspects of the treatment therapy including dosage, regimen, formulation, manufacturing, etc. We intend to pursue marketing and orphan drug exclusivity periods that are available under regulatory provisions in certain countries.

Triheptanoin

We are the licensee or owner of patents and patent applications relating to triheptanoin and its use for a number of diseases including FAOD and Glut1 DS. In particular, we have an exclusive license from Baylor Research Institute, or BRI, with respect to its triheptanoin patent portfolio. We have licensed from BRI 26 issued patents, including 8 U.S. patents and 7 pending U.S. applications and patents and applications in other jurisdictions covering composition, formulation, use and manufacturing of triheptanoin and related odd carbon fatty acids. The patent terms for issued patents in the United States are from 2020 to 2025 (without patent term extension). The projected patent terms for pending applications in the United States are from 2020 to 2034. We intend to pursue marketing and orphan drug exclusivity periods that are available under regulatory provisions in certain countries. Triheptanoin for the treatment of Glut1 DS has received orphan drug designation in the United States.

SA-ER

We are the licensee or owner of patents and patent applications relating to sialic acid and its use for the treatment of HIBM. We have 9 pending U.S. applications and patents and applications in other jurisdictions covering the use of sialic acid for the treatment of HIBM, biomarkers useful for such treatment as well as extended release formulations of sialic acid. The projected patent terms for pending applications in the United States are from 2028 to 2033.

We intend to pursue marketing and orphan drug exclusivity periods that are available under regulatory provisions in certain countries. SA-ER has received orphan drug designation in both the United States and the EU for the treatment of HIBM.

Trademarks

We have filed trademark applications for the Ultragenyx brand in the U.S. and multiple other jurisdictions.

Other

We rely upon unpatented trade secrets, know-how, and continuing technological innovation to develop and maintain our competitive position. We seek to protect our ownership of know-how and trade secrets through an active program of legal mechanisms including assignments, confidentiality agreements, material transfer agreements, research collaborations, and licenses.

Manufacturing

We currently contract with third parties for the manufacturing and testing of our product candidates for preclinical studies and clinical studies and intend to do so in the future. We do not own or operate manufacturing facilities for the production of clinical quantities of our product candidates. We currently have no plans to build our own clinical or commercial scale manufacturing capabilities. The use of contracted manufacturing and reliance on collaboration partners is relatively cost-efficient and has eliminated the need for our direct investment in manufacturing facilities and additional staff early in development. Although we rely on contract manufacturers, we have personnel with extensive manufacturing experience to oversee our contract manufacturers.

To date, our third-party manufacturers have met our manufacturing requirements. We expect third-party manufacturers to be capable of providing sufficient quantities of our product candidates to meet anticipated full scale commercial demands. To meet our projected needs for commercial manufacturing, third parties with whom we currently work might need to increase their scale of production or we will need to secure alternate suppliers. We believe that there are alternate sources of supply that can satisfy our clinical and commercial requirements, although we cannot be certain that identifying and establishing relationships with such sources, if necessary, would not result in significant delay or material additional costs.

KRN23

The drug substance and drug product for KRN23 are made by KHK in Japan under the collaboration and license agreement with KHK. The cell line to produce KRN23 is specific for this product and is in KHK's control. All other raw materials are commercially available.

rhGUS

rhGUS drug substance and drug product are manufactured by Rentschler Biotechnologie GmbH, or Rentschler, under a development and clinical supply agreement executed in August 2012. Pursuant to the clinical supply agreement, we have agreed not to source larger quantities of drug substance or drug product from another supplier than from Rentschler in any given year. The supply agreement will continue in full force and effect until all clinical services have been completed or terminated per the terms of the supply agreement. Either party may terminate the supply agreement if the other party fails to pay any sum payable under the supply agreement within 30 days after a written demand is issued after the original due date, if the other party makes a material misrepresentation or commits a material breach of its obligations under the supply agreement and fails to cure such breach within specified time periods if curable, if the other party ceases to carry on its business for a period no less than 60 days, or if a party experiences certain insolvency events. Additionally, either party may terminate the supply agreement upon 30 days' prior written notice if the Steering Committee concludes that the services required under the supply agreement cannot be performed and we may terminate the agreement at any time before completion of the services rendered pursuant to the agreement upon 60 days' prior written notice. The cell line to produce rhGUS is specific for this product and is in our control and stored in multiple secure locations. All other raw materials are commercially available.

rhPPCA

No commercial supplier has yet been selected for rhPPCA. The cell line to produce rhPPCA is specific for this product and is in our control and stored in multiple secure locations. All other raw materials are commercially available. We are currently developing a manufacturing process for rhPPCA.

Triheptanoin

The pharmaceutical-grade drug substance for triheptanoin is manufactured by Cremer Oleo GmbH & Co. KG in Germany under an exclusive worldwide supply agreement, subject to certain limitations, executed in 2012. The supply agreement has an initial term of three years; thereafter, the agreement shall be automatically renewed for additional two-year periods unless either party notifies the other party of its intention not to renew in writing at least three calendar months before the expiration of the then current term. Additionally, if a party materially breaches an obligation under the agreement and does not cure such breach within 60 days of receiving notice of the breach from the non-breaching party, the non-breaching party may terminate the agreement immediately upon written notice to the breaching party. Triheptanoin drug product manufacturing has been done with more than one party and is not considered a very specialized task.

SA-ER

The drug substance for SA-ER is currently manufactured by Sanyo Fine Co., Ltd. in Japan through the license agreement with Nobelpharma. The SA-ER drug product is manufactured by AAIPharma under our license agreement and accompanying purchase orders with AAIPharma. We are in the process of securing secondary sources of drug substance and drug product for SA-ER. Manufacture of the drug substance requires a specialized enzyme-catalyzed step, and a secondary source of the enzyme itself is also under development. All raw materials to produce the drug substance and drug product are commercially available. The cell line to produce the specialized enzyme is under our control and is stored in multiple secured locations.

Sales and Marketing

We currently intend to build the commercial infrastructure in the United States and Europe necessary to effectively support the commercialization of all of our product candidates, if and when we believe a regulatory approval of the first of such product candidates in a particular geographic market appears imminent. The commercial infrastructure for rare disease products typically consists of a targeted, specialty sales force that calls on a limited and focused group of physicians supported by sales management, medical liaisons, internal sales support, an internal marketing group, and distribution support. One challenge unique to commercializing therapies for rare diseases is the difficulty in identifying eligible patients due to the very small and sometimes heterogeneous disease populations. Our management team is experienced in maximizing patient identification for both clinical development and commercialization purposes in rare diseases.

Additional capabilities important to the rare disease marketplace include the management of key accounts such as managed care organizations, group-purchasing organizations, specialty pharmacies, and government accounts. To develop the appropriate commercial infrastructure, we will have to invest significant amounts of financial and management resources, some of which will be committed prior to any confirmation that any of our product candidates will be approved.

Outside of the United States and Europe, where appropriate, we may elect in the future to utilize strategic partners, distributors, or contract sales forces to assist in the commercialization of our products. In certain instances we may consider building our own commercial infrastructure.

Government Regulation

Government authorities in the United States (including federal, state, and local authorities) and in other countries, extensively regulate, among other things, the manufacturing, research and clinical development, marketing, labeling and packaging, storage, distribution, post-approval monitoring and reporting, advertising and promotion, pricing, and export and import of pharmaceutical products, such as those we are developing. The process of obtaining regulatory approvals and the subsequent compliance with appropriate federal, state, local, and foreign statutes and regulations require the expenditure of substantial time and financial resources.

U.S. Government Regulation

In the United States, the FDA regulates drugs under the Federal Food, Drug, and Cosmetic Act, or FDCA, and its implementing regulations, and biologics under the FDCA and the Public Health Service Act, or PHSA, and its implementing regulations. FDA approval is required before any new unapproved drug or dosage form, including a new use of a previously approved drug, can be marketed in the United States. Drugs and biologics are also subject to other federal, state, and local statutes and regulations. If we fail to comply with applicable FDA or other requirements at any time during the drug development process, clinical testing, the approval process or after approval, we may become subject to administrative or judicial sanctions. These sanctions could include the FDA's refusal to approve pending applications, license suspension or revocation, withdrawal of an approval, warning letters, product recalls, product seizures, total or partial suspension of production or distribution, injunctions, fines, civil penalties or criminal prosecution. Any FDA enforcement action could have a material adverse effect on us.

The process required by the FDA before product candidates may be marketed in the United States generally involves the following:

- completion of extensive preclinical laboratory tests and preclinical animal studies performed in accordance with the Good Laboratory Practices, or GLP, regulations;
- submission to the FDA of an IND, which must become effective before human clinical studies may begin and must be updated annually;
- approval by an independent institutional review board, or IRB, or ethics committee representing each clinical site before each clinical study may be initiated;
- performance of adequate and well-controlled human clinical studies to establish the safety and efficacy of the product candidate for each proposed indication;
- preparation of and submission to the FDA of an NDA, or biologics license application, or BLA, after completion of all pivotal clinical studies;
- potential review of the product application by an FDA advisory committee, where appropriate and if applicable;
- satisfactory completion of an FDA pre-approval inspection of the manufacturing facilities where the proposed drug substance and drug product are produced to assess compliance with Good Manufacturing Practices, or GMP;
- FDA will typically inspect one or more clinical sites to assure compliance with GCP; and
- FDA review and approval of an NDA or BLA prior to any commercial marketing or sale of the drug in the United States.

The preclinical and clinical testing and approval process requires substantial time, effort, and financial resources, and we cannot be certain that any approvals for our product candidates will be granted on a timely basis, if at all. Additionally, the IND may be placed on clinical hold and the IND sponsor and the FDA must resolve any outstanding concerns or questions before clinical studies can begin.

Clinical Studies

Clinical studies involve the administration of the investigational new drug to human subjects under the supervision of qualified investigators in accordance with protocols and Good Clinical Practices, or GCPs. A protocol for each clinical study and any subsequent protocol amendments must be submitted to the FDA as part of the IND. Additionally, approval must also be obtained from each clinical study site's IRB, before the studies may be initiated, and the IRB must monitor the study until completed. There are also requirements governing the reporting of ongoing clinical studies and clinical study results to public registries.

The clinical investigation of a drug is generally divided into three or four phases. Although the phases are usually conducted sequentially, they may overlap or be combined.

- *Phase 1.* The drug is initially introduced into healthy human subjects or patients with the target disease or condition. These studies are designed to evaluate the safety, dosage tolerance, pharmacokinetics and pharmacologic actions of the investigational new drug in humans, and if possible, to gain early evidence on effectiveness.
- *Phase 2.* The drug is administered to a limited patient population to evaluate dosage tolerance and optimal dosage, identify possible adverse side effects and safety risks, and preliminarily evaluate efficacy.
- *Phase 3.* The drug is administered to an expanded patient population, generally at geographically dispersed clinical study sites to generate enough data to statistically evaluate dosage, clinical effectiveness and safety, to establish the overall benefit-risk relationship of the investigational new drug product, and to provide an adequate basis for product approval.
- *Phase 4*. In some cases, the FDA may condition approval of an NDA or BLA for a product candidate on the sponsor's agreement to conduct additional clinical studies after approval. In other cases, a sponsor may voluntarily conduct additional clinical studies after approval to gain more information about the drug. Such post-approval studies are typically referred to as Phase 4 clinical studies.

A pivotal study is a clinical study that adequately meets regulatory agency requirements for the evaluation of a drug candidate's efficacy and safety such that it can be used to justify the approval of the product. Generally, pivotal studies are Phase 3 studies, but the FDA may accept results from Phase 2 studies if the study design provides a well-controlled and reliable assessment of clinical benefit, particularly in situations where there is an unmet medical need and the results are sufficiently robust.

The FDA, the IRB, or the clinical study sponsor may suspend or terminate a clinical study at any time on various grounds, including a finding that the research subjects are being exposed to an unacceptable health risk.

Additionally, some clinical studies are overseen by an independent group of qualified experts organized by the clinical study sponsor, known as a data safety monitoring board or committee. This group provides recommendations for whether or not a study may move forward at designated check points based on access to certain data from the study. The sponsor may also suspend or terminate a clinical study based on evolving business objectives and/or competitive climate.

The clinical study process can take three to ten years or more to complete, and there can be no assurance that the data collected will support FDA approval or licensure of the product.

Submission of an NDA or BLA to the FDA

Assuming successful completion of all required testing in accordance with all applicable regulatory requirements, detailed investigational new drug product information is submitted to the FDA in the form of an NDA or BLA requesting approval to market the product for one or more indications. Under federal law, the submission of most NDAs and BLAs is subject to an application user fee. For fiscal year 2014, the application user fee exceeds $2.1 million, and the sponsor of an approved NDA or BLA is also subject to annual product and establishment user fees, set at $104,060 per product and $554,600 per establishment, as well as new application fees in excess of $1 million for supplemental applications with clinical data. These fees are typically increased annually. Applications for orphan drug products are exempted from the NDA and BLA user fees and may be exempted from product and establishment user fees, unless the application includes an indication for other than a rare disease or condition.

An NDA or BLA must include all relevant data available from pertinent preclinical and clinical studies, including negative or ambiguous results as well as positive findings, together with detailed information relating to the product's chemistry, manufacturing, controls, and proposed labeling, among other things. Data can come from company-sponsored clinical studies intended to test the safety and effectiveness of a use of a product, or from a number of alternative sources, including studies initiated by investigators. To support marketing approval, the data submitted must be sufficient in quality and quantity to establish the safety and effectiveness of the investigational new drug product to the satisfaction of the FDA.

Once an NDA or BLA has been submitted, the FDA's goal is to review the application within ten months after it accepts the application for filing, or, if the application relates to an unmet medical need in a serious or life-threatening indication, six months after the FDA accepts the application for filing. The review process can be significantly extended by FDA requests for additional information or clarification.

The FDA's Decision on an NDA or BLA

FDA may issue an approval letter or a Complete Response Letter. An approval letter authorizes commercial marketing of the drug with specific prescribing information for specific indications. A Complete Response Letter indicates that the review cycle of the application is complete and the application is not ready for approval. A Complete Response Letter may require additional clinical data and/or an additional pivotal Phase 3 clinical study(ies), and/or other significant, expensive and time-consuming requirements related to clinical studies, preclinical studies or manufacturing. Even if such additional information is submitted, the FDA may ultimately decide that the NDA or BLA does not satisfy the criteria for approval. The FDA could also approve the NDA or BLA with a Risk Evaluation and Mitigation Strategy, or REMS, plan to mitigate risks, which could include medication guides, physician communication plans, or elements to assure safe use, such as restricted distribution methods, patient registries and other risk minimization tools. The FDA also may condition approval on, among other things, changes to proposed labeling, development of adequate controls and specifications, or a commitment to conduct one or more post-market studies or clinical studies. Such post-market testing may include Phase 4 clinical studies and surveillance to further assess and monitor the product's safety and effectiveness after commercialization. Also, new government requirements, including those resulting from new legislation, may be established, or the FDA's policies may change, which could delay or prevent regulatory approval of our products under development.

Expedited Review and Accelerated Approval Programs

A sponsor may seek approval of its product candidate under programs designed to accelerate FDA's review and approval of NDAs and BLAs. For example, Fast Track Designation may be granted to a drug intended for treatment of a serious or life-threatening disease or condition that has potential to address unmet medical needs for the disease or condition. The key benefits of fast track designation are the eligibility for priority review, rolling review (submission of portions of an application before the complete marketing application is submitted), and accelerated approval, if relevant criteria are met. Based on results of the Phase 3 clinical study(ies) submitted in an NDA or BLA, upon the request of an applicant, the FDA may grant the NDA or BLA a priority review designation, which sets the target date for FDA action on the application at six months after the FDA accepts the application for filing. Priority review is granted where there is evidence that the proposed product would be a significant improvement in the safety or effectiveness of the treatment, diagnosis, or prevention of a serious condition. If criteria are not met for priority review, the application is subject to the standard FDA review period of ten months after FDA accepts the application for filing. Priority review designation does not change the scientific/medical standard for approval or the quality of evidence necessary to support approval.

Under the accelerated approval program, the FDA may approve an NDA or BLA on the basis of either a surrogate endpoint that is reasonably likely to predict clinical benefit, or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments. Post-marketing studies or completion of ongoing studies after marketing approval are generally required to verify the drug's clinical benefit in relationship to the surrogate endpoint or ultimate outcome in relationship to the clinical benefit.

In addition, the Food and Drug Administration Safety and Innovation Act, or FDASIA, which was enacted and signed into law in 2012, established the new Breakthrough Therapy designation. A sponsor may seek FDA designation of its product candidate as a breakthrough therapy if the drug is intended, alone or in combination with one or more other drugs, to treat a serious or life-threatening disease or condition and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development.

Post-Approval Requirements

Drugs manufactured or distributed pursuant to FDA approvals are subject to pervasive and continuing regulation by the FDA, including, among other things, requirements relating to recordkeeping, periodic reporting, product sampling and distribution, advertising and promotion and reporting of adverse experiences with the product. After approval, most changes to the approved product, such as adding new indications or other labeling claims are subject to prior FDA review and approval.

Drug manufacturers are subject to periodic unannounced inspections by the FDA and state agencies for compliance with cGMP requirements. Changes to the manufacturing process are strictly regulated, and, depending on the significance of the change, may require prior FDA approval before being implemented. FDA regulations also require investigation and correction of any deviations from cGMP and impose reporting and documentation requirements upon us and any third-party manufacturers that we may decide to use. Accordingly, manufacturers must continue to expend time, money and effort in the area of production and quality control to maintain compliance with cGMP and other aspects of regulatory compliance.

Future FDA and state inspections may identify compliance issues with our pharmacovigilance systems or at our facilities or at the facilities of our contract manufacturers that may disrupt production or distribution, or require substantial resources to correct. In addition, discovery of previously unknown problems with a product or the failure to comply with applicable requirements may result in restrictions on a product, manufacturer or holder of an approved NDA or BLA, including withdrawal or recall of the product from the market or other voluntary, FDA-initiated or judicial action that could delay or prohibit further marketing. Also, new government requirements, including those resulting from new legislation, may be established, or the FDA's policies may change, which could delay or prevent regulatory approval of our products under development.

The FDA may withdraw approval if compliance with regulatory requirements and standards is not maintained or if problems occur after the product reaches the market. Later discovery of previously unknown problems with a product, including adverse events of unanticipated severity or frequency, or with manufacturing processes, or failure to comply with regulatory requirements, may result in revisions to the approved labeling to add new safety information; imposition of post-market studies or clinical studies to assess new safety risks; or imposition of distribution restrictions or other restrictions under a REMS program. Other potential consequences include, among other things:

- restrictions on the marketing or manufacturing of the product, complete withdrawal of the product from the market or product recalls;
- fines, warning letters or holds on post-approval clinical studies;
- refusal of the FDA to approve pending NDAs or supplements to approved NDAs, or suspension or revocation of product license approvals;
- product seizure or detention, or refusal to permit the import or export of products; or
- injunctions or the imposition of civil or criminal penalties.

The FDA strictly regulates marketing, labeling, advertising, and promotion of products that are placed on the market. Drugs may be promoted only for the approved indications and in accordance with the provisions of the approved label. The FDA and other agencies actively enforce the laws and regulations prohibiting the promotion of off-label uses, and a company that is found to have improperly promoted off-label uses may be subject to significant liability.

Orphan Designation and Exclusivity

The FDA may grant orphan drug designation to drugs intended to treat a rare disease or condition that affects fewer than 200,000 individuals in the United States, or if it affects more than 200,000 individuals in the United States and there is no reasonable expectation that the cost of developing and making the drug for this type of disease or condition will be recovered from sales in the United States.

Orphan drug designation entitles a party to financial incentives such as opportunities for grant funding towards clinical study costs, tax advantages, and user-fee waivers. In addition, if a product receives FDA approval for the indication for which it has orphan designation, the product is entitled to orphan drug exclusivity, which means the FDA may not approve any other application to market the same drug for the same indication for a period of seven years, except in limited circumstances, such as a showing of clinical superiority over the product with orphan exclusivity.

Pediatric Studies and Exclusivity

NDAs and BLAs must contain data (or a proposal for post-marketing activity) to assess the safety and effectiveness of an investigational new drug product for the claimed indications in all relevant pediatric populations in order to support dosing and administration for each pediatric subpopulation for which the drug is safe and effective. The FDA may, on its own initiative or at the request of the applicant, grant deferrals for submission of some or all pediatric data until after approval of the product for use in adults or full or partial waivers if certain criteria are met. Discussions about pediatric development plans can be discussed with the FDA at any time, but usually occur any time between the end-of-Phase II meeting and submission of the NDA or BLA. The requirements for pediatric data do not apply to any drug for an indication for which orphan designation has been granted.

Pediatric exclusivity is another type of non-patent exclusivity in the United States that may be granted if an NDA or BLA sponsor submits pediatric data that fairly respond to a written request from the FDA for such data. The data do not need to show the product to be effective in the pediatric population studied. If reports of FDA-requested pediatric studies are submitted to and accepted by the FDA within the statutory time limits, whatever statutory or regulatory periods of exclusivity or patent protection cover the product are extended by six months. This is not a patent term extension, but it effectively extends the regulatory period during which the FDA cannot accept or approve another application relying on the NDA or BLA sponsor's data.

Patent Term Restoration

Some of our U.S. patents may be eligible for limited patent term extension under the Drug Price Competition and Patent Term Restoration Act of 1984, commonly referred to as the Hatch-Waxman Amendments. The Hatch-Waxman Amendments permit a patent restoration term of up to five years as compensation for patent term lost during product development and the FDA regulatory review process. However, patent term restoration cannot extend the remaining term of a patent beyond a total of 14 years from the product's approval date. The patent term restoration period is generally one-half the time between the effective date of an IND and the submission date of an NDA or BLA, plus the time between the submission date and the approval of that application. Only one patent applicable to an approved product is eligible for the extension and the application for the extension must be submitted prior to the expiration of the patent. The U.S. Patent and Trademark Office, in consultation with the FDA, reviews and approves the application for any patent term extension or restoration. In the future, we may apply for restoration of patent term for one of our currently owned or licensed patents to add patent life beyond its current expiration date, depending on the expected length of the clinical studies and other factors involved in the filing of the relevant NDA or BLA.

Biosimilars and Exclusivity

The Patient Protection and Affordable Care Act, or Affordable Care Act, signed into law on March 23, 2010, includes a subtitle called the Biologics Price Competition and Innovation Act of 2009, or BPCI Act, which created an abbreviated approval pathway for biological products shown to be similar to, or interchangeable with, an FDA-licensed reference biological product. This amendment to the PHSA attempts to minimize duplicative testing. Biosimilarity, which requires that there be no clinically meaningful differences between the biological product and the reference product in terms of safety, purity, and potency, can be shown through analytical studies, animal studies, and a clinical study or studies. Interchangeability requires that a product is biosimilar to the reference product and the product must demonstrate that it can be expected to produce the same clinical results as the reference product and, for products administered multiple times, the biologic and the reference biologic may be switched after one has been previously administered without increasing safety risks or risks of diminished efficacy relative to exclusive use of the reference biologic. However, complexities associated with the larger, and often more complex, structure of biological products, as well as the process by which such products are manufactured, pose significant hurdles to implementation that are still being worked out by the FDA.

A reference biologic is granted twelve years of exclusivity from the time of first licensure of the reference product. The first biologic product submitted under the abbreviated approval pathway that is determined to be interchangeable with the reference product has exclusivity against other biologics submitting under the abbreviated approval pathway for the lesser of (i) one year after the first commercial marketing, (ii) eighteen months after approval if there is no legal challenge, (iii) eighteen months after the resolution in the applicant's favor of a lawsuit challenging the biologics' patents if an application has been submitted, or (iv) 42 months after the application has been approved if a lawsuit is ongoing within the 42-month period.

Abbreviated New Drug Applications for Generic Drugs

In 1984, with passage of the Hatch-Waxman Act, Congress authorized the FDA to approve generic drugs that are the same as drugs previously approved by the FDA under the NDA provisions of the statute. To obtain approval of a generic drug, an applicant must submit an abbreviated new drug application, or ANDA, to the agency. In support of such applications, a generic manufacturer may rely on the preclinical and clinical testing previously conducted for a drug product previously approved under an NDA, known as the reference listed drug, or RLD.

Specifically, in order for an ANDA to be approved, the FDA must find that the generic version is identical to the RLD with respect to the active ingredients, the route of administration, the dosage form, and the strength of the drug. At the same time, the FDA must also determine that the generic drug is "bioequivalent" to the innovator drug. Under the statute, a generic drug is bioequivalent to an RLD if "the rate and extent of absorption of the [generic] drug does not show a significant difference from the rate and extent of absorption of the listed drug. . . ."

Upon approval of an ANDA, the FDA indicates that the generic product is "therapeutically equivalent" to the RLD and it assigns a therapeutic equivalence rating to the approved generic drug in its publication "Approved Drug Products with Therapeutic Equivalence Evaluations," also referred to as the "Orange Book." Physicians and pharmacists consider an "AB" therapeutic equivalence rating to mean that a generic drug is fully substitutable for the RLD. In addition, by operation of certain state laws and numerous health insurance programs, the FDA's designation of an "AB" rating often results in substitution of the generic drug without the knowledge or consent of either the prescribing physician or patient.

The FDCA provides a period of five years of non-patent exclusivity for a new drug containing a new chemical entity. In cases where such exclusivity has been granted, an ANDA may not be filed with the FDA until the expiration of five years unless the submission is accompanied by a Paragraph IV certification, in which case the applicant may submit its application four years following the original product approval. The FDCA also provides for a period of three years of exclusivity if an NDA or supplement includes reports of one or more new clinical investigations, other than bioavailability or bioequivalence studies, that were conducted by or for the applicant and are essential to the approval of the application. This three-year exclusivity period often protects changes to a previously approved drug product, such as a new dosage form, route of administration, combination or indication.

Hatch-Waxman Patent Certification and the 30-Month Stay

Upon approval of an NDA or a supplement thereto, NDA sponsors are required to list with the FDA each patent with claims that cover the applicant's product or a method of using the product. Each of the patents listed by the NDA sponsor is published in the Orange Book. When an ANDA applicant files its application with the FDA, the applicant is required to certify to the FDA concerning any patents listed for the reference product in the Orange Book, except for patents covering methods of use for which the ANDA applicant is not seeking approval.

Specifically, the applicant must certify with respect to each patent that:

- the required patent information has not been filed;
- the listed patent has expired;
- the listed patent has not expired, but will expire on a particular date and approval is sought after patent expiration; or
- the listed patent is invalid, unenforceable or will not be infringed by the new product.

A certification that the new product will not infringe the already approved product's listed patents or that such patents are invalid or unenforceable is called a Paragraph IV certification. If the applicant does not challenge the listed patents or indicates that it is not seeking approval of a patented method of use, the ANDA application will not be approved until all the listed patents claiming the referenced product have expired.

If the ANDA applicant has provided a Paragraph IV certification to the FDA, the applicant must also send notice of the Paragraph IV certification to the NDA and patent holders once the ANDA has been accepted for filing by the FDA. The NDA and patent holders may then initiate a patent infringement lawsuit in response to the notice of the Paragraph IV certification. The filing of a patent infringement lawsuit within 45 days after the receipt of a Paragraph IV certification automatically prevents the FDA from approving the ANDA until the earlier of 30 months after the receipt of the Paragraph IV notice, expiration of the patent, or a decision in the infringement case that is favorable to the ANDA applicant.

European Union/Rest of World Government Regulation

In addition to regulations in the United States, we will be subject to a variety of regulations in other jurisdictions governing, among other things, clinical studies and any commercial sales and distribution of our products.

Whether or not we obtain FDA approval for a product, we must obtain the requisite approvals from regulatory authorities in foreign countries prior to the commencement of clinical studies or marketing of the product in those countries. Certain countries outside of the United States have a similar process that requires the submission of a clinical study application much like the IND prior to the commencement of human clinical studies. In the EU, for example, a clinical study application, or CTA, must be submitted for each clinical protocol to each country's national health authority and an independent ethics committee, much like the FDA and IRB, respectively. Once the CTA is accepted in accordance with a country's requirements, the clinical study may proceed.

The requirements and process governing the conduct of clinical studies vary from country to country. In all cases, the clinical studies are conducted in accordance with GCP, the applicable regulatory requirements, and the ethical principles that have their origin in the Declaration of Helsinki.

To obtain regulatory approval of an investigational medicinal product under EU regulatory systems, we must submit an MAA. The content of the NDA or BLA filed in the United States is similar to that required in the EU, with the exception of, among other things, country-specific document requirements.

For other countries outside of the EU, such as countries in Eastern Europe, Latin America or Asia, the requirements governing product licensing, pricing, and reimbursement vary from country to country.

Countries that are part of the EU, as well as countries outside of the EU, have their own governing bodies, requirements, and processes with respect to the approval of pharmaceutical products. If we fail to comply with applicable foreign regulatory requirements, we may be subject to, among other things, fines, suspension or withdrawal of regulatory approvals, product recalls, seizure of products, operating restrictions and criminal prosecution.

Authorization Procedures in the European Union

Medicines can be authorized in the EU by using either the centralized authorization procedure or national authorization procedures.

- *Centralized procedure.* The EMA implemented the centralized procedure for the approval of human medicines to facilitate marketing authorizations that are valid throughout the European Economic Area, or EEA, which is comprised of the 28 member states of the EU plus Norway, Iceland, and Lichtenstein. This procedure results in a single marketing authorization issued by the EMA that is valid across the EEA. The centralized procedure is compulsory for human medicines that are derived from biotechnology processes, such as genetic engineering; contain a new active substance indicated for the treatment of certain diseases, such as HIV/AIDS, cancer, diabetes, neurodegenerative disorders or autoimmune diseases and other immune dysfunctions; and officially designated orphan medicines.
- For medicines that do not fall within these categories, an applicant has the option of submitting an application for a centralized marketing authorization to the European Commission following a favorable opinion by the EMA, as long as the medicine concerned is a significant therapeutic, scientific or technical innovation, or if its authorization would be in the interest of public health.
- *National authorization procedures.* There are also two other possible routes to authorize medicinal products in several EU countries, which are available for investigational medicinal products that fall outside the scope of the centralized procedure:
  - *Decentralized procedure.* Using the decentralized procedure, an applicant may apply for simultaneous authorization in more than one EU country of medicinal products that have not yet been authorized in any EU country and that do not fall within the mandatory scope of the centralized procedure.
  - *Mutual recognition procedure.* In the mutual recognition procedure, a medicine is first authorized in one EU Member State, in accordance with the national procedures of that country. Following this, further marketing authorizations can be sought from other EU countries in a procedure whereby the countries concerned agree to recognize the validity of the original, national marketing authorization.

In most cases, a Pediatric Investigation Plan, or PIP, and/or a request for waiver or deferral, is required for submission prior to submitting a marketing authorization application. A PIP describes, among other things, proposed pediatric studies and their timing relative to clinical studies in adults.

New Chemical Entity Exclusivity

In the EU, new chemical entities, sometimes referred to as new active substances, qualify for eight years of data exclusivity upon marketing authorization and an additional two years of market exclusivity. This data exclusivity, if granted, prevents regulatory authorities in the EU from referencing the innovator’s data to assess a generic (abbreviated) application for eight years, after which generic marketing authorization can be submitted, and the innovator’s data may be referenced, but not approved for two years. The overall ten-year period will be extended to a maximum of eleven years if, during the first eight years of those ten years, the marketing authorization holder obtains an authorization for one or more new therapeutic indications which, during the scientific evaluation prior to their authorization, are held to bring a significant clinical benefit in comparison with existing therapies.

Orphan Designation and Exclusivity

In the EU, the EMA’s Committee for Orphan Medicinal Products, or COMP, grants orphan drug designation to promote the development of products that are intended for the diagnosis, prevention or treatment of life-threatening or chronically debilitating conditions affecting not more than 5 in 10,000 persons in the EU Community and for which no satisfactory method of diagnosis, prevention, or treatment has been authorized (or the product would be a significant benefit to those affected). Additionally, designation is granted for products intended for the diagnosis, prevention, or treatment of a life-threatening, seriously debilitating or serious and chronic condition when, without incentives, it is unlikely that sales of the drug in the EU would be sufficient to justify the necessary investment in developing the medicinal product.

In the EU, orphan drug designation entitles a party to financial incentives such as reduction of fees or fee waivers and 10 years of market exclusivity is granted following medicinal product approval. This period may be reduced to six years if the orphan drug designation criteria are no longer met, including where it is shown that the product is sufficiently profitable not to justify maintenance of market exclusivity.

Orphan drug designation must be requested before submitting an application for marketing approval. Orphan drug designation does not convey any advantage in, or shorten the duration of, the regulatory review and approval process.

Exceptional Circumstances/Conditional Approval

Orphan drugs or drugs with unmet medical needs may be eligible for EU approval under exceptional circumstances or with conditional approval. Approval under exceptional circumstances is applicable to orphan products and is used when an applicant is unable to provide comprehensive data on the efficacy and safety under normal conditions of use because the indication for which the product is intended is encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence, when the present state of scientific knowledge does not allow comprehensive information to be provided, or when it is medically unethical to collect such information. Conditional marketing authorization is applicable to orphan medicinal products, medicinal products for seriously debilitating or life-threatening diseases, or medicinal products to be used in emergency situations in response to recognized public threats. Conditional marketing authorization can be granted on the basis of less complete data than is normally required in order to meet unmet medical needs and in the interest of public health, provided the risk-benefit balance is positive, it is likely that the applicant will be able to provide the comprehensive clinical data, and unmet medical needs will be fulfilled. Conditional marketing authorization is subject to certain specific obligations to be reviewed annually.

Accelerated Review

Under the Centralized Procedure in the EU, the maximum timeframe for the evaluation of a marketing authorization application is 210 days (excluding clock stops when additional written or oral information is to be provided by the applicant in response to questions asked by the EMA's Committee for Medicinal Products for Human Use, or CHMP). Accelerated evaluation might be granted by the CHMP in exceptional cases, when a medicinal product is expected to be of a major public health interest, particularly from the point of view of therapeutic innovation. In this circumstance, EMA ensures that the opinion of the CHMP is given within 150 days, excluding clock stops.

Pharmaceutical Coverage, Pricing and Reimbursement

Significant uncertainty exists as to the coverage and reimbursement status of any drug products for which we obtain regulatory approval. In the United States and markets in other countries, sales of any products for which we receive regulatory approval for commercial sale will depend in part on the availability of coverage and reimbursement from third-party payors. Third-party payors include government authorities, managed care providers, private health insurers and other organizations. The process for determining whether a payor will provide coverage for a drug product may be separate from the process for setting the reimbursement rate that the payor will pay for the drug product. Third-party payors may limit coverage to specific drug products on an approved list, or formulary, which might not include all of the approved drugs for a particular indication. Moreover, a payor's decision to provide coverage for a drug product does not imply that an adequate reimbursement rate will be approved. Adequate third-party reimbursement may not be available to enable us to maintain price levels sufficient to realize an appropriate return on our investment in product development.

Third-party payors are increasingly challenging the price and examining the medical necessity and cost-effectiveness of medical products and services, in addition to their safety and efficacy. In order to obtain coverage and reimbursement for any product that might be approved for sale, we may need to conduct expensive pharmacoeconomic studies in order to demonstrate the medical necessity and cost-effectiveness of our products, in addition to the costs required to obtain regulatory approvals. Our product candidates may not be considered medically necessary or cost-effective. If third-party payors do not consider a product to be cost-effective compared to other available therapies, they may not cover the product after approval as a benefit under their plans or, if they do, the level of payment may not be sufficient to allow a company to sell its products at a profit.

The U.S. government, state legislatures and foreign governments have shown significant interest in implementing cost containment programs to limit the growth of government-paid health care costs, including price controls, restrictions on reimbursement and requirements for substitution of generic products for branded prescription drugs. By way of example, the Affordable Care Act, as amended by the Health Care and Education Reconciliation Act, collectively, the Healthcare Reform Law, contains provisions that may reduce the profitability of drug products, including, for example, increased rebates for drugs sold to Medicaid programs, extension of Medicaid rebates to Medicaid managed care plans, mandatory discounts for certain Medicare Part D beneficiaries and annual fees based on pharmaceutical companies' share of sales to federal health care programs. Adoption of government controls and measures, and tightening of restrictive policies in jurisdictions with existing controls and measures, could limit payments for pharmaceuticals.

In the European Community, governments influence the price of pharmaceutical products through their pricing and reimbursement rules and control of national health care systems that fund a large part of the cost of those products to consumers. Some jurisdictions operate positive and negative list systems under which products may only be marketed once a reimbursement price has been agreed to by the government. Other member states allow companies to fix their own prices for medicines, but monitor and control company profits. The downward pressure on health care costs in general, particularly prescription drugs, has become very intense. As a result, increasingly high barriers are being erected to the entry of new products. In addition, in some countries, cross-border imports from low-priced markets exert a commercial pressure on pricing within a country.

The marketability of any products for which we receive regulatory approval for commercial sale may suffer if the government and third-party payors fail to provide adequate coverage and reimbursement. In addition, an increasing emphasis on cost containment measures in the United States and other countries has increased and we expect will continue to increase the pressure on pharmaceutical pricing. Coverage policies and third-party reimbursement rates may change at any time. Even if favorable coverage and reimbursement status is attained for one or more products for which we receive regulatory approval, less favorable coverage policies and reimbursement rates may be implemented in the future.

Other Healthcare Laws and Compliance Requirements

If we obtain regulatory approval for any of our product candidates, we may be subject to various federal and state laws targeting fraud and abuse in the healthcare industry. These laws may impact, among other things, our proposed sales, marketing, and education programs. In addition, we may be subject to patient privacy regulation by both the federal government and the states in which we conduct our business. The laws that may affect our ability to operate include:

- the federal Anti-Kickback Statute, which prohibits, among other things, persons from knowingly and willfully soliciting, receiving, offering or paying remuneration, directly or indirectly, to induce, or in return for, the purchase or recommendation of an item or service reimbursable under a federal healthcare program, such as the Medicare and Medicaid programs;
- federal civil and criminal false claims laws and civil monetary penalty laws, which prohibit, among other things, individuals or entities from knowingly presenting, or causing to be presented, claims for payment from Medicare, Medicaid, or other third-party payers that are false or fraudulent;
- the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, which created new federal criminal statutes that prohibit executing a scheme to defraud any healthcare benefit program and making false statements relating to healthcare matters;
- the federal transparency laws, including the federal Physician Payment Sunshine Act, that requires drug manufacturers to disclose payments and other transfers of value provided to physicians and teaching hospitals;
- HIPAA, as amended by the Health Information Technology and Clinical Health Act, or HITECH, and its implementing regulations, which imposes certain requirements relating to the privacy, security and transmission of individually identifiable health information; and
- state law equivalents of each of the above federal laws, such as anti-kickback and false claims laws which may apply to items or services reimbursed by any third-party payer, including commercial insurers, and state laws governing the privacy and security of health information in certain circumstances, many of which differ from each other in significant ways and may not have the same effect, thus complicating compliance efforts.

The Healthcare Reform Law broadened the reach of the fraud and abuse laws by, among other things, amending the intent requirement of the federal Anti-Kickback Statute and the applicable criminal healthcare fraud statutes contained within 42 U.S.C. § 1320a-7b, effective March 23, 2010. Pursuant to the statutory amendment, a person or entity no longer needs to have actual knowledge of this statute or specific intent to violate it in order to have committed a violation. In addition, the Healthcare Reform Law provides that the government may assert that a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the civil False Claims Act (discussed below) or the civil monetary penalties statute. Many states have adopted laws similar to the federal Anti-Kickback Statute, some of which apply to the referral of patients for healthcare items or services reimbursed by any source, not only the Medicare and Medicaid programs.

We are also subject to the Foreign Corrupt Practices Act, or FCPA, which prohibits improper payments or offers of payments to foreign governments and their officials for the purpose of obtaining or retaining business. Safeguards we implement to discourage improper payments or offers of payments by our employees, consultants, and others may be ineffective, and violations of the FCPA and similar laws may result in severe criminal or civil sanctions, or other liabilities or proceedings against us, any of which would likely harm our reputation, business, financial condition and result of operations.

If our operations are found to be in violation of any of the laws described above or any other governmental regulations that apply to us, we may be subject to penalties, including civil and criminal penalties, exclusion from participation in government healthcare programs, such as Medicare and Medicaid and imprisonment, damages, fines and the curtailment or restructuring of our operations, any of which could adversely affect our ability to operate our business and our results of operations.

Employees

As of December 31, 2014, we had 107 full-time employees. None of our employees is represented by labor unions or covered by collective bargaining agreements. We consider our relationship with our employees to be good.

Research and Development

We recognized $46.0 million, $27.8 million, and $12.6 million in research and development expense in the years ended December 31, 2014, 2013, and 2012, respectively.

Facilities

Our offices are located at two leased facilities. The first is a 19,916 square foot facility in Novato, California used primarily for corporate, clinical, regulatory, manufacturing, and quality functions. On February 20, 2014, we executed an amendment to this lease adding approximately 25,000 square feet of additional space. The rental term for the additional space commenced on May 1, 2014 and will expire on April 30, 2019. The rental term for the original space shall also now expire on April 30, 2019, unless extended as permitted by the amendment. On March 9, 2015, we executed an additional addendum to this lease adding approximately 20,000 square feet of additional space. The rental term for this additional space shall commence on May 1, 2015 and expires on April 30, 2019, unless extended as permitted by the amendment.

We also lease a 910 square foot facility in Novato, California used for research laboratory space. On August 17, 2014, we executed an amendment to this lease adding approximately 1,955 square feet of additional space. The rental term for the additional space commenced on September 15, 2014 and will expire on September 15, 2019. The rental term for the current space shall also now expire on September 15, 2019, unless extended as permitted by the amendment.

Legal Proceedings

We are not currently a party to any material legal proceedings.

Product Liability Insurance

We maintain product liability insurance that provides coverage in the amount of $10.0 million per incident and $10.0 million in aggregate.

Executive Officers of the Registrant

Information concerning our executive officers, including their names, ages and certain biographical information can be found in Part III, Item 10. This information is incorporated by reference into Part I of this report.

Financial Information about Segments

We operate in a single accounting segment — the identification, acquisition, development and commercialization of novel products for the treatment of rare and ultra-rare diseases. Refer to Note 1, “Organization and Basis of Presentations” in the Notes to Financial Statements.

General Information

We were incorporated in California in April 2010 and reincorporated in Delaware in June 2011. Our principal executive offices are located at 60 Leveroni Court, Novato, California 94949. Our telephone number is (415) 483-8800 and our e-mail address is *info@ultragenyx.com*. Our Internet website address is *www.ultragenyx.com*. No portion of our website is incorporated by reference into this Annual Report on Form 10-K.

You are advised to read this Annual Report on Form 10-K in conjunction with other reports and documents that we file from time to time with the Securities and Exchange Commission, or SEC. In particular, please read our definitive proxy statements, our Quarterly Reports on Form 10-Q and any Current Reports on Form 8-K that we may file from time to time. You may obtain copies of these reports after the date of this annual report directly from us or from the SEC at the SEC’s Public Reference Room at 100 F Street, N.E. Washington, D.C. 20549. In addition, the SEC maintains information for electronic filers (including Ultragenyx) at its website at *www.sec.gov*. The public may obtain information regarding the operation of the Public Reference Room by calling the SEC at 1-800-SEC-0330. We make our periodic and current reports available on our internet website, free of charge, as soon as reasonably practicable after such material is electronically filed with, or furnished to, the SEC.

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 $59.8 million, $35.1 million and $16.3 million for the years ended December 31, 2014, 2013 and 2012, respectively. As of December 31, 2014, we had incurred cumulative net losses of $119.4 million.

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 it may be several years, if ever, before a product candidate is 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, 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 sales, marketing, and distribution infrastructure 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 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 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 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;
- 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 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 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.

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 December 31, 2014, our available cash, cash equivalents and short-term investments were $187.5 million. We expect that our existing cash, cash equivalents and short-term investments, including the net proceeds received from the financing we closed in February 2015, will be sufficient to fund our current operations into 2018; 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, 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 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. 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 identifying, acquiring, and developing 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 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 multiple programs that are in clinical studies. One of our product candidates has advanced into a pivotal study, but such study may not result in approval. For SA-ER, we plan to file for conditional marketing authorization in the EU, which initially allows for approval without providing comprehensive clinical data and may entail a higher risk for rejection than the standard approval pathway. 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 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 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.

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 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 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.

This lengthy approval process, as well as the unpredictability of the results of clinical and nonclinical 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 nonclinical 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 clinical studies. For example, the safety or efficacy results generated to date in clinical studies for KRN23, rhGUS, triheptanoin, and SA-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. 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. Moreover, nonclinical and clinical data are often susceptible to varying interpretations and analyses. We do not know whether any 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.

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 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 approximately 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. For example, the 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 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. 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 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, and clinical study sites, and other clinical trial-related vendors, the terms of which can be subject to extensive negotiation and may vary significantly among different CROs and clinical study sites, and vendors;
- delays in obtaining required 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 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 or nonclinical studies or 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.

Often the disease states we are evaluating will not have clear regulatory paths for an 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 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.

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, or new formulations of triheptanoin, 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 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. 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, 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. Other side effects may result from longer-term exposure and treatment of pediatric patients. 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. While we have not completed our own clinical studies for 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 as further development proceeds. 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.

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 $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 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, or losses may exceed the amount of insurance that we carry. 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 or restricted 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, 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, 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, or GMP, regulations. As such, we and our contract manufacturers will be subject to continual review and inspections 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 to the 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 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. 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 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 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, 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 including costs and efforts completed, and we 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 GMP, GCP, and GLP, which are regulations and guidelines enforced by the FDA, the Competent Authorities of the Member States of the EEA, 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 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 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 product produced under GMP regulations. If we fail to comply with these regulations, we may be required to repeat clinical or nonclinical studies, which would delay the regulatory approval process.

Our CROs and other vendors 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 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 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, 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 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 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 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 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 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 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 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, raw material shortages, natural disasters, power failures, and numerous other factors.

Although we have not experienced any significant 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 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 and CPM 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 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 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 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 triheptanoin 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, or in compliance with GMP or other pertinent regulatory requirements, and within our planned timeframe and cost parameters, the development and sales of our products, if approved, may be materially harmed.

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, the cost to us for the supply of our product candidates by such third-parties may be high and limit our profitability. 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 and is currently being studied 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 triheptanoin. Glut1 DS is currently treated primarily with the ketogenic diet and anti-epileptic drugs, which may also compete with triheptanoin. Additionally, we are aware of a program at the National Institutes of Health, whose intellectual property rights are licensed to a company in New Zealand that is investigating the use of another metabolite in the sialic acid pathway, ManNAc, for the treatment of HIBM, which could compete with SA-ER. ManNAc may have a potential advantage over SA-ER in that it is not a charged molecule like sialic acid is, which might improve its distribution and uptake. 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 currently have no marketing and sales organization. If we are unable to establish sales 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 no marketing or sales organization. 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 sales and marketing organization with technical expertise and 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 sales, 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 sales force may be materially more or less than the size of the sales force actually required to effectively commercialize our product candidates. As such, we may be required to hire substantially more sales representatives to adequately support the commercialization of our product candidates or we may incur excess costs as a result of hiring more sales representatives 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 marketing and sales 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 third-party 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, third-party 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;
- the clinical indications for which approval is granted;
- relative convenience and ease of administration;
- the cost of treatment, particularly in relation to competing treatments;
- the willingness of the target patient population to try new therapies and of physicians to prescribe these therapies;
- the effectiveness of our sales and marketing efforts;
- the strength of marketing and distribution support and timing of market introduction of competitive products;
- publicity concerning our products or competing products and treatments; and
- sufficient third-party insurance coverage and reimbursement.

Even if a potential product displays a favorable efficacy and safety profile in nonclinical and clinical studies, market acceptance of the product will not be fully known until after it is launched. Our efforts to educate the medical community and third-party payors on the benefits of the product candidates may require significant resources and may never be successful. If our product candidates are approved but fail to achieve an adequate level of acceptance by physicians, patients, third-party payors, and others in the medical community, we will not be able to generate sufficient revenue to become or remain profitable.

The insurance coverage and reimbursement status of newly-approved products is uncertain. Failure to obtain or maintain adequate coverage and reimbursement for new or current products could limit our ability to market those products and decrease our ability to generate revenue.

Our target patient populations are small, and accordingly the pricing, coverage, and reimbursement of our product candidates, if approved, must be adequate to support our commercial infrastructure. Our per-patient prices must be sufficient to recover our development and manufacturing costs and potentially achieve profitability. Accordingly, the availability and adequacy of coverage and reimbursement by governmental and private payors are essential for most patients to be able to afford expensive treatments such as ours, assuming approval. Sales of our product candidates will depend substantially, both domestically and abroad, on the extent to which the costs of our product candidates will be paid for by health maintenance, managed care, pharmacy benefit, and similar healthcare management organizations, or reimbursed by government authorities, private health insurers, and other third-party payors. If coverage and reimbursement are not available, or are available only to limited levels, we may not be able to successfully commercialize our product candidates. Even if coverage is provided, the approved reimbursement amount may not be high enough to allow us to establish or maintain pricing sufficient to realize a return on our investment.

There is significant uncertainty related to the insurance coverage and reimbursement of newly approved products. In the United States, the principal decisions about coverage and reimbursement for new drugs are typically made by the Centers for Medicare & Medicaid Services, or CMS, an agency within the U.S. Department of Health and Human Services, as CMS decides whether and to what extent a new drug will be covered and reimbursed under Medicare. Private payors tend to follow the coverage reimbursement policies established by CMS to a substantial degree. It is difficult to predict what CMS will decide with respect to reimbursement for products such as ours.

Outside the United States, international operations are generally subject to extensive governmental price controls and other market regulations, and we believe the increasing emphasis on cost-containment initiatives in Europe, Canada, and other countries will put pressure on the pricing and usage of our product candidates. In many countries, the prices of medical products are subject to varying price control mechanisms as part of national health systems. Other countries allow companies to fix their own prices for medicinal products, but monitor and control company profits. Additional foreign price controls or other changes in pricing regulation could restrict the amount that we are able to charge for our product candidates. Accordingly, in markets outside the United States, the reimbursement for our products may be reduced compared with the United States and may be insufficient to generate commercially reasonable revenue and profits.

Moreover, increasing efforts by governmental and third-party payors in the United States and abroad to cap or reduce healthcare costs may cause such organizations to limit both coverage and the level of reimbursement for new products approved and, as a result, they may not cover or provide adequate payment for our product candidates. We expect to experience pricing pressures in connection with the sale of any of our product candidates due to the trend toward managed healthcare, the increasing influence of health maintenance organizations, and additional legislative changes. The downward pressure on healthcare costs in general, particularly prescription drugs and surgical procedures and other treatments, has become very intense. As a result, increasingly high barriers are being erected to the entry of new products.

Risks Related to Our Intellectual Property

If we are unable to obtain and maintain effective patent rights for our product candidates or any future product candidates, we may not be able to compete effectively in our markets.

We rely upon a combination of patents, trade secret protection, and confidentiality agreements to protect the intellectual property related to our technologies and product candidates. Our success depends in large part on our and our licensors' ability to obtain and maintain patent and other intellectual property protection in the United States and in other countries with respect to our proprietary technology and products.

We have sought to protect our proprietary position by filing patent applications in the United States and abroad related to our novel technologies and products that are important to our business. This process is expensive and time consuming, and we may not be able to file and prosecute all necessary or desirable patent applications at a reasonable cost or in a timely manner. It is also possible that we will fail to identify patentable aspects of our research and development output before it is too late to obtain patent protection.

The patent position of biotechnology and pharmaceutical companies generally is highly uncertain and involves complex legal and factual questions for which legal principles remain unsolved. The patent applications that we own or in-license may fail to result in issued patents with claims that cover our product candidates in the United States or in other foreign countries. There is no assurance that all potentially relevant prior art relating to our patents and patent applications has been found, which can invalidate a patent or prevent a patent from issuing from a pending patent application. Even if patents do successfully issue, and even if such patents cover our product candidates, third parties may challenge their validity, enforceability, or scope, which may result in such patents being narrowed, found unenforceable or invalidated. Furthermore, even if they are unchallenged, our patents and patent applications may not adequately protect our intellectual property, provide exclusivity for our product candidates, or prevent others from designing around our claims. Any of these outcomes could impair our ability to prevent competition from third parties, which may have an adverse impact on our business.

We, independently or together with our licensors, have filed several patent applications covering various aspects of our product candidates. We cannot offer any assurances about which, if any, patents will issue, the breadth of any such patent or whether any issued patents will be found invalid and unenforceable or will be threatened by third parties. Any successful opposition to these patents or any other patents owned by or licensed to us after patent issuance could deprive us of rights necessary for the successful commercialization of any product candidates that we may develop. Further, if we encounter delays in regulatory approvals, the period of time during which we could market a product candidate under patent protection could be reduced.

Although we have a number of patents covering methods of use and certain compositions of matter, we do not have complete patent protection for our product candidates. For example, there is no patent coverage for KRN23 in Latin America, where we have rights to commercialize the compound. Therefore, a competitor could develop the same or similar antibody as well as other approaches that target FGF23. Additionally, there are currently no patents that cover rhPPCA. Therefore, it is possible that a competitor could develop the same or similar enzyme with respect to rhPPCA, subject to any regulatory exclusivities. With respect to SA-ER, none of the patents relating to SA-ER cover composition of matter. Therefore, it is possible that a competitor could develop the same or similar molecule. If we cannot obtain and maintain effective patent rights for our product candidates, we may not be able to compete effectively and our business and results of operations would be harmed.

We may not have sufficient patent terms to effectively protect our products and business.

Patents have a limited lifespan. In the United States, the natural expiration of a patent is generally 20 years after it is filed. Although various extensions may be available, the life of a patent, and the protection it affords, is limited. Even if patents covering our product candidates are obtained, once the patent life has expired for a product, we may be open to competition from generic medications.

While patent term extensions under the Hatch-Waxman Act in the United States and under supplementary protection certificates in Europe may be available to extend the patent exclusivity term for KRN23, rhGUS, triheptanoin, and SA-ER, we cannot provide any assurances that any such patent term extension will be obtained and, if so, for how long. In addition, upon issuance in the United States any patent term can be adjusted based on certain delays caused by the applicant(s) or the United States Patent and Trademark Office, or USPTO. For example, a patent term can be reduced based on certain delays caused by the patent applicant during patent prosecution. If we do not have sufficient patent terms or regulatory exclusivity to protect our products, our business and results of operations will be adversely affected.

Patent policy and rule changes could increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our issued patents.

Changes in either the patent laws or interpretation of the patent laws in the United States and other countries may diminish the value of our patents or narrow the scope of our patent protection. The laws of foreign countries may not protect our rights to the same extent as the laws of the United States. Publications of discoveries in the scientific literature often lag behind the actual discoveries, and patent applications in the United States and other jurisdictions are typically not published until 18 months after filing, or in some cases not at all. We therefore cannot be certain that we or our licensors were the first to make the invention claimed in our owned and licensed patents or pending applications, or that we or our licensor were the first to file for patent protection of such inventions. Assuming the other requirements for patentability are met, in the United States prior to March 15, 2013, the first to make the claimed invention is entitled to the patent, while outside the United States, the first to file a patent application is entitled to the patent. After March 15, 2013, under the Leahy-Smith America Invents Act, or the Leahy-Smith Act, enacted on September 16, 2011, the United States has moved to a first to file system. The Leahy-Smith Act also includes a number of significant changes that affect the way patent applications will be prosecuted and may also affect patent litigation. The effects of these changes are currently unclear as the USPTO must still implement various regulations, the courts have yet to address any of these provisions and the applicability of the act and new regulations on specific patents discussed herein have not been determined and would need to be reviewed. In general, the Leahy-Smith Act and its implementation could increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our issued patents, all of which could have a material adverse effect on our business and financial condition.

If we are unable to maintain effective proprietary rights for our product candidates or any future product candidates, we may not be able to compete effectively in our markets.

In addition to the protection afforded by patents, we rely on trade secret protection and confidentiality agreements to protect proprietary know-how that is not patentable or that we elect not to patent, processes for which patents are difficult to enforce and any other elements of our product candidate discovery and development processes that involve proprietary know-how, information or technology that is not covered by patents. However, trade secrets can be difficult to protect. We seek to protect our proprietary technology and processes, in part, by entering into confidentiality agreements with our employees, consultants, scientific advisors, and contractors. We also seek to preserve the integrity and confidentiality of our data and trade secrets by maintaining physical security of our premises and physical and electronic security of our information technology systems. While we have confidence in these individuals, organizations and systems, agreements or security measures may be breached, and we may not have adequate remedies for any breach. In addition, our trade secrets may otherwise become known or be independently discovered by competitors.

Although we expect all of our employees and consultants to assign their inventions to us, and all of our employees, consultants, advisors, and any third parties who have access to our proprietary know-how, information, or technology to enter into confidentiality agreements, we cannot provide any assurances that all such agreements have been duly executed or that our trade secrets and other confidential proprietary information will not be disclosed or that competitors will not otherwise gain access to our trade secrets or independently develop substantially equivalent information and techniques. Misappropriation or unauthorized disclosure of our trade secrets could impair our competitive position and may have a material adverse effect on our business. Additionally, if the steps taken to maintain our trade secrets are deemed inadequate, we may have insufficient recourse against third parties for misappropriating the trade secret.

Third-party claims of intellectual property infringement may prevent or delay our development and commercialization efforts.

Our commercial success depends in part on our avoiding infringement of the patents and proprietary rights of third parties. There have been many lawsuits and other proceedings involving patent and other intellectual property rights in the biotechnology and pharmaceutical industries, including patent infringement lawsuits, interferences, oppositions, and reexamination proceedings before the USPTO and corresponding foreign patent offices. Numerous U.S. and foreign issued patents and pending patent applications, which are owned by third parties, exist in the fields in which we are developing product candidates. As the biotechnology and pharmaceutical industries expand and more patents are issued, the risk increases that our product candidates may be subject to claims of infringement of the patent rights of third parties.

Third parties may assert that we are employing their proprietary technology without authorization. There may be third-party patents or patent applications with claims to materials, formulations, methods of manufacture, or methods for treatment related to the use or manufacture of our product candidates. We have conducted freedom to operate analyses with respect to only certain of our product candidates, and therefore we do not know whether there are any third-party patents that would impair our ability to commercialize all of our product candidates. We also cannot guarantee that any of our analyses are complete and thorough, nor can we be sure that we have identified each and every patent and pending application in the United States and abroad that is relevant or necessary to the commercialization of our product candidates. Because patent applications can take many years to issue, there may be currently pending patent applications that may later result in issued patents that our product candidates may infringe.

In addition, third parties may obtain patents in the future and claim that use of our technologies infringes upon these patents. If any third-party patents were held by a court of competent jurisdiction to cover aspects of our formulations, the manufacturing process of any of our product candidates, methods of use, any molecules formed during the manufacturing process or any final product itself, the holders of any such patents may be able to block our ability to commercialize such product candidate unless we obtained a license under the applicable patents, or until such patents expire or are finally determined to be invalid or unenforceable. Such a license may not be available on commercially reasonable terms or at all.

Parties making claims against us may obtain injunctive or other equitable relief, which could effectively block our ability to further develop and commercialize one or more of our product candidates. Defense of these claims, regardless of their merit, would involve substantial litigation expense and would be a substantial diversion of employee resources from our business. In the event of a successful claim of infringement against us, we may have to pay substantial damages, including treble damages and attorneys' fees for willful infringement, pay royalties, redesign our infringing products or obtain one or more licenses from third parties, which may be impossible or require substantial time and monetary expenditure.

We may not be successful in obtaining or maintaining necessary rights to our product candidates through acquisitions and in-licenses.

We currently have rights to the intellectual property, through licenses from third parties and under patents that we own, to develop our product candidates. Because our programs may require the use of proprietary rights held by third parties, the growth of our business will likely depend in part on our ability to acquire, in-license, or use these proprietary rights. For example, our product candidates may require specific formulations to work effectively and efficiently and the rights to these formulations may be held by others. We may be unable to acquire or in-license any compositions, methods of use, processes, or other third-party intellectual property rights from third parties that we identify as necessary for our product candidates. The licensing and acquisition of third-party intellectual property rights is a competitive area, and a number of more established companies are also pursuing strategies to license or acquire third-party intellectual property rights that we may consider attractive. These established companies may have a competitive advantage over us due to their size, cash resources, and greater clinical development and commercialization capabilities. In addition, companies that perceive us to be a competitor may be unwilling to assign or license rights to us. We also may be unable to license or acquire third-party intellectual property rights on terms that would allow us to make an appropriate return on our investment.

We sometimes collaborate with U.S. and foreign academic institutions to accelerate our preclinical research or development under written agreements with these institutions. Typically, these institutions provide us with an option to negotiate a license to any of the institution's rights in technology resulting from the collaboration. Regardless of such option, we may be unable to negotiate a license within the specified timeframe or under terms that are acceptable to us. If we are unable to do so, the institution may offer the intellectual property rights to other parties, potentially blocking our ability to pursue our program.

If we are unable to successfully obtain rights to required third-party intellectual property rights or maintain the existing intellectual property rights we have, we may have to abandon development of that program and our business and financial condition could suffer.

We may face competition from biosimilars, which may have a material adverse impact on the future commercial prospects of KRN23, rhGUS, and rhPPCA.

Even if we are successful in achieving regulatory approval to commercialize a product candidate faster than our competitors, we may face competition from biosimilars with respect to KRN23, rhGUS, and rhPPCA. In the United States, the BPCI Act created an abbreviated approval pathway for biological products that are demonstrated to be "highly similar," or biosimilar, to or "interchangeable" with an FDA-approved biological product. This new pathway could allow competitors to reference data from innovative biological products 12 years after the time of approval of the innovative biological product. The 12-year data exclusivity period does not prevent another company from developing a product that is highly similar to the innovative product, generating its own data, and seeking approval. Data exclusivity only assures that another company cannot rely upon the data within the innovator's application to support the biosimilar product's approval. In his proposed budget for fiscal year 2014, President Obama proposed to cut this 12-year period of exclusivity down to seven years. He also proposed to prohibit additional periods of exclusivity due to minor changes in product formulations, a practice often referred to as "evergreening." It is possible that Congress may take these or other measures to reduce or eliminate periods of exclusivity. The BPCI Act is complex and only beginning to be interpreted and implemented by the FDA. As a result, its ultimate impact, implementation, and meaning is subject to uncertainty. While it is uncertain when any such processes may be fully adopted by the FDA, any such processes could have a material adverse effect on the future commercial prospects for KRN23, rhGUS, and rhPPCA.

In Europe, the European Commission has granted marketing authorizations for several biosimilars pursuant to a set of general and product class-specific guidelines for biosimilar approvals issued over the past few years. In Europe, a competitor may reference data supporting approval of an innovative biological product, but will not be able to get on the market until 10 years after the time of approval of the innovative product. This 10-year marketing exclusivity period will be extended to 11 years if, during the first eight of those 10 years, the marketing authorization holder obtains an approval for one or more new therapeutic indications that bring significant clinical benefits compared with existing therapies. In addition, companies may be developing biosimilars in other countries that could compete with our products.

If competitors are able to obtain marketing approval for biosimilars referencing our products, our products may become subject to competition from such biosimilars, with the attendant competitive pressure and consequences.

Additional competitors could enter the market with generic versions of our small-molecule product candidates, which may result in a material decline in sales of triheptanoin and SA-ER.

Under the Hatch-Waxman Act, a pharmaceutical manufacturer may file an abbreviated new drug application, or ANDA, seeking approval of a generic copy of an approved innovator product. Under the Hatch-Waxman Act, a manufacturer may also submit an NDA under section 505(b)(2) that references the FDA's finding of safety and effectiveness of a previously approved drug. A 505(b)(2) NDA product may be for a new or improved version of the original innovator product. Innovative small molecule drugs may be eligible for certain periods of regulatory exclusivity (e.g., five years for new chemical entities, three years for changes to an approved drug requiring a new clinical study, seven years for orphan drugs), which preclude FDA approval (or in some circumstances, FDA filing and review of) an ANDA or 505(b)(2) NDA relying on the FDA's finding of safety and effectiveness for the innovative drug. In addition to the benefits of regulatory exclusivity, an innovator NDA holder may have patents claiming the active ingredient, product formulation or an approved use of the drug, which would be listed with the product in the FDA publication, "Approved Drug Products with Therapeutic Equivalence Evaluations," known as the "Orange Book." If there are patents listed in the Orange Book, a generic applicant that seeks to market its product before expiration of the patents must include in the ANDA or 505(b)(2) what is known as a "Paragraph IV certification," challenging the validity or enforceability of, or claiming non-infringement of, the listed patent or patents. Notice of the certification must be given to the innovator, too, and if within 45 days of receiving notice the innovator sues to protect its patents, approval of the ANDA is stayed for 30 months, or as lengthened or shortened by the court.

Accordingly, if triheptanoin and SA-ER are approved, competitors could file ANDAs for generic versions of triheptanoin and SA-ER, or 505(b)(2) NDAs that reference triheptanoin and SA-ER, respectively. If there are patents listed for triheptanoin and SA-ER in the Orange Book, those ANDAs and 505(b)(2) NDAs would be required to include a certification as to each listed patent indicating whether the ANDA applicant does or does not intend to challenge the patent. We cannot predict whether any patents issuing from our pending patent applications will be eligible for listing in the Orange Book, how any generic competitor would address such patents, whether we would sue on any such patents, or the outcome of any such suit.

We may not be successful in securing or maintaining proprietary patent protection for products and technologies we develop or license. Moreover, if any patents that are granted and listed in the Orange Book are successfully challenged by way of a Paragraph IV certification and subsequent litigation, the affected product could more immediately face generic competition and its sales would likely decline materially. Should sales decline, we may have to write off a portion or all of the intangible assets associated with the affected product and our results of operations and cash flows could be materially and adversely affected.

The patent protection and patent prosecution for some of our product candidates is dependent on third parties.

While we normally seek and gain the right to fully prosecute the patents relating to our product candidates, there may be times when patents relating to our product candidates are controlled by our licensors. This is the case with our agreement with KHK, who is primarily responsible for the prosecution of patents and patent applications licensed to us under the collaboration agreement. If KHK or any of our future licensing partners fail to appropriately prosecute and maintain patent protection for patents covering any of our product candidates, our ability to develop and commercialize those product candidates may be adversely affected and we may not be able to prevent competitors from making, using, and selling competing products. In addition, even where we now have the right to control patent prosecution of patents and patent applications we have licensed from third parties, we may still be adversely affected or prejudiced by actions or inactions of our licensors and their counsel that took place prior to us assuming control over patent prosecution.

If we fail to comply with our obligations in the agreements under which we license intellectual property and other rights from third parties or otherwise experience disruptions to our business relationships with our licensors, we could lose license rights that are important to our business.

We are a party to a number of intellectual property license agreements that are important to our business and expect to enter into additional license agreements in the future. Our existing license agreements impose, and we expect that future license agreements will impose, various diligence, milestone payment, royalty, and other obligations on us. If we fail to comply with our obligations under these agreements, or we are subject to a bankruptcy, we may be required to make certain payments to the licensor, we may lose the exclusivity of our license, or the licensor may have the right to terminate the license, in which event we would not be able to develop or market products covered by the license. Additionally, the milestone and other payments associated with these licenses will make it less profitable for us to develop our drug candidates. See "Business—License Agreements" for a description of our license agreements with KHK, Baylor Research Institute, Nobelpharma, AAIPharma, HIBM Research Group, St. Louis University and St. Jude Children's Research Hospital, which includes a description of the termination provisions of these agreements.

In some cases, patent prosecution of our licensed technology is controlled solely by the licensor. If our licensors fail to obtain and maintain patent or other protection for the proprietary intellectual property we license from them, we could lose our rights to the intellectual property or our exclusivity with respect to those rights, and our competitors could market competing products using the intellectual property. In certain cases, we control the prosecution of patents resulting from licensed technology. In the event we breach any of our obligations related to such prosecution, we may incur significant liability to our licensing partners. Licensing of intellectual property is of critical importance to our business and involves complex legal, business, and scientific issues. Disputes may arise regarding intellectual property subject to a licensing agreement, including but not limited to:

- the scope of rights granted under the license agreement and other interpretation-related issues;
- the extent to which our technology and processes infringe on intellectual property of the licensor that is not subject to the licensing agreement;
- the sublicensing of patent and other rights;
- our diligence obligations under the license agreement and what activities satisfy those diligence obligations;
- the ownership of inventions and know-how resulting from the joint creation or use of intellectual property by our licensors and us and our collaborators; and
- the priority of invention of patented technology.

If disputes over intellectual property and other rights that we have licensed prevent or impair our ability to maintain our current licensing arrangements on acceptable terms, we may be unable to successfully develop and commercialize the affected product candidates.

Although we are not currently involved in any litigation, we may be involved in lawsuits to protect or enforce our patents or the patents of our licensors, which could be expensive, time consuming, and unsuccessful.

Competitors may infringe our patents or the patents of our licensors. Although we are not currently involved in any litigation, if we or one of our licensing partners were to initiate legal proceedings against a third party to enforce a patent covering one of our product candidates, the defendant could counterclaim that the patent covering our product candidate is invalid and/or unenforceable. In patent litigation in the United States, defendant counterclaims alleging invalidity and/or unenforceability are commonplace. Grounds for a validity challenge could be an alleged failure to meet any of several statutory requirements, including lack of novelty, obviousness, or non-enablement. Grounds for an unenforceability assertion could be an allegation that someone connected with prosecution of the patent withheld relevant information from the USPTO, or made a misleading statement, during prosecution. The outcome following legal assertions of invalidity and unenforceability is unpredictable.

Interference proceedings provoked by third parties or brought by us or declared by the USPTO may be necessary to determine the priority of inventions with respect to our patents or patent applications or those of our licensors. An unfavorable outcome could require us to cease using the related technology or to attempt to license rights to it from the prevailing party. Our business could be harmed if the prevailing party does not offer us a license on commercially reasonable terms. Our defense of litigation or interference proceedings may fail and, even if successful, may result in substantial costs and distract our management and other employees. In addition, the uncertainties associated with litigation could have a material adverse effect on our ability to raise sufficient capital to continue our clinical studies, continue our research programs, license necessary technology from third parties, or enter into development partnerships that would help us bring our product candidates to market.

Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation, there is a risk that some of our confidential information could be compromised by disclosure during this type of litigation. There could also be public announcements of the results of hearings, motions, or other interim proceedings or developments. If securities analysts or investors perceive these results to be negative, it could have a material adverse effect on the price of our common stock.

We may be subject to claims that our employees, consultants, or independent contractors have wrongfully used or disclosed confidential information of third parties or that our employees have wrongfully used or disclosed alleged trade secrets of their former employers.

We employ certain individuals who were previously employed at universities or other biotechnology or pharmaceutical companies, including our competitors or potential competitors. Although we try to ensure that our employees, consultants, and independent contractors do not use the proprietary information or know-how of others in their work for us, and we are not currently subject to any claims that our employees, consultants, or independent contractors have wrongfully used or disclosed confidential information of third parties, we may in the future be subject to such claims. Litigation may be necessary to defend against these claims. If we fail in defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights or personnel, which could adversely impact our business. Even if we are successful in defending against such claims, litigation could result in substantial costs and be a distraction to management and other employees.

We may be subject to claims challenging the inventorship of our patents and other intellectual property.

Although we are not currently experiencing any claims challenging the inventorship of our patents or ownership of our intellectual property, we may in the future be subject to claims that former employees, collaborators or other third parties have an interest in our patents or other intellectual property as an inventor or co-inventor. For example, we may have inventorship disputes arise from conflicting obligations of consultants or others who are involved in developing our product candidates. Litigation may be necessary to defend against these and other claims challenging inventorship. If we fail in defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights, such as exclusive ownership of, or right to use, valuable intellectual property. Such an outcome could have a material adverse effect on our business. Even if we are successful in defending against such claims, litigation could result in substantial costs and be a distraction to management and other employees.

Changes in U.S. patent law could diminish the value of patents in general, thereby impairing our ability to protect our products.

As is the case with other biopharmaceutical companies, our success is heavily dependent on intellectual property, particularly patents. Obtaining and enforcing patents in the biotechnology industry involves both technological and legal complexity. Therefore, obtaining and enforcing biotechnology patents is costly, time consuming, and inherently uncertain. In addition, the United States has recently enacted and is currently implementing wide-ranging patent reform legislation. Recent U.S. Supreme Court rulings have narrowed the scope of patent protection available in certain circumstances and weakened the rights of patent owners in certain situations. In addition to increasing uncertainty with regard to our ability to obtain patents in the future, this combination of events has created uncertainty with respect to the value of patents, once obtained. Depending on future actions by the U.S. Congress, the federal courts, and the USPTO, the laws and regulations governing patents could change in unpredictable ways that would weaken our ability to obtain new patents or to enforce our existing patents and patents that we might obtain in the future.

We may not be able to protect our intellectual property rights throughout the world.

Filing, prosecuting, and defending patents on product candidates in all countries throughout the world would be prohibitively expensive, and our intellectual property rights in some countries outside the United States can be less extensive than those in the United States. In addition, the laws of some foreign countries do not protect intellectual property rights to the same extent as federal and state laws in the United States. Further, licensing partners such as KHK may not prosecute patents in certain jurisdictions in which we may obtain commercial rights, thereby precluding the possibility of later obtaining patent protection in these countries. Consequently, we may not be able to prevent third parties from practicing our inventions in all countries outside the United States, or from selling or importing products made using our inventions in and into the United States or other jurisdictions. Competitors may use our technologies in jurisdictions where we have not obtained patent protection to develop their own products and may also export infringing products to territories where we have patent protection, but enforcement is not as strong as that in the United States. These products may compete with our products and our patents or other intellectual property rights may not be effective or sufficient to prevent them from competing.

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

Risks Related to Our Business Operations

Our future success depends in part on our ability to retain our Founder, President, and Chief Executive Officer and to attract, retain, and motivate other qualified personnel.

We are dependent on Emil D. Kakkis, M.D., Ph.D., our Founder, President, and Chief Executive Officer, the loss of whose services may adversely impact the achievement of our objectives. Dr. Kakkis could leave our employment at any time, as he is an “at will” employee. Recruiting and retaining other qualified employees, consultants, and advisors for our business, including scientific and technical personnel, will also be critical to our success. There is currently a shortage of skilled personnel in our industry, which is likely to continue. As a result, competition for skilled personnel is intense and the turnover rate can be high. We may not be able to attract and retain personnel on acceptable terms given the competition among numerous pharmaceutical and biotechnology companies for individuals with similar skill sets. In addition, failure to succeed in preclinical or clinical studies may make it more challenging to recruit and retain qualified personnel. The inability to recruit and retain qualified personnel, or the loss of the services of Dr. Kakkis, may impede the progress of our research, development, and commercialization objectives.

If we fail to obtain or maintain orphan drug exclusivity for our products, our competitors may sell products to treat the same conditions and our revenue will be reduced.

Our business strategy focuses on the development of drugs that are eligible for FDA and EU orphan drug designation. Under the Orphan Drug Act, the FDA may designate a product as an orphan drug if it is intended to treat a rare disease or condition, defined as a patient population of fewer than 200,000 in the United States, or a patient population greater than 200,000 in the United States where there is no reasonable expectation that the cost of developing the drug will be recovered from sales in the United States. In the EU, the EMA’s COMP, grants orphan drug designation to promote the development of products that are intended for the diagnosis, prevention, or treatment of a life-threatening or chronically debilitating condition when the prevalence of the condition is not more than five in 10,000 persons in the EU or when, without incentives, it is unlikely that sales of the drug in the EU would be sufficient to justify the necessary investment in developing the drug or biological product. Additionally, there must be no satisfactory method of diagnosis, prevention, or treatment, or, if such a method exists, the medicine must be of significant benefit to those affected by the condition.

In the United States, orphan drug designation entitles a party to financial incentives such as opportunities for grant funding towards clinical study costs, tax advantages, and user-fee waivers. In addition, if a product receives the first FDA approval for the indication for which it has orphan designation, the product is entitled to orphan drug exclusivity, which means the FDA may not approve any other application to market the same drug for the same indication for a period of seven years, except in limited circumstances, such as a showing of clinical superiority over the product with orphan exclusivity or where the manufacturer is unable to assure sufficient product quantity. In the EU, orphan drug designation entitles a party to financial incentives such as reduction of fees or fee waivers and ten years of market exclusivity following drug or biological product approval. This period may be reduced to six years if the orphan drug designation criteria are no longer met, including where it is shown that the product is sufficiently profitable not to justify maintenance of market exclusivity.

Because the extent and scope of patent protection for our products may in some cases be limited, orphan drug designation is especially important for our products for which orphan drug designation may be available. For eligible drugs, we plan to rely on the exclusivity period under the Orphan Drug Act to maintain a competitive position. If we do not obtain orphan drug exclusivity for our drug products and biologic products that do not have broad patent protection, our competitors may then sell the same drug to treat the same condition sooner than if we had obtained orphan drug exclusivity and our revenue will be reduced.

Even though we have orphan drug designation for triheptanoin for Glut1 DS in the United States, and KRN23, rhGUS and SA-ER in the United States and Europe, we may not be the first to obtain marketing approval for any particular orphan indication due to the uncertainties associated with developing pharmaceutical products. Further, even if we obtain orphan drug exclusivity for a product, that exclusivity may not effectively protect the product from competition because different drugs with different active moieties can be approved for the same condition or the same drug can be approved for a different indication unless there are other exclusivities such as new chemical entity exclusivity preventing such approval. Even after an orphan drug is approved, the FDA or EMA can subsequently approve the same drug with the same active moiety for the same condition if the FDA or EMA concludes that the later drug is safer, more effective, or makes a major contribution to patient care. Orphan drug designation neither shortens the development time or regulatory review time of a drug nor gives the drug any advantage in the regulatory review or approval process.

We will need to expand our organization and we may experience difficulties in managing this growth, which could disrupt our operations.

As of December 31, 2014, we had 107 full-time employees. As our development and commercialization plans and strategies develop, we expect to need additional managerial, operational, sales, marketing, financial, legal, and other resources. Our management may need to divert a disproportionate amount of its attention away from our day-to-day activities and devote a substantial amount of time to managing these growth activities. We may not be able to effectively manage the expansion of our operations, which may result in weaknesses in our infrastructure, operational mistakes, loss of business opportunities, loss of employees, and reduced productivity among remaining employees. Our expected growth could require significant capital expenditures and may divert financial resources from other projects, such as the development of additional product candidates. If our management is unable to effectively manage our growth, our expenses may increase more than expected, our ability to generate and/or grow revenue could be reduced and we may not be able to implement our business strategy. Our future financial performance and our ability to commercialize product candidates and compete effectively will depend, in part, on our ability to effectively manage any future growth.

We may not be successful in our efforts to identify, license, discover, develop, or commercialize additional product candidates.

Although a substantial amount of our effort will focus on the continued clinical testing, potential approval, and commercialization of our existing product candidates, the success of our business also depends upon our ability to identify, license, discover, develop, or commercialize additional product candidates. Research programs to identify new product candidates require substantial technical, financial, and human resources. We may focus our efforts and resources on potential programs or product candidates that ultimately prove to be unsuccessful. Our research programs or licensing efforts may fail to yield additional product candidates for clinical development and commercialization for a number of reasons, including but not limited to the following:

- our research or business development methodology or search criteria and process may be unsuccessful in identifying potential product candidates;
- we may not be able or willing to assemble sufficient resources to acquire or discover additional product candidates;
- we may face competition in obtaining and/or developing additional product candidates;
- our product candidates may not succeed in preclinical or clinical testing;
- our potential product candidates may be shown to have harmful side effects or may have other characteristics that may make the products unmarketable or unlikely to receive marketing approval;
- competitors may develop alternatives that render our product candidates obsolete or less attractive;
- product candidates we develop may be covered by third parties' patents or other exclusive rights;
- the market for a product candidate may change during our program so that such a product may become unreasonable to continue to develop;
- a product candidate may not be capable of being produced in commercial quantities at an acceptable cost or at all; and
- a product candidate may not be accepted as safe and effective by regulatory authorities, patients, the medical community, or third-party payors.

If any of these events occur, we may be forced to abandon our development efforts for a program or programs, or we may not be able to identify, license, discover, develop, or commercialize additional product candidates, which would have a material adverse effect on our business and could potentially cause us to cease operations.

We incur increased costs as a result of operating as a public company, and our management is now required to devote substantial time to new compliance initiatives and corporate governance practices.

As a public company, we incur significant legal, accounting, and other expenses that we did not incur as a private company. The Sarbanes-Oxley Act of 2002, or the Sarbanes-Oxley Act, as well as rules subsequently implemented by the SEC and The NASDAQ Global Select Market, impose various requirements on public companies, including establishment and maintenance of effective disclosure and financial controls and corporate governance practices. In July 2010, the Dodd-Frank Wall Street Reform and Consumer Protection Act, or the Dodd-Frank Act, was enacted. There are significant corporate governance and executive compensation related provisions in the Dodd-Frank Act that require the SEC to adopt additional rules and regulations in these areas such as "say on pay" and pay parity. Stockholder activism, the current political environment, and the current high level of government intervention and regulatory reform may lead to substantial new regulations and disclosure obligations, which may lead to additional compliance costs and impact the manner in which we operate our business in ways we cannot currently anticipate. Our management and other personnel devote a substantial amount of time to these compliance initiatives. Moreover, these rules and regulations have increased our legal and financial compliance costs and will make some activities more time consuming and costly. For example, being a public company could make it more difficult and more expensive for us to obtain director and officer liability insurance and we may be required to incur substantial costs to maintain adequate levels of such coverage.

Additionally, the Sarbanes-Oxley Act requires, among other things, that we maintain effective internal controls for financial reporting and disclosure controls and procedures. In particular, we are required to perform system and process evaluation and testing of our internal controls over financial reporting to allow management to report on the effectiveness of our internal controls over financial reporting, as required by Section 404(a) of the Sarbanes-Oxley Act. In the event we lose our eligibility as an emerging growth company, or EGC, as a result of meeting the large accelerated filing requirement as defined by the SEC, we would then be subject to the compliance requirements of Section 404(b) of the Sarbanes-Oxley Act. We could lose our EGC eligibility as early as December 31, 2015, thereby requiring compliance with Section 404(b), which would cause us to incur substantial accounting expense and expend significant management efforts. We currently do not have an internal audit group, and we will need to hire additional accounting and financial staff with appropriate public company experience and technical accounting knowledge. Moreover, if we are not able to comply with the requirements of Section 404(b) in a timely manner or if we identify or our independent registered public accounting firm identifies deficiencies in our internal controls over financial reporting that are deemed to be material weaknesses, the market price of our stock could decline and we could be subject to sanctions or investigations by NASDAQ, the SEC, or other regulatory authorities, which would require additional financial and management resources.

For as long as we remain an EGC, we may take advantage of certain exemptions from various reporting requirements that are applicable to other public companies that are not emerging growth companies as described in the risk factor entitled "We are an 'emerging growth company,' and, due to the reduced reporting requirements applicable to emerging growth companies, certain investors may find investing in our common stock less attractive." We intend to take advantage of these exemptions from various reporting requirements but cannot guarantee that we will not be required to implement these requirements sooner than budgeted or planned and thereby incur unexpected expenses and also be subject to shorter timelines within which we must file our periodic reports; having to file our periodic reports on shorter timelines may also result in increased expense to us. Additionally, new laws and regulations, as well as changes to existing laws and regulations affecting public companies, including the provisions of the Sarbanes-Oxley Act and rules adopted by the SEC and by NASDAQ, would likely result in increased costs to us as we respond to their requirements.

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

In the United States, there have been and continue to be a number of legislative initiatives to contain healthcare costs. For example, in March 2010, the Affordable Care Act, as amended by the Health Care and Education Reconciliation Act, or the Health Care Reform Law, was passed, which substantially changes the way health care is financed by both governmental and private insurers, and significantly impacts the U.S. pharmaceutical industry. The Health Care Reform Law, among other things, subjects biologic products to potential competition by lower-cost biosimilars, addresses a new methodology by which rebates owed by manufacturers under the Medicaid Drug Rebate Program are calculated for drugs that are inhaled, infused, instilled, implanted, or injected, increases the minimum Medicaid rebates owed by manufacturers under the Medicaid Drug Rebate Program and extends the rebate program to individuals enrolled in Medicaid managed care organizations, establishes annual fees and taxes on manufacturers of certain branded prescription drugs, and promotes a new Medicare Part D coverage gap discount program.

In addition, other legislative changes have been proposed and adopted in the United States since the Health Care Reform Law was enacted. On August 2, 2011, the Budget Control Act of 2011, among other things, created measures for spending reductions by Congress. A Joint Select Committee on Deficit Reduction, tasked with recommending a targeted deficit reduction of at least $1.2 trillion for the years 2013 through 2021, was unable to reach required goals, thereby triggering the legislation's automatic reduction to several government programs. This includes aggregate reductions of Medicare payments to providers up to 2% per fiscal year. On January 2, 2013, President Obama signed into law the American Taxpayer Relief Act of 2012, or the ATRA, which, among other things, delayed for another two months the budget cuts mandated by these sequestration provisions of the Budget Control Act of 2011. On March 1, 2013, the President signed an executive order implementing sequestration, and on April 1, 2013, the 2% Medicare payment reductions went into effect. We expect that additional state and federal healthcare reform measures will be adopted in the future, any of which could limit the amounts that federal and state governments will pay for healthcare products and services, which could result in reduced demand for our product candidates or additional pricing pressures.

We may be subject, directly or indirectly, to federal and state healthcare fraud and abuse laws, false claims laws, and health information privacy and security laws. If we are unable to comply, or have not fully complied, with such laws, we could face substantial penalties.

If we obtain FDA approval for any of our product candidates and begin commercializing those products in the United States, our operations may be directly, or indirectly through our customers, subject to various federal and state fraud and abuse laws, including, without limitation, the federal Anti-Kickback Statute, the federal False Claims Act, and physician sunshine laws and regulations. These laws may impact, among other things, our proposed sales, marketing, and education programs. In addition, we may be subject to patient privacy regulation by both the federal government and the states in which we conduct our business. The laws that may affect our ability to operate include:

- the federal Anti-Kickback Statute, which prohibits, among other things, persons from knowingly and willfully soliciting, receiving, offering or paying remuneration, directly or indirectly, to induce, or in return for, the purchase or recommendation of an item or service reimbursable under a federal healthcare program, such as the Medicare and Medicaid programs;
- federal civil and criminal false claims laws and civil monetary penalty laws, which prohibit, among other things, individuals or entities from knowingly presenting, or causing to be presented, claims for payment from Medicare, Medicaid, or other third-party payors that are false or fraudulent;
- HIPAA, which created new federal criminal statutes that prohibit executing a scheme to defraud any healthcare benefit program and making false statements relating to healthcare matters;
- HIPAA, as amended by HITECH, and its implementing regulations, which imposes certain requirements relating to the privacy, security, and transmission of individually identifiable health information;
- the federal physician sunshine requirements under the Health Care Reform Laws requires manufacturers of drugs, devices, biologics, and medical supplies to report annually to the U.S. Department of Health and Human Services information related to payments and other transfers of value to physicians, other healthcare providers, and teaching hospitals, and ownership and investment interests held by physicians and other healthcare providers and their immediate family members and applicable group purchasing organizations; and
- state law equivalents of each of the above federal laws, such as anti-kickback and false claims laws that may apply to items or services reimbursed by any third-party payor, including commercial insurers, state laws that require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government, or otherwise restrict payments that may be made to healthcare providers and other potential referral sources; state laws that require drug manufacturers to report information related to payments and other transfers of value to physicians and other healthcare providers or marketing expenditures, and state laws governing the privacy and security of health information in certain circumstances, many of which differ from each other in significant ways and may not have the same effect, thus complicating compliance efforts.

Because of the breadth of these laws and the narrowness of the statutory exceptions and safe harbors available, it is possible that some of our business activities could be subject to challenge under one or more of such laws. In addition, recent health care reform legislation has strengthened these laws. For example, the Health Care Reform Law, among other things, amends the intent requirement of the federal anti-kickback and criminal healthcare fraud statutes. A person or entity no longer needs to have actual knowledge of this statute or specific intent to violate it. Moreover, the Health Care Reform Law provides that the government may assert that a claim including items or services resulting from a violation of the federal anti-kickback statute constitutes a false or fraudulent claim for purposes of the False Claims Act.

If our operations are found to be in violation of any of the laws described above or any other governmental regulations that apply to us, we may be subject to penalties, including civil and criminal penalties, damages, fines, exclusion from participation in government health care programs, such as Medicare and Medicaid, imprisonment, and the curtailment or restructuring of our operations, any of which could adversely affect our ability to operate our business and our results of operations.

International expansion of our business exposes us to business, regulatory, political, operational, financial, and economic risks associated with doing business outside of the United States.

We currently have limited international operations, but our business strategy incorporates potentially significant international expansion, particularly in anticipation of approval of our product candidates. We currently conduct physician and patient association outreach activities, as well as clinical studies, outside of the United States and plan to maintain sales representatives internationally in the future. Doing business internationally involves a number of risks, including but not limited to:

- multiple, conflicting, and changing laws and regulations such as privacy regulations, tax laws, export and import restrictions, employment laws, regulatory requirements, and other governmental approvals, permits, and licenses;
- failure by us to obtain and maintain regulatory approvals for the use of our products in various countries;

- additional potentially relevant third-party patent rights;
- complexities and difficulties in obtaining protection and enforcing our intellectual property;
- difficulties in staffing and managing foreign operations;
- complexities associated with managing multiple payor reimbursement regimes, government payors, or patient self-pay systems;
- limits in our ability to penetrate international markets;
- financial risks, such as longer payment cycles, difficulty collecting accounts receivable, the impact of local and regional financial crises on demand and payment for our products, and exposure to foreign currency exchange rate fluctuations;
- natural disasters, political and economic instability, including wars, terrorism, and political unrest, outbreak of disease, boycotts, curtailment of trade, and other business restrictions;
- certain expenses including, among others, expenses for travel, translation, and insurance; and
- regulatory and compliance risks that relate to maintaining accurate information and control over sales and activities that may fall within the purview of the U.S. Foreign Corrupt Practices Act, or FCPA, its books and records provisions, or its anti-bribery provisions.

Any of these factors could significantly harm our future international expansion and operations and, consequently, our results of operations.

If we fail to comply with environmental, health and safety laws and regulations, we could become subject to fines or penalties or incur costs that could have a material adverse effect on the success of our business.

Our research and development activities and our third-party manufacturers' and suppliers' activities involve the controlled storage, use, and disposal of hazardous materials, including the components of our product candidates and other hazardous compounds. We and our manufacturers and suppliers are subject to laws and regulations governing the use, manufacture, storage, handling, and disposal of these hazardous materials. In some cases, these hazardous materials and various wastes resulting from their use are stored at our and our manufacturers' facilities pending their use and disposal. We cannot eliminate the risk of contamination, which could cause an interruption of our commercialization efforts, research and development efforts and business operations, environmental damage resulting in costly clean-up and liabilities under applicable laws and regulations governing the use, storage, handling, and disposal of these materials and specified waste products. Although we believe that the safety procedures utilized by us and our third-party manufacturers for handling and disposing of these materials generally comply with the standards prescribed by these laws and regulations, we cannot guarantee that this is the case or eliminate the risk of accidental contamination or injury from these materials. In such an event, we may be held liable for any resulting damages and such liability could exceed our resources and state or federal or other applicable authorities may curtail our use of certain materials and/or interrupt our business operations. Furthermore, environmental laws and regulations are complex, change frequently, and have tended to become more stringent. We cannot predict the impact of such changes and cannot be certain of our future compliance. We do not currently carry biological or hazardous waste insurance coverage.

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

Our corporate headquarters and laboratory are located in the San Francisco Bay Area, and our collaboration partner for KRN23, KHK, is located in Japan, which have both in the past experienced severe earthquakes and other natural disasters. We do not carry earthquake insurance. Earthquakes or other natural disasters could severely disrupt our operations or those of our collaborators, and have a material adverse effect on our business, results of operations, financial condition, and prospects. If a natural disaster, power outage, or other event occurred that prevented us from using all or a significant portion of our headquarters, that damaged critical infrastructure (such as the manufacturing facilities of our third-party contract manufacturers) or that otherwise disrupted operations, it may be difficult or, in certain cases, impossible for us to continue our business for a substantial period of time. The disaster recovery and business continuity plans we have in place currently are limited and are unlikely to prove adequate in the event of a serious disaster or similar event. We may incur substantial expenses as a result of the limited nature of our disaster recovery and business continuity plans, which, particularly when taken together with our lack of earthquake insurance, could have a material adverse effect on our business.

Risks Related to Ownership of Our Common Stock

The market price of our common stock may be highly volatile.

The market price of our common stock has been, and is likely to continue to be, volatile. Our stock price could be subject to wide fluctuations in response to a variety of factors, including but not limited to the following:

- adverse results or delays in preclinical or clinical studies;
- any inability to obtain additional funding;
- any delay in filing an IND, NDA, BLA, or other regulatory submission for any of our product candidates and any adverse development or perceived adverse development with respect to the applicable regulatory agency's review of that IND, NDA, BLA, or other regulatory submission;
- the perception of limited market sizes or pricing for our product candidates;
- failure to successfully develop and commercialize our product candidates;
- post-marketing safety issues;
- failure to maintain our existing strategic collaborations or enter into new collaborations;
- failure by us or our licensors and strategic collaboration partners to prosecute, maintain, or enforce our intellectual property rights;
- changes in laws or regulations applicable to our products;
- any inability to obtain adequate product supply for our product candidates or the inability to do so at acceptable prices;
- adverse regulatory decisions;
- introduction of new products, services, or technologies by our competitors;
- failure to meet or exceed financial projections we may provide to the public;
- failure to meet or exceed the financial projections of the investment community;
- the perception of the pharmaceutical industry by the public, legislatures, regulators, and the investment community;
- announcements of significant acquisitions, strategic partnerships, joint ventures, or capital commitments by us, our strategic collaboration partner, or our competitors;
- disputes or other developments relating to proprietary rights, including patents, litigation matters, and our ability to obtain patent protection for our technologies;
- additions or departures of key scientific or management personnel;
- significant lawsuits, including patent or stockholder litigation;
- if securities or industry analysts do not publish research or reports about our business, or if they issue an adverse or misleading opinion regarding our stock;
- changes in the market valuations of similar companies;
- general market or macroeconomic conditions;
- sales of our common stock by us or our stockholders in the future; and
- trading volume of our common stock.

In addition, biotechnology and biopharmaceutical companies in particular have experienced extreme price and volume fluctuations that have often been unrelated or disproportionate to the operating performance of these companies. Broad market and industry factors may negatively affect the market price of our common stock, regardless of our actual operating performance.

Our principal stockholders and management own a significant percentage of our stock and may be able to exert significant control over matters subject to stockholder approval.

As of March 23, 2015, our executive officers, directors, greater than five percent stockholders, and their affiliates beneficially owned approximately 35% of our voting stock. Therefore, these stockholders may have the ability to influence us through their ownership positions, which may prevent or discourage unsolicited acquisition proposals or offers for our common stock that you may believe are in your best interest as one of our stockholders.

We are an "emerging growth company" and, due to the reduced reporting requirements applicable to emerging growth companies, certain investors may find investing in our common stock less attractive.

We are an "emerging growth company," as defined in the Jumpstart Our Business Startups Act of 2012, or the JOBS Act. For as long as we continue to be an EGC, we may take advantage of exemptions from various reporting requirements that are applicable to other public companies that are not EGCs, including not being required to comply with the auditor attestation requirements of Section 404(b) of the Sarbanes-Oxley Act, reduced disclosure obligations regarding executive compensation in our periodic reports and proxy statements, and exemptions from the requirements of holding a nonbinding advisory vote on executive compensation and stockholder approval of any golden parachute payments not previously approved. We could be an EGC for up to five years from the pricing of our initial public offering, although circumstances could cause us to lose that status earlier, including if we have total annual gross revenue of $1.0 billion or more during any fiscal year before that time or if we issue more than $1.0 billion in non-convertible debt during any three-year period before that time, in which we would cease to be an EGC immediately, or on the date which we become a large accelerated filer, as defined by the SEC, in which case we would no longer be an EGC. We would become a large accelerated filer, as currently defined, if the market value of our common stock held by non-affiliates exceeds $700.0 million as of any June 30 of any year in which we have been a public company for at least 12 calendar months. We cannot predict if investors will find our common stock less attractive because we may rely on this exemption. If some investors find our common stock less attractive as a result, there may be a less active trading market for our common stock and our stock price may be more volatile.

Sales of a substantial number of shares of our common stock in the public market could cause our stock price to fall.

If our existing stockholders sell, or indicate an intention to sell, substantial amounts of our common stock in the public market after the lapse of the lock-up agreements entered into in connection with our underwritten public offering in February 2015, the market price of our common stock could decline. As of March 23, 2015, we had a total of 35,596,219 shares of common stock outstanding. Of these shares, the shares of our common stock sold in our IPO and our underwritten public offerings in July 2014 and February 2015 are currently freely tradable, without restriction (except as otherwise applicable), in the public market.

In addition, as of March 23, 2015, approximately 6.7 million shares of common stock that are either subject to outstanding options or restricted stock units, reserved for future issuance under our equity incentive plans, employee stock purchase plan, or subject to outstanding warrants will become eligible for sale in the public market to the extent permitted by the provisions of various vesting schedules, and Rule 144 and Rule 701 under the Securities Act. If these additional shares of common stock are sold, or if it is perceived that they will be sold, in the public market, the market price of our common stock could decline.

Future sales and issuances of our common stock or rights to purchase common stock, including pursuant to our equity incentive plans, could result in additional dilution of the percentage ownership of our stockholders and could cause our stock price to fall.

We will need additional capital in the future to continue our planned operations. To the extent we raise additional capital by issuing equity securities, our stockholders may experience substantial dilution. We may sell common stock, convertible securities, or other equity securities in one or more transactions at prices and in a manner we determine from time to time. If we sell common stock, convertible securities, or other equity securities in more than one transaction, investors may be materially diluted by subsequent sales. These sales may also result in material dilution to our existing stockholders, and new investors could gain rights superior to our existing stockholders.

Pursuant to our 2014 Incentive Plan, or the 2014 Plan, our management is authorized to grant stock options and other equity-based awards to our employees, directors, and consultants. An aggregate of 2,250,000 shares were available for issuance at the inception of the 2014 Plan. The number of shares available for future grant under the 2014 Plan will automatically increase on January 1 of each year (beginning January 1, 2015) by the lesser of 2,500,000 shares or 4% of all shares of our capital stock outstanding as of December 31 of the prior calendar year, subject to the ability of our compensation committee to take action to reduce the size of the increase in any given year. Currently, we plan to register the increased number of shares available for issuance under the 2014 Plan each year.

Pursuant to our 2014 Employee Stock Purchase Plan, or 2014 ESPP, eligible employees can acquire shares of our common stock at a discount to the prevailing market price, and an aggregate of 600,000 shares are available for issuance under the 2014 ESPP. The number of shares available for issuance under the 2014 ESPP will automatically increase on January 1 of each year (beginning January 1, 2015) by the lesser of 1,200,000 shares or 1% of all shares of our capital stock outstanding as of December 31 of the prior calendar year, subject to the ability of our compensation committee to take action to reduce the size of the increase in any given year. If our board of directors elects to increase the number of shares available for future grant under the 2014 Plan or the 2014 ESPP, our stockholders may experience additional dilution, which could cause our stock price to fall.

Our ability to use our net operating loss carryforwards and certain other tax attributes may be limited.

We have incurred substantial losses during our history and do not expect to become profitable in the near future and we may never achieve profitability. To the extent that we continue to generate taxable losses, unused losses will carry forward to offset future taxable income, if any, until such unused losses expire. Under Sections 382 and 383 of the Internal Revenue Code of 1986, as amended, if a corporation undergoes an "ownership change," generally defined as a greater than 50% change (by value) in its equity ownership over a three-year period, the corporation's ability to use its pre-change net operating loss carryforwards, or NOLs, and other pre-change tax attributes (such as research tax credits) to offset its post-change income may be limited. A Section 382 analysis to determine the limitation of the net operating loss carryforwards has not been performed. As a result of ownership changes that may have occurred previously or that could occur in the future, our ability to use our pre-change net operating loss carryforwards to offset U.S. federal taxable income may be subject to limitations, which could potentially result in increased future tax liability to us. In addition, at the state level, there may be periods during which the use of NOLs is suspended or otherwise limited, which could accelerate or permanently increase state taxes owed.

We do not intend to pay dividends on our common stock so any returns will be limited to the value of our stock.

We have never declared or paid any cash dividends on our common stock. Although we have paid dividends to our holders of preferred stock in the past, including a $4.3 million cash dividend paid in connection with our IPO in February 2014, all dividends paid were agreed to at the time of the private placement financings. We currently intend to retain all available funds and any future earnings, if any, for the development, operation, and expansion of our business and do not anticipate declaring or paying any cash dividends for the foreseeable future. Any return to stockholders will therefore be limited to the appreciation of their stock.

Provisions in our amended and restated certificate of incorporation and by-laws, as well as provisions of Delaware law, could make it more difficult for a third party to acquire us or increase the cost of acquiring us, even if doing so would benefit our stockholders or remove our current management.

Our amended and restated certificate of incorporation, amended and restated by-laws, and Delaware law contain provisions that may have the effect of delaying or preventing a change in control of us or changes in our management. Our amended and restated certificate of incorporation and by-laws include provisions that:

- authorize "blank check" preferred stock, which could be issued by our board of directors without stockholder approval and may contain voting, liquidation, dividend, and other rights superior to our common stock;
- create a classified board of directors whose members serve staggered three-year terms;
- specify that special meetings of our stockholders can be called only by our board of directors or the chairperson of our board of directors;
- prohibit stockholder action by written consent;
- establish an advance notice procedure for stockholder approvals to be brought before an annual meeting of our stockholders, including proposed nominations of persons for election to our board of directors;
- provide that our directors may be removed only for cause;
- provide that vacancies on our board of directors may be filled only by a majority of directors then in office, even though less than a quorum;
- specify that no stockholder is permitted to cumulate votes at any election of directors;
- expressly authorize our board of directors to modify, alter or repeal our amended and restated by-laws; and
- require holders of 75% of our outstanding common stock to amend specified provisions of our amended and restated certificate of incorporation and amended and restated by-laws.

These provisions, alone or together, could delay, deter, or prevent hostile takeovers and changes in control or changes in our management.

In addition, because we are incorporated in Delaware, we are governed by the provisions of Section 203 of the Delaware General Corporation Law, which limits the ability of stockholders owning in excess of 15% of our outstanding voting stock to merge or combine with us.

Any provision of our amended and restated certificate of incorporation or amended and restated by-laws or Delaware law that has the effect of delaying or deterring a change in control could limit the opportunity for our stockholders to receive a premium for their shares of our common stock, and could also affect the price that some investors are willing to pay for our common stock.

Item 1B. ***Unresolved Staff Comments***

None.

Item 2. ***Properties***

Our offices are located at two leased facilities. The first is a 19,916 square foot facility in Novato, California used primarily for corporate, clinical, regulatory, manufacturing, and quality functions. On February 20, 2014, we executed an amendment to this lease adding approximately 25,000 square feet of additional space. The rental term for the additional space commenced on May 1, 2014 and will expire on April 30, 2019. The rental term for the original space shall also now expire on April 30, 2019, unless extended as permitted by the amendment. On March 9, 2015, we executed an additional addendum to this lease adding approximately 20,000 square feet of additional space. The rental term for this additional space shall commence on May 1, 2015 and expire on April 30, 2019, unless extended as permitted by the amendment.

We also lease a 910 square foot facility in Novato, California used for research laboratory space. On August 17, 2014, we executed an amendment to this lease adding approximately 1,955 square feet of additional space. The rental term for the additional space commenced on September 15, 2014 and will expire on September 15, 2019. The rental term for the current space shall also now expire on September 15, 2019, unless extended as permitted by the amendment.

Item 3. ***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 4. ***Mine Safety Disclosures***

Not applicable.

PART II

Item 5. ***Market for Registrant's Common Equity, Related Stockholder Matters and Issuer Purchases of Equity Securities***

Our common stock has been traded on The NASDAQ Global Select Market since January 31, 2014 under the symbol "RARE". Prior to such time, there was no public market for our common stock. As a result, we have not set forth quarterly information with respect to the high and low prices for our common stock for the two most recent fiscal years. The following tables set forth the intraday high and low prices of our common stock as reported by NASDAQ from January 31, 2014, our first day of trading on NASDAQ, to March 23, 2015.

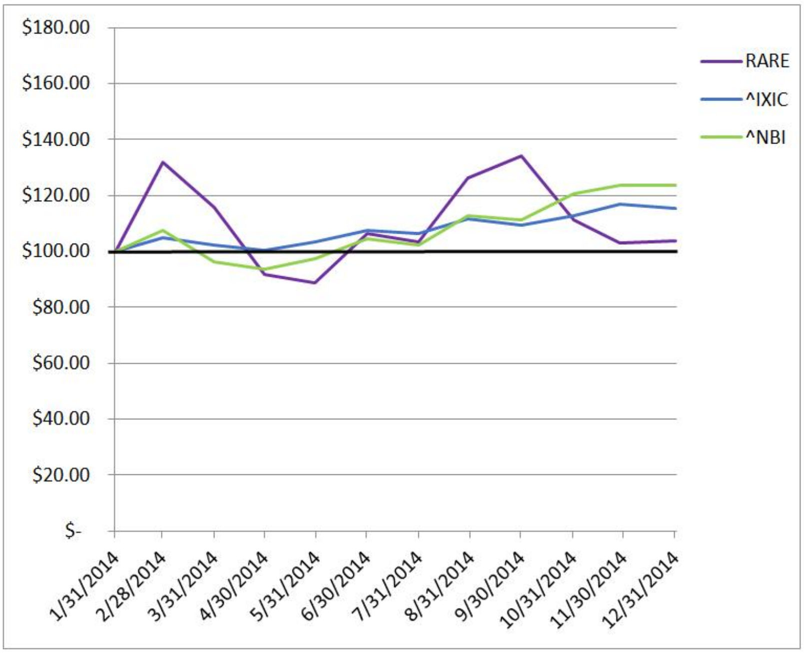
	Fiscal 2014	
	High	Low
First Quarter (January 31, 2014 through March 31, 2014)	$ 69.77	$ 35.15
Second Quarter (April 1, 2014 through June 30, 2014)	$ 60.00	$ 32.02
Third Quarter (July 1, 2014 through September 30, 2014)	$ 60.04	$ 37.77
Fourth Quarter (October 1, 2014 through December 31, 2014)	$ 58.33	$ 38.01

	Fiscal 2015	
	High	Low
First Quarter (January 1, 2015 through March 23, 2015)	$ 64.99	$ 44.27

As of December 31, 2014, we had approximately 16 holders of record of our common stock. Certain shares are held in "street" name and, accordingly, the number of beneficial owners of such shares is not known or included in the foregoing number.

STOCK PRICE PERFORMANCE GRAPH

The following stock performance graph compares our total stock return with the total return for (i) the NASDAQ Composite Index and the (ii) the NASDAQ Biotechnology Index for the period from January 31, 2014 (the date our common stock commenced trading on the NASDAQ Global Market) through December 31, 2014. The figures represented below assume an investment of $100 in our common stock at the closing price of $42.25 on January 31, 2014 and in the NASDAQ Composite Index and the NASDAQ Biotechnology Index on January 31, 2014 and the reinvestment of dividends into shares of common stock. The comparisons in the table are required by the Securities and Exchange Commission, or SEC, and are not intended to forecast or be indicative of possible future performance of our common stock. This graph shall not be deemed "soliciting material" or be deemed "filed" for purposes of Section 18 of the Securities Exchange Act of 1934, as amended, or the Exchange Act, or otherwise subject to the liabilities under that Section, and shall not be deemed to be incorporated by reference into any of our filings under the Securities Act of 1933, as amended, or the Securities Act, whether made before or after the date hereof and irrespective of any general incorporation language in any such filing.



$100 investment in stock or index	Ticker	January 31, 2014	March 31, 2014	June 30, 2014	September 30, 2014	December 31, 2014
Ultragenyx Pharmaceutical Inc.	RARE	$ 100.00	$ 115.72	$ 106.25	$ 133.96	$ 103.86
NASDAQ Composite Index	^IXIC	$ 100.00	$ 102.32	$ 107.41	$ 109.49	$ 115.40
NASDAQ Biotechnology Index	^NBI	$ 100.00	$ 96.11	$ 111.30	$ 111.30	$ 123.70

Dividend Policy

We have never declared or paid cash dividends on our common stock. Although we paid dividends to our holders of preferred stock in the past, including a $4.3 million cash dividend paid in connection with our IPO in February 2014, all dividends paid were agreed to at the time of the private placement financings. We currently intend to retain all available funds and any future earnings, if any, to fund the development, operation, and expansion of our business, and we do not anticipate paying any cash dividends on our common stock in the foreseeable future. Any future determination to pay dividends will be made at the discretion of our board of directors or any authorized committee thereof.

Use of Proceeds

On January 30, 2014, the Company's registration statements on Form S-1 (File Nos. 333-192244 and 333-193675) relating to the IPO of 5,760,369 shares of its common stock was declared effective by the SEC. As a result of our IPO and the exercise of the over-allotment option (864,054 additional shares of common stock) granted to the underwriters, both of which closed on February 5, 2014, the Company received total proceeds from the offering of $129.4 million, net of underwriting discounts and commissions of $9.7 million. After deducting offering expenses of approximately $3.3 million and a cash dividend of $4.3 million paid to the preferred stockholders at the closing of the IPO, net proceeds were approximately $121.7 million. J.P. Morgan Securities LLC and Morgan Stanley & Co. LLC acted as joint book-running managers of the IPO and as representatives of the underwriters.

The net proceeds from the offerings described above have been used and will be used, together with our cash, cash equivalents and short-term investments, to fund continued advancement of our KRN23, rhGUS, LC-FAOD, Glut 1 DS, SA-ER, and pre-clinical programs, with the balance to be used to fund working capital, capital expenditures and other general corporate purposes, which may include in-licenses, acquiring, or investing in additional businesses, technologies, products, or assets the acquisition or licensing of other products, businesses or technologies.

There has been no material change in the planned use of proceeds from our initial public offering as described in our prospectus dated January 31, 2014, filed with the SEC pursuant to Rule 424(b) of the Securities Act.

Information About Our Equity Compensation Plans

Information regarding our equity compensation plans is incorporated by reference to Item 12, "Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters—Equity Compensation Plan Information" of Part III of this Annual Report on Form 10-K.

Recent Sales of Unregistered Securities

From January 1, 2014 until the filing of our Registration Statement on Form S-8 on March 24, 2014, we granted stock options to employees and directors under our 2011 Equity Incentive Plan and our 2014 Plan, as amended, covering an aggregate of 227,925 shares of common stock, at a weighted-average average exercise price of $33.66 per share. During this same time period we also sold an aggregate of 60,456 shares of common stock to employees for cash consideration in the aggregate amount of $43,000 upon the exercise of stock options. The sales of the above securities were exempt from registration under Rule 701 promulgated under the Securities Act as transactions pursuant to a compensatory benefit plan or a written contract relating to compensation.

Issuer's Purchases of Equity Securities

None

Item 6. ***Selected Financial Data***

The selected statements of operations data for the years ended December 31, 2014, 2013, and 2012 and the selected balance sheet data as of December 31, 2014 and 2013 are derived from our audited financial statements included elsewhere in this Form 10-K. Our historical results are not necessarily indicative of the results that may be expected in the future and interim results are not necessarily indicative of results to be expected for the full year. You should read the selected historical financial data below in conjunction with the section titled "Management's Discussion and Analysis of Financial Condition and Results of Operations" and the financial statements and related notes included elsewhere in this Annual Report on Form 10-K.

	Year Ended December 31,			
	2014	2013	2012	2011
	(in thousands, except share and per share amounts)			
Statements of Operations Data:				
Operating expenses:				
Research and development	$ 45,967	$ 27,829	$ 12,641	$ 4,717
General and administrative	10,811	4,451	3,344	1,844
Total operating expenses	56,778	32,280	15,985	6,561
Loss from operations	(56,778)	(32,280)	(15,985)	(6,561)
Interest income	608	216	1	4
Interest expense	—	—	—	(270)
Other expense	(3,632)	(3,006)	(350)	(22)
Net loss	$ (59,802)	$ (35,070)	$ (16,334)	$ (6,849)
Net loss attributable to common stockholders(1)	$ (64,610)	$ (50,289)	$ (19,561)	$ (7,466)
Net loss per share attributable to common stockholders, basic and diluted	$ (2.25)	$ (14.87)	$ (14.20)	$ (4.62)
Shares used to compute net loss per share attributable to common stockholders, basic and diluted	28,755,758	3,382,489	1,377,207	1,617,384

(1) See Notes 2 and 13 to our audited financial statements of this report for an explanation of the calculations of basic and diluted net loss per share attributable to common stockholders.

	As of December 31,			
	2014	2013	2012	2011
	(in thousands)			
Balance Sheets Data:				
Cash, cash equivalents and short-term investments	$ 187,487	$ 53,377	$ 86,190	$ 10,645
Working capital	180,899	49,304	83,257	9,954
Total assets	197,967	59,649	88,316	12,129
Convertible preferred stock warrant liability	—	3,419	518	216
Convertible preferred stock	—	124,930	111,387	18,604
Total stockholders' equity (deficit)	184,945	(74,821)	(27,047)	(7,961)

Item 7. ***Management's Discussion and Analysis of Financial Condition and Results of Operations***

MANAGEMENT'S DISCUSSION AND ANALYSIS OF FINANCIAL CONDITION AND RESULTS OF OPERATIONS

You should read the following discussion and analysis of our financial condition and results of operations together with the section of this annual report entitled "Selected Financial Data" and our financial statements and related notes included elsewhere in this annual report. This discussion and other parts of this annual report contain forward-looking statements that involve risk and uncertainties, such as statements of our plans, objectives, expectations, and intentions. In this annual report, words such as "may," "will," "expect," "anticipate," "estimate," "intend," and similar expressions (as well as other words or expressions referencing future events, conditions or circumstances) are intended to identify forward-looking statements. As a result of many factors, including those factors set forth in the "Risk Factors" section of this annual report, our actual results could differ materially from the results described in or implied by the forward-looking statements contained in the following discussion and analysis.

Overview

We are a clinical-stage biopharmaceutical company 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 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 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.

Our biologics pipeline includes the following three product candidates:

- KRN23, or UX023, is an antibody targeting fibroblast growth factor 23, or FGF23, intended for the treatment of 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. We also expect to continue the clinical development of KRN23 in adults with XLH.
- KRN23 is also intended for the treatment of 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 are enrolling a Phase 2 study of KRN23 in adult inoperable TIO patients.
- 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 initiated a Phase 3 clinical study in December 2014.
- rhPPCA, or UX004, is an enzyme replacement therapy in preclinical development for galactosialidosis, a rare lysosomal storage disease that can cause multi-system clinical disease similar to MPS 7 including enlarged liver, joint disease, abnormal bone development, short stature, and death. We continue preclinical development of rhPPCA.

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

- Triheptanoin, or UX007, is a synthetic triglyceride with a specifically designed chemical composition being studied in an international open-label Phase 2 study for the treatment of LC-FAOD. LC-FAOD is a set of rare metabolic diseases that prevent the conversion of fat into energy and can cause low blood sugar, muscle rupture, and heart and liver disease.
- Triheptanoin is also in a Phase 2 study for the treatment of Glut1 DS, a rare metabolic disease of brain energy deficiency that is characterized by seizures, developmental delay, and movement disorder.
- SA-ER, or UX001, is an extended-release form of sialic acid in a Phase 2 extension study for the treatment of HIBM, a neuromuscular disorder that causes muscle weakness and wasting. We plan to initiate a Phase 3 study by the second half of 2015, and we intend to file an MAA, seeking conditional approval from the EMA, for the use of SA-ER in the treatment of HIBM in the second half of 2015.

We are considered a clinical-stage company under U.S. generally accepted accounting principles, or U.S. GAAP, 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 convertible preferred stock and equity securities.

We have never been profitable and have incurred net losses in each year since inception. Our net losses were $59.8 million, $35.1 million and $16.3 million for the years ended December 31, 2014, 2013, and 2012. As of December 31, 2014 we had incurred cumulative net losses of $119.4 million. 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.

Financial Operations Overview

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 our products or enter into collaborative agreements with third parties.

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 short-term investments.

Other expense

Other expense primarily consists of gains and losses resulting from the remeasurement of our convertible preferred stock warrant liability. We continued to record adjustments to the estimated fair value of the convertible preferred stock warrants until their conversion into warrants to purchase shares of our common stock at the completion of our initial public offering. At that time, we reclassified the convertible preferred stock warrant liability as additional paid-in capital, and we will no longer record any related periodic fair value adjustments.

Critical Accounting Policies and Significant Judgments and Estimates

Our management's discussion and analysis of our financial condition and results of operations is based on our financial statements, which have been prepared in accordance with U.S. GAAP. The preparation of these 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. We believe that the accounting policies discussed below are critical to understanding our historical and future performance, as these policies relate to the more significant areas involving management's judgments and estimates.

Accrued Research and Development, and Research and Development Expenses

As part of the process of preparing financial statements, we are required to estimate and accrue expenses, the largest of which is related to accrued research and development expenses. This process involves reviewing contracts and purchase orders, identifying services that have been performed on our behalf, and estimating the level of service performed and the associated cost incurred for the service when we have not yet been invoiced or otherwise notified of the actual costs.

We record accruals for estimated costs of research, preclinical and clinical studies, and manufacturing development. These costs are a significant component of our research and development expenses. A substantial portion of our ongoing research and development activities is conducted by third-party service providers. We accrue the costs incurred under our agreements with these third parties based on actual work completed in accordance with agreements established with these third parties. We determine the actual costs through discussions with internal personnel and external service providers as to the progress or stage of completion of the services and the agreed-upon fee to be paid for such services. We make significant judgments and estimates in determining the accrual balance in each reporting period. As actual costs become known, we adjust our accruals. Although we do not expect our estimates to be materially different from amounts actually incurred, our understanding of the status and timing of services performed relative to the actual status and timing of services performed may vary and could result in us reporting amounts that are too high or too low in any particular period. Our accrual is dependent, in part, upon the receipt of timely and accurate reporting from clinical research organizations and other third-party vendors.

Research and development costs are expensed as incurred and consist of salaries and benefits, stock-based compensation, lab supplies, materials and facility costs, as well as fees paid to other nonemployees and entities that conduct certain research and development activities on our behalf. Amounts incurred in connection with collaboration and license agreements are also included in research and development expense. Payments made prior to the receipt of goods or services to be used in research and development are capitalized until the goods or services are received.

To date, there have been no material differences from our accrued estimated expenses to the actual clinical trial expenses; however, due to the nature of estimates, we cannot assure you that we will not make changes to our estimates in the future as we become aware of additional information about the status or conduct of our clinical studies and other research activities.

Estimated Fair Value of Convertible Preferred Stock Warrant Liability

Warrants for the purchase of Series A convertible preferred stock that are contingently redeemable are classified as liabilities on the balance sheet at their estimated fair value. At the end of each reporting period, changes in estimated fair value during the period are recorded in other expense, net. We have continued to adjust the carrying value of the warrants until the completion of our initial public offering, at which time the liabilities were reclassified to additional paid-in capital.

We estimated the fair values of our convertible preferred stock warrants using an option-pricing model based on inputs as of the valuation measurement dates, including our estimated equity value at the valuation measurement dates, the estimated volatility of the price of our convertible preferred stock, the remaining contractual terms of the warrants, and the risk-free interest rates. In January 2014, in connection with our IPO, the warrants to purchase preferred stock converted into warrants to purchase common stock.

Stock-Based Compensation

Stock-based compensation costs related to stock options granted to employees are measured at the date of grant based on the estimated fair value of the award, net of estimated forfeitures. We estimate the grant date fair value, and the resulting stock-based compensation expense, using the Black-Scholes option-pricing model. The grant date fair value of the stock-based awards is recognized on a straight-line basis over the requisite service period, which is generally the vesting period of the respective awards. We expect to continue to grant stock options in the future, and to the extent that we do, our actual stock-based compensation will likely increase. The Black-Scholes option-pricing model requires the use of highly subjective assumptions which determine the estimated fair value of stock-based awards. These assumptions include:

- *Expected term* — The expected term represents the period that the stock-based awards are expected to be outstanding and is determined using the simplified method (based on the midpoint between the vesting date and the end of the contractual term).
- *Expected volatility* — Prior to our IPO we were privately held and did not have any trading history for our common stock; accordingly, the expected volatility was estimated based on the average volatility for comparable publicly traded biopharmaceutical companies over a period equal to the expected term of the stock option grants. When selecting comparable publicly traded biopharmaceutical companies on which we based our expected stock price volatility, we selected companies with comparable characteristics to us, including enterprise value, risk profiles, position within the industry, and with historical share price information sufficient to meet the expected life of the stock-based awards. The historical volatility data was computed using the daily closing prices for the selected companies' shares during the equivalent period of the calculated expected term of the stock-based awards. In 2014, we modified our approach by phasing in our own common stock trading history and supplemented the remaining historical information with a blended volatility from the trading history from the common stock of the same set of comparable publicly traded biopharmaceutical companies. We will continue to use comparable company information until historical volatility of our common stock is relevant to measure expected volatility for future option grants.
- *Risk-free interest rate* — The risk-free interest rate is based on the U.S. Treasury zero coupon issues in effect at the time of grant for periods corresponding with the expected term of option.
- *Expected dividend* — We have never paid dividends on our common stock and have no plans to pay dividends on our common stock. Therefore, we used an expected dividend yield of zero.

In addition to the assumptions used in the Black-Scholes option-pricing model, we must also estimate a forfeiture rate to calculate the stock-based compensation for our awards. We will continue to use judgment in evaluating the expected volatility, expected terms, and forfeiture rates utilized for our stock-based compensation calculations on a prospective basis and will revise in subsequent periods if actual forfeitures differ from those estimates.

For the years ended December 31, 2014, 2013, and 2012 stock-based compensation expense was $5.4 million, $0.7 million and $0.9 million, respectively. As of December 31, 2014, we had $23.9 million of total unrecognized stock-based compensation costs, net of estimated forfeitures, which we expect to recognize over a weighted-average period of 3.2 years.

Fair Value of Common Stock

We are required to estimate the fair value of the common stock underlying our stock-based awards when performing the fair value calculations with the Black-Scholes option-pricing model. Prior to our IPO in January 2014, the estimated fair value of the common stock underlying our stock-based awards was determined on each grant date by our board of directors, with input from management. Given the absence of a public trading market of our common stock, and in accordance with the American Institute of Certified Public Accountants, or AICPA, Practice Guide, *Valuation of Privately-Held-Company Equity Securities Issued as Compensation*, our board of directors exercised reasonable judgment and considered numerous objective and subjective factors to estimate the fair value of our common stock.

All options to purchase shares of our common stock have been granted with an exercise price per share equal to the fair value per share of our common stock underlying those options on the date of grant. To assist our board of directors with the determination of the exercise price of our stock options and the fair value of the common stock underlying the options, we obtained third-party valuations of our common stock as of June 30, 2012, December 31, 2012, June 30, 2013, September 30, 2013, and November 30, 2013. Our board of directors considered the fair values of the common stock derived in the third-party valuations as one of the factors it considered when setting the exercise prices for options granted. Our board of directors also considered a range of objective and subjective factors and assumptions in estimating the fair value of our common stock on the date of grant, including:

- progress of our research and development efforts;
- our operating results and financial condition, including our levels of available capital resources;
- rights and preferences of our common stock compared to the rights and preferences of our other outstanding equity securities;

- our stage of development and material risks related to our business;
- the achievement of enterprise milestones, including entering into collaboration or license agreements and our progress in clinical trials;
- the valuation of publicly-traded companies in the life sciences and biotechnology sectors, as well as recently completed mergers and acquisitions of peer companies;
- equity market conditions affecting comparable public companies;
- the likelihood of achieving a liquidity event for the shares of common stock, such as an initial public offering given prevailing market and biotechnology sector conditions; and
- that the grants involved illiquid securities in a private company.

The fair value of the underlying common stock was determined by the board of directors until the IPO when our common stock started trading on The NASDAQ Global Select Market under the ticker symbol RARE on January 31, 2014. Consequently, after our IPO the fair value of the shares of common stock underlying the stock options is the closing market price on the option grant date.

Income Taxes

We use the liability method of accounting for income taxes. Under this method, deferred tax assets and liabilities are determined based on the differences between the financial reporting and the tax bases of assets and liabilities and are measured using the enacted tax rates and laws that will be in effect when the differences are expected to reverse. We assess the likelihood that the resulting deferred tax assets will be realized. A valuation allowance is provided when it is more likely than not that some portion or all of a deferred tax asset will not be realized.

As of December 31, 2014, our total deferred tax assets were $51.3 million. Due to our lack of earnings history and uncertainties surrounding our ability to generate future taxable income, the net deferred tax assets have been fully offset by a valuation allowance. The deferred tax assets were primarily comprised of federal and state tax net operating losses and tax credit carryforwards. Utilization of the net operating loss and tax credit carryforwards may be subject to an annual limitation due to historical or future ownership percentage change rules provided by the Internal Revenue Code of 1986, and similar state provisions. The annual limitation may result in the expiration of certain net operating loss and tax credit carryforwards before their utilization.

Results of Operations

Comparison of Years Ended December 31, 2014 and 2013

Research and Development Expenses (dollars in thousands)

	Year Ended December 31, 2014	Year Ended December 31, 2013	Dollar Change	% Change
Development candidate:				
KRN23	$ 4,691	$ 821	$ 3,870	471%
rhGUS	9,445	7,180	2,265	32%
rhPPCA	1,271	316	955	302%
Triheptanoin (LC-FAOD)	8,739	5,792	2,947	51%
Triheptanoin (Glut1 DS)	4,475	2,400	2,075	86%
SA-ER	10,851	8,054	2,797	35%
Other research costs and preclinical costs	6,495	3,266	3,229	99%
Total research and development expenses	$ 45,967	$ 27,829	$ 18,138	65%

Research and development expenses increased $18.1 million for the twelve months ended December 31, 2014 compared to the same period in 2013. The increase in research and development expenses above is primarily due to:

- for KRN23, an increase of $3.9 million related to the development and initiation of our pediatric study (in July 2014) and other development expenses since the product candidate was in-licensed in August 2013;
- for rhGUS, an increase of $2.3 million related to an increase in manufacturing and clinical study related activities;
- for rhPPCA, an increase of $1.0 million related to an increase in manufacturing related activities;
- for triheptanoin (LC-FAOD), an increase of $2.9 million related to the initiation of our clinical program in 2013, support of investigator-sponsored studies, and costs related to manufacturing, partially offset by the $0.8 million we paid to exercise the option with Baylor Research Institute, or BRI, pursuant to our license agreement with BRI to license the rights to triheptanoin in all territories outside of North America in June 2013;

- for triheptanoin (Glut1 DS), an increase of $2.1 million related to costs associated with the initiation of our clinical program and costs related to manufacturing;
- for SA-ER, an increase of $2.8 million related to the increase in clinical activities and related manufacturing for this program; and
- an increase of $3.2 million in other research costs and preclinical costs for various other potential product candidates.

General and Administrative Expenses (dollars in thousands)

	Year Ended December 31,		Dollar	%
	2014	2013	Change	Change
General and administrative	$ 10,811	$ 4,451	$ 6,360	143%

General and administrative expenses increased $6.4 million for the year ended December 31, 2014 compared to the same period in 2013. The increase in general and administrative expenses was primarily due to increases in professional services costs, costs associated with being a public company, and an increase in personnel costs as a result of increases in employee headcount.

Interest Income (dollars in thousands)

	Year Ended December 31,		Dollar	%
	2014	2013	Change	Change
Interest income	$ 608	$ 216	$ 392	181%

Interest income increased $0.4 million for the year ended December 31, 2014 compared to the same period in 2013, primarily due to funds invested in 2014 from our IPO and underwritten public offering which were completed in January 2014 and July 2014, respectively.

Other Expense, net (dollars in thousands)

	Year Ended December 31,		Dollar	%
	2014	2013	Change	Change
Other expense, net	$ 3,632	$ 3,006	$ 626	21%

Other expense, net increased $0.6 million for the year ended December 31, 2014 compared to the same period in 2013. This was primarily due to a $0.4 million increase in expense for the fair value remeasurement of the liability related to our convertible preferred stock warrants combined with a $0.3 million increase in state tax fees offset by $0.1 million in foreign currency gains.

Comparison of Years Ended December 31, 2013 and 2012

Research and Development Expenses (dollars in thousands)

	Year Ended December 31,		Dollar	%
	2013	2012	Change	Change
Development candidate:				
KRN23	$ 821	$ —	$ 821	*
rhGUS	7,180	3,198	3,982	125%
rhPPCA	316	172	144	84%
Triheptanoin (LC-FAOD)	5,792	546	5,246	961%
Triheptanoin (Glut1 DS)	2,400	—	2,400	*
SA-ER	8,054	6,840	1,214	18%
Other research costs and preclinical costs	3,266	1,885	1,381	73%
Total research and development expenses	$ 27,829	$ 12,641	$ 15,188	120%

**not meaningful*

Research and development expenses increased $15.2 million for the year ended December 31, 2013 compared to the same period in 2012. The increase in research and development expenses above is primarily due to:

- for KRN23, an increase of $0.8 million related to KHK's completed adult clinical trial, development of our pediatric trial design, other development planning, and regulatory activities;
- for rhGUS, an increase of $4.0 million related to process development, manufacturing, toxicology testing, and clinical trial activities;

- for triheptanoin (LC-FAOD), an increase of $5.2 million related to the initiation of our clinical program in 2013, which included $0.8 million we paid to exercise the option with Baylor Research Institute, or BRI, pursuant to our license agreement with BRI to license the rights to triheptanoin in all territories outside of North America, $1.5 million in personnel-related costs as we allocated resources to clinical trial initiation and support of investigator-sponsored trials, and costs related to the manufacture of clinical and nonclinical supply;
- for triheptanoin (Glut1 DS), an increase of $2.4 million related to costs associated with the startup of clinical activities, drug production, and $0.8 million in personnel costs as we allocated resources to this program;
- for SA-ER, an increase of $1.2 million related to the increase in clinical activities and related manufacturing for this program; and
- an increase of $1.4 million in other research costs and preclinical costs for various other potential product candidates.

General and Administrative Expenses (dollars in thousands)

	Year Ended December 31,		Dollar	%
	2013	2012	Change	Change
General and administrative	$ 4,451	$ 3,344	$ 1,107	33%

General and administrative expenses increased $1.1 million for the year ended December 31, 2013 compared to the same period in 2012. The increase in general and administrative expenses was primarily due to increases in professional services costs and in personnel costs as a result of an increase in employee headcount.

Interest Income (dollars in thousands)

	Year Ended December 31,		Dollar	%
	2013	2012	Change	Change
Interest income	$ 216	$ 1	$ 215	21500%

Interest income increased $0.2 million for the year ended December 31, 2013 compared to the same period in 2012, primarily due to funds invested in 2013 from our Series B convertible stock financing which was completed in December 2012.

Other Expense, net (dollars in thousands)

	Year Ended December 31,		Dollar	%
	2013	2012	Change	Change
Other expense, net	$ 3,006	$ 350	$ 2,656	759%

Other expense, net increased $2.7 million for the year ended December 31, 2013 compared to the same period in 2012. This was primarily due to the $2.7 million increase in expense for the fair value remeasurement of the liability related to our convertible preferred stock warrants.

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 our common stock as part of our IPO in January 2014, and $60.2 million in net proceeds from the sale of our common stock as part of our underwritten public offering in July 2014. As of December 31, 2014, we had $187.5 million in available cash, cash equivalents, and short-term investments and had incurred cumulative net losses of $119.4 million. Our cash, cash equivalents and short-term investments are held in a variety of interest-bearing accounts, including corporate debt securities asset backed securities and money market funds. 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.

In February 2015, the Company completed an underwritten public offering in which the Company sold 3,450,000 shares of common stock, which included 450,000 shares of common stock purchased by the underwriters pursuant to an option granted to them in connection with the offering, at a public offering price of $54.00 per share. The offer and sale of all of the shares in the offering were registered under the Securities Act pursuant to an automatically effective registration statement on Form S-3ASR (File No. 333-201838). The total proceeds that the Company received from the offering were approximately $175.1 million, net of underwriting discounts and commissions of approximately $11.2 million. After deducting estimated offering expenses payable of approximately $0.6 million, net proceeds were $174.5 million.

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

	Year Ended December 31,		
	2014	2013	2012
Cash used in operating activities	$ (44,634)	$ (31,200)	$ (12,504)
Cash used in investing activities	(123,440)	(47,734)	(1,191)
Cash provided by financing activities	184,971	171	89,240
Net increase (decrease) in cash and cash equivalents	$ 16,897	$ (78,763)	$ 75,545

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 impacted 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 year ended December 31, 2014 was $44.6 million and reflected a net loss of $59.8 million, offset by non-cash charges of $0.7 million for depreciation and amortization, $3.6 million for the amortization of premium paid on purchased short-term investments, $5.4 million for stock-based compensation and $3.3 million for the revaluation of convertible preferred stock warrant liability. Cash used in operating activities also reflected a $4.1 million increase in prepaid expenses and other current assets primarily due to an increase in CRO prepaid expenses and an increase in interest income receivable as our invested funds increased with the closing of our IPO in February 2014 and our underwritten public offering in July 2014. Cash used in operations also reflected a $0.4 million increase in long-term other assets primarily from the increase in CRO prepaid expenses and value added tax receivables. These increases were offset $6.7 million increase in accounts payable and accrued liabilities primarily due to 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 year ended December 31, 2013 was $31.2 million and reflected a net loss of $35.1 million, offset by non-cash charges of $0.4 million for depreciation and amortization, $1.4 million for the amortization of premium paid on purchased short-term investments, $0.7 million for stock-based compensation and $2.9 million for the revaluation of convertible preferred stock warrant liability. Cash used in operating activities also reflected a $1.6 million increase in prepaid expenses and other current assets primarily due to an increase in CRO prepaid expenses and an increase in interest income receivable as our invested funds increased with the sale of our Series B convertible preferred stock in December 2012, and a $2.6 million increase in other assets primarily related to deferred offering costs related to our IPO. These increases were offset by a $2.7 million increase in accounts payable and accrued liabilities primarily due to higher clinical study and related costs as we continued to increase our research and development activities.

Cash used in operating activities for the year ended December 31, 2012 was $12.5 million and reflected a net loss of $16.3 million, offset by non-cash charges of $0.9 million for stock-based compensation, $0.3 million for depreciation and amortization, and $0.3 million expense for the revaluation of the convertible preferred stock warrant liability. Cash used in operating activities also reflected an increase in accounts payable and accrued and other liabilities of $2.4 million related to higher clinical study and related costs and other research and development activities.

Cash Used in Investing Activities

Cash used in investing activities for the year ended December 31, 2014 was $123.4 million and was related to purchases of short-term investments of $209.0 million and property and equipment of $2.1 million and an increase in restricted cash of $0.3 million for the expansion of the space under our current lease, offset by proceeds from maturities of short-term investments of $83.0 million, sales of investments of $5.0 million.

Cash used in investing activities for the year ended December 31, 2013 was $47.7 million and was related to purchases of short-term investments of $64.0 million and property and equipment of $0.4 million, offset by proceeds from maturities of short-term investments of $16.6 million.

Cash used in investing activities for the year ended December 31, 2012 was $1.2 million and related to purchases of property and equipment of $1.1 million related to our move to a new leased facility in March 2012 and an increase in restricted cash of $0.1 million.

Cash Flows Provided by Financing Activities

Cash provided by financing activities for the year ended December 31, 2014 was $185.0 million and was comprised of $189.3 million in proceeds from the issuance of common stock from our IPO and our underwritten public offering and proceeds from the exercise of stock options, offset by the payment of $4.3 million dividend to our preferred stockholders in connection with the closing of our IPO.

Cash provided by financing activities for the year ended December 31, 2013 was $0.2 million related to proceeds from the issuance of common stock for the exercise of stock options.

Cash provided by financing activities for the year ended December 31, 2012 was $89.2 million and primarily related to net proceeds from the issuance of convertible preferred stock of $89.0 million.

Funding Requirements

We believe that our existing capital resources, including net proceeds we received from the closing of our underwritten public offering in February 2015, will be sufficient to meet to fund our current operations into 2018. 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 expect that we will 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 finance future cash needs through equity or debt financings, strategic collaborations, or grants. 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, or terminate our product development or future commercialization efforts or grant rights to develop and market product candidates that we would otherwise prefer to develop and market ourselves.

Our future 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 sales, marketing, 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.

Contractual Obligations

The following table summarizes our contractual obligations at December 31, 2014 (in thousands):

	Payments due by period *				
	Less than 1 year	1 to 3 years	3 to 5 years	More than 5 years	Total
Operating leases	$ 1,173	$ 2,640	$ 1,926	$ —	$ 5,739

*-Includes additional lease payments under the lease amendment entered into in March 2015

JOBS Act Accounting Election

The Jumpstart our Business Startups Act of 2012, or the JOBS Act, permits an “emerging growth company” such as us to take advantage of an extended transition period to comply with new or revised accounting standards applicable to public companies. We have chosen to “opt out” of this provision and, as a result, we will comply with new or revised accounting standards as required when they are adopted. This decision to opt out of the extended transition period under the JOBS Act is irrevocable.

Newly Adopted Accounting Pronouncements

In June 2014, the FASB issued ASU 2014-10, *Development Stage Enterprises (Topic 915): Elimination of Certain Financial Reporting Requirements, Including an Amendment to Variable Interest Entities Guidance in Topic 810, Consolidation* (ASU 2014-10). ASU 2014-10 removes the definition of a development stage entity from the Master Glossary of the Accounting Standards Codification, thereby removing the financial reporting distinction between development stage entities and other reporting entities from U.S. GAAP. ASU 2014-10 also eliminates the requirements for development stage entities to (1) present inception-to-date information in the statements of income, cash flows, and shareholder equity, (2) label the financial statements as those of a development stage entity, (3) disclose a description of the development stage activities in which the entity is engaged, and (4) disclose in the first year in which the entity is no longer a development stage entity that in prior years it had been in the development stage. The amendments also clarify that the guidance in Topic 275, Risks and Uncertainties, is applicable to entities that have not commenced planned principal operations. We elected to early adopt the provisions of ASU 2014-10 in 2014, as reflected in our financial statements.

In August 2014, the FASB issued ASU No. 2014-15, *Presentation of Financial Statements — Going Concern (Subtopic 205-40): Disclosure of Uncertainties about an Entity's Ability to Continue as a Going Concern*, which requires management to evaluate, in connection with preparing financial statements for each annual and interim reporting period, whether there are conditions or events, considered in the aggregate, that raise substantial doubt about an entity's ability to continue as a going concern within one year after the date that the financial statements are issued and provide related disclosures. This ASU will be effective for the Company in fiscal year 2016. Early adoption is permitted. We are currently assessing the future impact of this ASU on our financial statements.

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 7A. ***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 short-term 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 December 31, 2014, we had cash, cash equivalents, and short-term investments totaling $187.5 million consisting of 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 10% change in interest rates during any of the period 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 10% change in foreign exchange rates during any of the periods presented would not have had a material impact on our financial statements.

Item 8. ***Financial Statements and Supplementary Data***

Our financial statements are annexed to this report beginning on page F-1 and are incorporated by reference into this Item 8.

Item 9. ***Changes in and Disagreements with Accountants on Accounting and Financial Disclosure***

None.

Item 9A. ***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.

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 Securities and Exchange Commission rules and forms as of December 31, 2014. 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, principal financial officer and principal accounting 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.

Management's Annual Report on Internal Control Over Financial Reporting

This Annual Report on Form 10-K includes a report of management's assessment regarding internal control over financial reporting. This Annual Report on Form 10-K does not include an attestation report of our independent registered public accounting firm because, as an "emerging growth company" under the JOBS Act, our independent registered public accounting firm is not required to issue such an attestation report.

The following report is provided by management in respect of our internal control over financial reporting (as defined in Rule 13a-15(f) of the Exchange Act):

1. Our management is responsible for establishing and maintaining adequate internal control over financial reporting.
2. Our management used the Committee of Sponsoring Organizations of the Treadway Commission Internal Control - Integrated Framework (2013), or the COSO framework, to evaluate the effectiveness of internal control over financial reporting. Management believes that the COSO framework is a suitable framework for its evaluation of financial reporting because it is free from bias, permits reasonably consistent qualitative and quantitative measurements of our internal control over financial reporting, is sufficiently complete so that those relevant factors that would alter a conclusion about the effectiveness of our internal control over financial reporting are not omitted and is relevant to an evaluation of internal control over financial reporting.
3. Management has assessed the effectiveness of our internal control over financial reporting as of December 31, 2014 and has concluded that such internal control over financial reporting was effective.

Changes in Internal Control over Financial Reporting

There has been no change in our internal control over financial reporting (as defined in Rule 13a-15(f) under the Exchange Act) during our fourth fiscal quarter ended December 31, 2014, that has materially affected, or is reasonably likely to materially affect our internal control over financial reporting.

Item 9B. Other Information

None.

PART III

Item 10. *Directors, Executive Officers and Corporate Governance*

Incorporated by reference from the information in our Proxy Statement for our 2015 Annual Meeting of Stockholders, which we will file with the SEC within 120 days of the end of the fiscal year to which this Annual Report on Form 10-K relates.

We have adopted a Code of Ethics that applies to all of our directors, officers and employees, including our principal executive, principal financial and principal accounting officers, or persons performing similar functions. Our Code of Ethics is posted on our corporate governance website located at *www.ultragenyx.com*. We intend to disclose future amendments to certain provisions of the Code of Ethics, and waivers of the Code of Ethics granted to executive officers and directors, on the website within four business days following the date of the amendment or waiver.

Item 11. *Executive Compensation*

Incorporated by reference from the information in our Proxy Statement for our 2015 Annual Meeting of Stockholders, which we will file with the SEC within 120 days of the end of the fiscal year to which this Annual Report on Form 10-K relates.

Item 12. *Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters*

Incorporated by reference from the information in our Proxy Statement for our 2015 Annual Meeting of Stockholders, which we will file with the SEC within 120 days of the end of the fiscal year to which this Annual Report on Form 10-K relates.

Item 13. *Certain Relationships and Related Transactions and Director Independence*

Incorporated by reference from the information in our Proxy Statement for our 2015 Annual Meeting of Stockholders, which we will file with the SEC within 120 days of the end of the fiscal year to which this Annual Report on Form 10-K relates.

Item 14. *Principal Accounting Fees and Services*

Incorporated by reference from the information in our Proxy Statement for our 2015 Annual Meeting of Stockholders, which we will file with the SEC within 120 days of the end of the fiscal year to which this Annual Report on Form 10-K relates.

PART IV

Item 15. ***Exhibits and Financial Statement Schedules***

(a) The following documents are filed as part of this report.

(1) Financial Statements

Financial Statements—See Index to Financial Statements at page F-1 of this report.

(2) Financial Statement Schedules

Financial statement schedules have been omitted in this report because they are not applicable, not required under the instructions, or the information requested is set forth in the financial statements or related notes thereto.

(b) Exhibits

The exhibits listed in the accompanying index to exhibits are incorporated by reference or filed as part of this report.

SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) of the Securities Exchange Act of 1934, the Registrant has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized.

ULTRAGENYX PHARMACEUTICAL INC.

By: /s/ Emil D. Kakkis
Emil D. Kakkis, M.D., Ph.D.
President and Chief Executive Officer and Director

Date: March 27, 2015

POWER OF ATTORNEY

KNOW ALL MEN BY THESE PRESENTS, that each person whose signature appears below constitutes and appoints Emil D. Kakkis, M.D., Ph.D. and Shalini Sharp, and each of them, as his or her true and lawful attorneys-in-fact and agents, with full power of substitution for him or her, and in his or her name in any and all capacities, to sign any and all amendments to this Annual Report on Form 10-K, and to file the same, with exhibits thereto and other documents in connection therewith, with the Securities and Exchange Commission, granting unto said attorneys-in-fact and agents, and each of them, full power and authority to do and perform each and every act and thing requisite and necessary to be done therewith, as fully to all intents and purposes as he or she might or could do in person, hereby ratifying and confirming all that said attorneys-in-fact and agents, and any of them, his or her substitute or substitutes, may lawfully do or cause to be done by virtue hereof. Pursuant to the requirements of the Securities Exchange Act of 1934, as amended, this Annual Report on Form 10-K has been signed below by the following persons on behalf of the registrant and in the capacities and on the dates indicated.

Signature	Title	Date
/s/ Emil D. Kakkis Emil D. Kakkis, M.D., Ph.D.	President and Chief Executive Officer and Director (Principal Executive Officer)	March 27, 2015
/s/ Shalini Sharp Shalini Sharp	Chief Financial Officer (Principal Financial Officer)	March 27, 2015
/s/ Theodore A. Huizenga Theodore A. Huizenga	Corporate Controller (Principal Accounting Officer)	March 27, 2015
/s/ Eran Nadav Eran Nadav, Ph.D.	Chairman of the Board	March 27, 2015
/s/ William Aliski William Aliski	Director	March 27, 2015
/s/ Matthew K. Fust Matthew K. Fust	Director	March 27, 2015
/s/ Michael Narachi Michael Narachi	Director	March 27, 2015
/s/ Clay B. Siegall Clay B. Siegall, Ph.D.	Director	March 27, 2015

Ultragenyx Pharmaceutical Inc.

INDEX TO FINANCIAL STATEMENTS

REPORT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

The Board of Directors and Stockholders of
Ultragenyx Pharmaceutical Inc.

We have audited the accompanying balance sheets of Ultragenyx Pharmaceutical Inc. (the "Company") as of December 31, 2014 and 2013, and the related statements of operations, comprehensive loss, convertible preferred stock and stockholders' equity (deficit), and cash flows for each of the three years in the period ended December 31, 2014. These financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on these financial statements based on our audits.

We conducted our audits in accordance with the standards of the Public Company Accounting Oversight Board (United States). Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement. We were not engaged to perform an audit of the Company's internal control over financial reporting. Our audits included consideration of internal control over financial reporting as a basis for designing audit procedures that are appropriate in the circumstances, but not for the purpose of expressing an opinion on the effectiveness of the Company's internal control over financial reporting. Accordingly, we express no such opinion. An audit also includes examining, on a test basis, evidence supporting the amounts and disclosures in the financial statements, assessing the accounting principles used and significant estimates made by management, and evaluating the overall financial statement presentation. We believe that our audits provide a reasonable basis for our opinion.

In our opinion, the financial statements referred to above present fairly, in all material respects, the financial position of the Ultragenyx Pharmaceutical Inc. at December 31, 2014 and 2013, and the results of its operations and its cash flows for each of the three years in the period ended December 31, 2014, in conformity with U.S. generally accepted accounting principles.

/s/ Ernst & Young LLP
Redwood City, California
March 27, 2015

ULTRAGENYX PHARMACEUTICAL INC.

BALANCE SHEETS

(In thousands, except share and per share amounts)

	December 31,	
	2014	**2013**
Assets		
Current assets:		
Cash and cash equivalents	$ 24,324	$ 7,427
Short-term investments	163,163	45,950
Prepaid expenses and other current assets	5,929	1,848
Total current assets	193,416	55,225
Property and equipment, net	3,033	1,325
Restricted cash	744	451
Other assets	774	2,648
Total assets	$ 197,967	$ 59,649
Liabilities, Convertible Preferred Stock and Stockholders' Equity (Deficit)		
Current liabilities:		
Accounts payable	$ 4,857	$ 1,437
Accrued liabilities	7,575	4,406
Deferred rent—current portion	85	78
Total current liabilities	12,517	5,921
Convertible preferred stock warrant liability	—	3,419
Other liabilities	505	200
Total liabilities	13,022	9,540
Commitments and contingencies (Note 12)		
Series A redeemable convertible preferred stock, par value of $0.001 per share — nil and 35,377,556 shares authorized as of December 31, 2014 and 2013; nil and 34,349,894 shares issued and outstanding as of December 31, 2014 and 2013	—	51,001
Series B convertible preferred stock, par value of $0.001 per share—nil and 27,081,680 shares authorized, issued and outstanding as of December 31, 2014 and 2013	—	73,929
Stockholders' equity (deficit):		
Preferred stock, par value of $0.001 per share—25,000,000 shares authorized; nil outstanding as of December 31, 2014 and 2013	—	—
Common stock, par value of $0.001 per share—250,000,000 shares authorized; 31,934,682 and 3,766,289 shares issued and outstanding as of December 31, 2014 and 2013	32	4
Additional paid-in capital	324,128	—
Accumulated other comprehensive income (loss)	(174)	11
Accumulated deficit	(139,041)	(74,836)
Total stockholders' equity (deficit)	184,945	(74,821)
Total liabilities, convertible preferred stock and stockholders' equity (deficit)	$ 197,967	$ 59,649

See accompanying notes.

ULTRAGENYX PHARMACEUTICAL INC.

STATEMENTS OF OPERATIONS
(In thousands, except share and per share amounts)

	Year Ended December 31,		
	2014	2013	2012
Operating expenses:			
Research and development	$ 45,967	$ 27,829	$ 12,641
General and administrative	10,811	4,451	3,344
Total operating expenses	56,778	32,280	15,985
Loss from operations	(56,778)	(32,280)	(15,985)
Other income (expense), net:			
Interest income	608	216	1
Other expense, net	(3,632)	(3,006)	(350)
Total other income (expense), net	(3,024)	(2,790)	(349)
Net loss	$ (59,802)	$ (35,070)	$ (16,334)
Net loss attributable to common stockholders	$ (64,610)	$ (50,289)	$ (19,561)
Net loss per share attributable to common stockholders, basic and diluted	$ (2.25)	$ (14.87)	$ (14.20)
Shares used in computing net loss per share attributable to common stockholders, basic and diluted	28,755,758	3,382,489	1,377,207

See accompanying notes.

ULTRAGENYX PHARMACEUTICAL INC.

STATEMENTS OF COMPREHENSIVE LOSS
(In thousands)

	Year Ended December 31,		
	2014	**2013**	**2012**
Net loss	$ (59,802)	$ (35,070)	$ (16,334)
Other comprehensive income (loss):			
Unrealized gain (loss) on available-for-sale securities	(185)	11	—
Total comprehensive loss	$ (59,987)	$ (35,059)	$ (16,334)

See accompanying notes.

ULTRAGENYX PHARMACEUTICAL INC.

STATEMENTS OF CONVERTIBLE PREFERRED STOCK AND STOCKHOLDERS' EQUITY (DEFICIT)
(In thousands, except share and per share amounts)

	Convertible Preferred Stock				Stockholders' Equity (Deficit)					
	Series A Redeemable Convertible Preferred Stock		Series B Convertible Preferred Stock		Common Stock		Additional Paid-In Capital	Accumulated Deficit	Accumulated Other Comprehensive Income	Total Stockholders' Equity (Deficit)
	Shares	Amount	Shares	Amount	Shares	Amount				
Balance as of December 31, 2011	18,052,464	$ 18,604	—	$ —	3,038,620	$ 3	$ 191	$ (8,155)	$ —	$ (7,961)
Issuance of common stock upon exercise of stock options	—	—	—	—	420,308	—	131		—	131
Issuance of Series A redeemable convertible preferred stock for cash at $1.034 per share, net of $20 of issuance cost in June 2012	14,604,895	15,080	—	—	—	—	—	—	—	—
Issuance of Series A redeemable convertible preferred stock in lieu of cash dividend	1,692,535	2,070	—	—	—	—	(1,205)	(865)	—	(2,070)
Issuance of Series B convertible preferred stock for cash at $2.77 per share, net of $1,071 of issuance cost in December 2012	—	—	27,081,680	73,929	—	—	—	—	—	—
Employee stock-based compensation	—	—	—	—	—	—	178	—	—	178
Stock-based compensation expense related to founder's stock	—	—	—	—	—	—	713	—	—	713
Accretion on convertible preferred stock	—	1,704	—	—	—	—	—	(1,704)	—	(1,704)
Net loss	—	—	—	—	—	—	—	(16,334)	—	(16,334)
Balance as of December 31, 2012	34,349,894	37,458	27,081,680	73,929	3,458,928	3	8	(27,058)	—	(27,047)
Issuance of common stock upon exercise of stock options	—	—	—	—	307,361	1	170	—	—	171
Employee stock-based compensation	—	—	—	—	—	—	389	—	—	389
Stock-based compensation expense related to founder's stock	—	—	—	—	—	—	268	—	—	268
Accretion on convertible preferred stock	—	13,543	—	—	—	—	(835)	(12,708)	—	(13,543)
Unrealized gain on available-for-sale securities	—	—	—	—	—	—	—	—	11	11
Net loss	—	—	—	—	—	—	—	(35,070)	—	(35,070)
Balance as of December 31, 2013	34,349,894	51,001	27,081,680	73,929	3,766,289	4	—	(74,836)	11	(74,821)
Accretion on convertible preferred stock	—	4,430	—	—	—	—	(27)	(4,403)		(4,430)
Conversion of convertible preferred stock to common stock	(34,349,894)	(55,431)	(27,081,680)	(73,929)	19,598,486	19	129,341	—	—	129,360
Reclassification of preferred stock warrant liability	—	—	—	—	—	—	6,743	—	—	6,743
Issuance of common stock in connection with initial public offering, net of issuance costs and preferred stock dividend	—	—	—	—	6,624,423	7	121,704	—	—	121,711
Issuance of common stock in connection with underwritten public offering, net of issuance costs	—	—	—	—	1,613,879	2	60,237	—	—	60,239
Employee stock-based compensation	—	—	—	—	—	—	5,394	—	—	5,394
Issuance of common stock upon exercise of stock options and warrants	—	—	—	—	331,605	—	736	—	—	736
Unrealized loss on available-for-sale securities	—	—	—	—	—	—	—	—	(185)	(185)
Net loss	—	—	—	—	—	—	—	(59,802)	—	(59,802)
Balance as of December 31, 2014	—	$ —	—	$ —	31,934,682	$ 32	$ 324,128	$ (139,041)	$ (174)	$ 184,945

See accompanying notes.

ULTRAGENYX PHARMACEUTICAL INC.

STATEMENTS OF CASH FLOWS
(In thousands)

	Year Ended December 31, 2014	2013	2012
Operating activities:			
Net loss	$ (59,802)	$ (35,070)	$ (16,334)
Adjustments to reconcile net loss to net cash used in operating activities:			
Depreciation and amortization	684	444	313
Amortization of premium on investment securities	3,600	1,413	—
Stock-based compensation	5,394	657	891
Revaluation of convertible preferred stock warrant liability	3,324	2,901	302
Changes in operating assets and liabilities:			
Prepaid expenses and other current assets	(4,081)	(1,593)	(47)
Other assets	(411)	(2,615)	8
Accounts payable	3,177	237	858
Accrued expenses, deferred rent and other liabilities	3,481	2,426	1,505
Net cash used in operating activities	(44,634)	(31,200)	(12,504)
Investing activities:			
Purchase of property and equipment	(2,149)	(407)	(1,091)
Purchase of investments	(208,972)	(63,953)	—
Proceeds from sale of investments	5,002	—	—
Proceeds from maturities of investments	82,972	16,601	—
Decrease (increase) in restricted cash	(293)	25	(100)
Net cash used in investing activities	(123,440)	(47,734)	(1,191)
Financing activities:			
Proceeds from issuance of convertible preferred stock, net	—	—	89,009
Proceeds from issuance of common stock, net	189,317	171	131
Payment of preferred stock dividend	(4,346)	—	—
Proceeds from issuance of promissory notes	—	—	100
Net cash provided by financing activities	184,971	171	89,240
Net increase (decrease) in cash and cash equivalents	16,897	(78,763)	75,545
Cash and cash equivalents at beginning of year	7,427	86,190	10,645
Cash and cash equivalents at end of year	$ 24,324	$ 7,427	$ 86,190
Supplemental disclosures of non-cash investing and financing information:			
Issuance of Series A redeemable convertible preferred stock in lieu of cash dividend	$ —	$ —	$ 2,070
Reclassification of warrant liability to equity upon conversion to common stock warrants	$ 6,743	$ —	$ —
Conversion of Series A and Series B preferred stock to common stock	$ 129,360	$ —	$ —

See accompanying notes.

1. Organization and Basis of Presentation

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 2 extension study of sialic acid, extended release (SA-ER) in patients with 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 triheptanoin in patients with glucose transporter type-1 deficiency syndrome (Glut1 DS), a brain energy deficiency; a Phase 2 clinical study of triheptanoin 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 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 genetic diseases that impair bone growth mineralization. The Company is in the clinical stage as of December 31, 2014, and since inception has been engaged in developing its product candidates, raising capital and recruiting personnel. The Company operates in one reportable segment in the United States of America.

In the course of its research activities, the Company has sustained operating losses and expects such losses to continue over the next several years. The Company's ultimate success depends on the outcome of its research and development activities. From April 22, 2010 (Inception) through December 31, 2014, the Company has incurred cumulative net losses of $119.4 million. Management expects to incur additional losses in the future to conduct product research and development and recognizes the need to raise additional capital to fully implement its business plan. Through December 31, 2014, the Company has relied primarily on the proceeds from equity offerings to finance its operations.

On January 30, 2014, the Company's registration statements on Form S-1 (File Nos. 333-192244 and 333-193675) relating to its initial public offering (IPO) of its common stock were declared effective by the Securities and Exchange Commission (SEC). The shares began trading on The NASDAQ Global Select Market on January 31, 2014. The public offering price of the shares sold in the offering was $21.00 per share. The IPO closed on February 5, 2014 and included 6,624,423 shares of common stock, which included 864,054 shares of common stock issued pursuant to the over-allotment option granted to the underwriters. The Company received total proceeds from the offering of $129.4 million, net of underwriting discounts and commissions of $9.7 million. After deducting offering expenses of approximately $3.3 million and a cash dividend of $4.3 million, which was paid to the preferred stockholders on the closing date, net proceeds were approximately $121.7 million. Upon the closing of the IPO, all shares of convertible preferred stock then outstanding converted into 19,598,486 shares of common stock and the Series A convertible preferred stock warrants were converted into warrants to purchase common stock.

In July 2014, the Company completed an underwritten public offering in which the Company sold 1,613,879 shares of common stock, which included 302,602 shares of common stock purchased by the underwriters pursuant to an option granted to them in connection with the offering, at a public offering price of $40.00 per share. In addition, certain existing stockholders sold 706,072 shares of common stock in the underwritten public offering at the same per-share price. The total proceeds that the Company received from the offering were approximately $60.7 million, net of underwriting discounts and commissions of approximately $3.9 million. After deducting estimated offering expenses payable of approximately $0.4 million, net proceeds were $60.2 million.

In February 2015, the Company completed an underwritten public offering in which the Company sold 3,450,000 shares of common stock, which included 450,000 shares of common stock purchased by the underwriters pursuant to an option granted to them in connection with the offering, at a public offering price of $54.00 per share. The total proceeds that the Company received from the offering were approximately $175.1 million, net of underwriting discounts and commissions of approximately $11.2 million. After deducting estimated offering expenses payable of approximately $0.6 million, net proceeds were $174.5 million.

Management believes that the Company's existing capital resources, including net proceeds received from the closing of the underwritten public offering in February 2015, will be sufficient to fund current operations into 2018. The Company intends to raise additional capital through the issuance of equity, borrowings, or strategic alliances with partner companies. However, if such financing is not available at adequate levels, the Company will need to reevaluate its operating plans.

2. Summary of Significant Accounting Policies

Use of Estimates

The accompanying financial statements have been prepared in accordance with U.S. generally accepted accounting principles ("GAAP"). The preparation of the 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 financial statements and the accompanying notes. On an ongoing basis, management evaluates its estimates, including those related to clinical trial accruals, fair value of assets and liabilities, convertible preferred stock and related warrants, common stock, income taxes and stock-based compensation. 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.

Cash and Cash Equivalents

The Company considers all highly liquid investments with original maturities of three months or less from the date of purchase to be cash equivalents. Cash equivalents consist primarily of amounts invested in money market accounts and corporate bonds.

Short-Term Investments

All investments have been classified as "available-for-sale" and are carried at estimated fair value as determined based upon quoted market prices or pricing models for similar securities. Management determines the appropriate classification of its investments in debt securities at the time of purchase and reevaluates such designation as of each balance sheet date. Unrealized gains and losses are excluded from earnings and are reported as a component of comprehensive loss. Realized gains and losses and declines in fair value judged to be other than temporary, if any, on available-for-sale securities are included in interest income and other expense, net, respectively. The cost of securities sold is based on the specific-identification method. Interest on marketable securities is included in interest income.

Concentration of Credit Risk and Other Risks and Uncertainties

Financial instruments that potentially subject the Company to a concentration of credit risk consist of cash, cash equivalents, and short-term investments. The Company's cash, cash equivalents, and short-term investments are held by financial institutions that management believes are of high credit quality. The Company's investment policy limits investments to fixed income securities denominated and payable in U.S. dollars such as U.S. government obligations, money market instruments and funds, corporate bonds, and asset-backed securities and places restrictions on maturities and concentrations by type and issuer. Such deposits may, at times, exceed federally insured limits. The Company has not experienced any losses on its deposits of cash and cash equivalents and its accounts are monitored by management to mitigate risk. The Company is exposed to credit risk in the event of default by the financial institutions holding its cash and cash equivalents and corporate bond issuers to the extent recorded in the balance sheets.

Property and Equipment

Property and equipment are stated at cost, less accumulated depreciation and amortization. Depreciation and amortization is computed using the straight-line method over the estimated useful lives of the respective assets. Depreciation and amortization begins at the time the asset is placed in service. Maintenance and repairs are charged to operations as incurred. Upon sale or retirement of assets, the cost and related accumulated depreciation are removed from the balance sheet and the resulting gain or loss, if any, is reflected in operations.

The useful lives of the property and equipment are as follows:

Research and development equipment	5 years
Furniture and office equipment	5 years
Computer equipment	3 years
Software	3 years
Leasehold improvements	Shorter of lease term or estimated useful life

Impairment of Long-Lived Assets

The Company evaluates its long-lived assets, including property and equipment, for impairment whenever events or changes in circumstances indicate that the carrying value of these assets may not be recoverable. Recoverability of these assets is measured by comparison of the carrying amount of each asset to the future undiscounted cash flows expected to result from the use of the asset and its eventual disposition. If the asset is considered to be impaired, the amount of any impairment is measured as the difference between the carrying value and the fair value of the impaired asset. The Company has not recorded impairment of any long-lived assets since inception.

Restricted Cash

Restricted cash includes a money market account with one of the Company's financial institutions as collateral for its obligations under its facility lease of the Company's corporate headquarters in Novato, California. Restricted cash also includes a savings account associated with a credit card agreement at one of the Company's financial institutions.

Deferred Offering Costs

Deferred offering costs, which primarily consist of direct incremental legal and accounting fees relating to the IPO and the Company's underwritten public offering in July 2014, were initially capitalized. IPO deferred offering costs of $3.3 million were subsequently offset against IPO proceeds upon the closing of the offering in February 2014. Underwritten public offering costs of $444,000 were subsequently offset against offering proceeds upon the completion of the underwritten public offering in July 2014. As of December 31, 2014 and 2013, deferred offering costs of $0 and $2.3 million, respectively, were capitalized and included in other assets on the balance sheet.

Accruals of Research and Development Costs

The Company records accruals for estimated costs of research, preclinical and clinical studies and manufacturing development. These costs are a significant component of the Company's research and development expenses. A substantial portion of the Company's ongoing research and development activities are conducted by third-party service providers, including contract research organizations. The Company accrues the costs incurred under its agreements with these third parties based on actual work completed in accordance with agreements established with these third parties. The Company determines the actual costs through discussions with internal personnel and external service providers as to the progress or stage of completion of the services and the agreed-upon fee to be paid for such services. The Company makes significant judgments and estimates in determining the accrual balance in each reporting period. As actual costs become known, the Company adjusts its accruals. The Company has not experienced any material deviations between accrued clinical trial expenses and actual clinical trial expenses. However, actual services performed, number of patients enrolled, and the rate of patient enrollment may vary from the Company's estimates, resulting in adjustments to clinical trial expense in future periods. Changes in these estimates that result in material changes to the Company's accruals could materially affect the Company's results of operations.

Leases

The Company enters into lease agreements for its office and laboratory facilities. These leases are classified as operating leases. Rent expense is recognized on a straight-line basis over the term of the lease and, accordingly, the Company records the difference between cash rent payments and the recognition of rent expense as a deferred rent liability. Incentives granted under the Company's facilities leases, including allowances to fund leasehold improvements, are deferred and are recognized as adjustments to rental expense on a straight-line basis over the term of the lease.

Convertible Preferred Stock Warrant Liability

Warrants for shares that are either puttable or that are contingently redeemable are classified as liabilities on the balance sheets. The warrants were subject to remeasurement at each balance sheet date, with changes in fair value recognized as a component of other expense, net. The Company continued to adjust the liability for changes in fair value until the completion of its IPO, whereby the warrants were converted to common stock warrants that are no longer subject to remeasurement.

Convertible Preferred Stock

The Company initially records all shares of convertible preferred stock net of offering costs on the dates of issuance, which represents the carrying value. Only the passage of time was required for Series A convertible preferred stock to become redeemable; accordingly, the Company was accreting the carrying value of Series A convertible preferred stock to its redemption value over the period from the date of issuance to June 16, 2017 (the earliest redemption date). The convertible preferred stock was classified outside of stockholders' equity (deficit) on the accompanying balance sheets, as Series A convertible preferred stock could have been redeemed and as events triggering the liquidation preferences for both classes of convertible preferred stock were not solely within the Company's control. In connection with the closing of Company's IPO in February 2014, all of the Company's outstanding convertible preferred stock was converted into common stock.

Comprehensive Loss

Comprehensive loss is the change in stockholders' equity (deficit) from transactions and other events and circumstances other than those resulting from investments by stockholders and distributions to stockholders. The Company's other comprehensive loss is comprised of unrealized gains and losses on investments in available-for-sale securities.

Research and Development

Research and development costs are expensed as incurred and consist of salaries and benefits, stock-based compensation expense, lab supplies and facility costs, as well as fees paid to other nonemployees and entities that conduct certain research and development activities on the Company's behalf. Amounts incurred in connection with license agreements are also included in research and development expense. Nonrefundable advance payments for goods or services to be received in the future for use in research and development activities are deferred and capitalized. The capitalized amounts are expensed as the related goods are delivered or the services are performed.

Stock-Based Compensation

Stock-based awards issued to employees, including stock options, are recorded at fair value as of the grant date using the Black-Scholes option-pricing model and recognized as expense on a straight-line basis over the employee's requisite service period (generally the vesting period). Because noncash stock compensation expense is based on awards ultimately expected to vest, it is reduced by an estimate for future forfeitures. Forfeitures are estimated at the time of grant and revised, if necessary, in subsequent periods if actual forfeitures differ from estimates.

Income Taxes

The Company uses the liability method of accounting for income taxes. Under this method, deferred tax assets and liabilities are determined based on the differences between the financial reporting and the tax bases of assets and liabilities and are measured using the enacted tax rates and laws that will be in effect when the differences are expected to reverse. The Company must then assess the likelihood that the resulting deferred tax assets will be realized. A valuation allowance is provided when it is more likely than not that some portion or all of a deferred tax asset will not be realized. Due to the Company's lack of earnings history, the net deferred tax assets have been fully offset by a valuation allowance.

The Company recognizes benefits of uncertain tax positions if it is more likely than not that such positions will be sustained upon examination based solely on their technical merits, as the largest amount of benefit that is more likely than not to be realized upon the ultimate settlement. The Company's policy is to recognize interest and penalties related to the underpayment of income taxes as a component of income tax expense or benefit. To date, there have been no interest or penalties charged in relation to the unrecognized tax benefits.

Net Loss per Share Attributable to Common Stockholders

Basic net loss per share attributable to common stockholders is calculated by dividing the net loss attributable to common stockholders by the weighted-average number of shares of common stock outstanding during the period, without consideration for common stock equivalents. The net loss attributable to common stockholders is calculated by adjusting the net loss of the Company for the accretion on the Series A convertible preferred stock and cumulative dividends on Series A and B convertible preferred stock. Diluted net loss per share attributable to common stockholders is the same as basic net loss per share attributable to common stockholders, since the effects of potentially dilutive securities are antidilutive.

Reverse Stock Split

In January 2014, the Company's board of directors and its stockholders approved an amendment to the Company's amended and restated certificate of incorporation to effect a reverse split of shares of its common stock on a 1-for-3.1345 basis (the "Reverse Stock Split"). The par values and the authorized shares of the common and convertible preferred stock were not adjusted as a result of the Reverse Stock Split, nor were the outstanding shares of preferred stock. All issued and outstanding common stock and related per share amounts contained in the financial statements have been retroactively adjusted to reflect this Reverse Stock Split for all periods presented. A proportional adjustment to the conversion ratio for each series of convertible preferred stock was also effected in connection with the reverse split. The Reverse Stock Split was effected on January 17, 2014.

Recent Accounting Pronouncements

In June 2014, the FASB issued ASU 2014-10, *Development Stage Enterprises (Topic 915): Elimination of Certain Financial Reporting Requirements, Including an Amendment to Variable Interest Entities Guidance in Topic 810, Consolidation* (ASU 2014-10). ASU 2014-10 removes the definition of a development stage entity from the Master Glossary of the Accounting Standards Codification, thereby removing the financial reporting distinction between development stage entities and other reporting entities from U.S. GAAP. ASU 2014-10 also eliminates the requirements for development stage entities to (1) present inception-to-date information in the statements of income, cash flows, and shareholder equity, (2) label the financial statements as those of a development stage entity, (3) disclose a description of the development stage activities in which the entity is engaged, and (4) disclose in the first year in which the entity is no longer a development stage entity that in prior years it had been in the development stage. The amendments also clarify that the guidance in Topic 275, Risks and Uncertainties, is applicable to entities that have not commenced planned principal operations. The Company elected to early adopt the provisions of ASU 2014-10, as reflected in the financial statements.

In August 2014, the FASB issued ASU No. 2014-15, *Presentation of Financial Statements — Going Concern (Subtopic 205-40): Disclosure of Uncertainties about an Entity's Ability to Continue as a Going Concern*, which requires management to evaluate, in connection with preparing financial statements for each annual and interim reporting period, whether there are conditions or events, considered in the aggregate, that raise substantial doubt about an entity's ability to continue as a going concern within one year after the date that the financial statements are issued and provide related disclosures. This ASU will be effective for the Company in fiscal year 2016. Early adoption is permitted. We are currently assessing the future impact of this ASU in the financial statements.

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 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 an 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 Company's financial instruments consist of Level 1 and Level 2 assets and Level 3 liabilities. Where quoted prices are available in an active market, securities are classified as Level 1. Money market funds are classified as Level 1. Level 2 assets consist primarily of corporate bonds, asset backed securities and U.S. Government agency securities based upon quoted market prices for similar movements in active markets, quoted prices for identical or similar instruments in markets that are not active and model-based valuation techniques for which all significant inputs are observable in the market or can be corroborated by observable market data for substantially the full term of the assets. Where applicable these models project future cash flows and discount the future amounts to a present value using market-based observable inputs obtained from various third party data providers, including but not limited to, benchmark yields, interest rate curves, reported trades, broker/dealer quotes and reference data. In certain cases where there is limited activity or less transparency around inputs to valuation, securities are classified as Level 3. Level 3 liabilities consist of the convertible preferred stock warrant liability.

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

	December 31, 2014			
	Level 1	Level 2	Level 3	Total
Financial Assets:				
Money market funds	$ 8,627	$ —	$ —	$ 8,627
Corporate bonds	—	152,942	—	152,942
Asset backed securities	—	9,542	—	9,542
U.S. Government agency securities	—	4,485	—	4,485
Other	—	209	—	209
Total financial assets	$ 8,627	$ 167,178	$ —	$ 175,805

	December 31, 2013			
	Level 1	Level 2	Level 3	Total
Financial Assets:				
Money market funds	$ 6,847	$ —	$ —	$ 6,847
Commercial paper	—	1,000	—	1,000
Corporate bonds	—	44,950	—	44,950
Total financial assets	$ 6,847	$ 45,950	$ —	$ 52,797
Financial Liabilities:				
Convertible preferred stock warrant liability	$ —	$ —	$ 3,419	$ 3,419
Total financial liabilities	$ —	$ —	$ 3,419	$ 3,419

The convertible preferred stock warrant liability was classified as a Level 3 liability. As of December 31, 2013, the Company determined the estimated fair value of the warrants using an option-pricing method to allocate the equity value of the Company to the warrants based on the Company's capital structure. The equity value was estimated using the back-solve method, whereby the equity value was derived from a recent transaction involving the Company's own securities. The key inputs used to determine value of the warrants was an estimated fair value of the Company's common stock of $12.14 per share, expected volatility of 70%, the expected time to liquidity event of 0.43 years and risk-free interest rate of 0.11%. The significant unobservable input used in the fair value measurement of the convertible preferred stock warrant liability was the equity value of the Company. Generally, increases (decreases) in the equity value of the Company would result in a directionally similar impact to the fair value measurement of the preferred stock warrant liability.

As of January 30, 2014, the Company determined the estimated fair value of the warrants using the Black-Scholes option-pricing model. Inputs used to determine the fair value included the value of the Company's common stock upon closing of the IPO of $21.00, the remaining contractual term of the warrants of 7.0 years, risk-free interest rate of 2.19% and expected volatility of 70%. The preferred stock warrants were converted to common stock warrants upon the completion of the IPO and are no longer subject to remeasurement.

The following table sets forth a summary of the changes in the estimated fair value of the Company's convertible preferred stock warrants, which were measured at fair value on a recurring basis until their conversion to common stock warrants and related reclassification to additional paid-in capital (in thousands):

	Year Ended December 31,	
	2014	2013
Fair value, beginning of year	$ 3,419	$ 518
Change in fair value recorded as a loss in other expense, net	3,324	2,901
Reclassification of warrant liability to additional paid-in capital	(6,743)	—
Fair value, end of year	$ —	$ 3,419

The determination of the fair value of the convertible preferred stock warrants is discussed in Note 6. Generally, increases or decreases in the fair value of the underlying convertible preferred stock would result in a directionally similar impact in the fair value measurement of the warrant liability.

4. Balance Sheet Components

Cash Equivalents and Short-term Investments

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

	December 31, 2014			
		Gross Unrealized		
	Amortized Cost	Gains	Losses	Estimated Fair Value
Money market funds classified as cash equivalents	$ 8,627	$ —	$ —	$ 8,627
Corporate bonds classified as cash equivalents	3,806	1	—	3,807
Commercial Paper classified as short-term investments	—	—	—	—
Corporate bonds classified as short-term investments	149,303	4	(172)	149,135
Asset backed securities	9,546	—	(4)	9,542
U.S. Government agency securities classified as short-term investments	4,488	1	(4)	4,485
Other	209	—	—	209
Total	$ 175,979	$ 6	$ (180)	$ 175,805

	December 31, 2013			
		Gross Unrealized		
	Amortized Cost	Gains	Losses	Estimated Fair Value
Money market funds classified as cash equivalents	$ 6,847	$ —	$ —	$ 6,847
Commercial Paper classified as short-term investments	1,000	—	—	1,000
Corporate bonds classified as short-term investments	44,939	17	(6)	44,950
Total	$ 52,786	$ 17	$ (6)	$ 52,797

At December 31, 2014, the remaining contractual maturities of available-for-sale securities were less than two years. There have been no significant realized gains or losses on available-for-sale securities for the periods presented.

Property and Equipment, net

Property and equipment, net consists of the following (in thousands):

	December 31,	
	2014	2013
Research and development equipment	$ 712	$ 277
Furniture and office equipment	572	385
Computer equipment	268	248
Software	821	58
Leasehold improvements	2,141	1,154
Property and equipment, gross	4,514	2,122
Less accumulated depreciation	(1,481)	(797)
Property and equipment, net	$ 3,033	$ 1,325

Depreciation expense for the years ended December 31, 2014, 2013 and 2012 was $684,000, $444,000 and $313,000 respectively. Amortization of leasehold improvements and software is included in depreciation expense.

Accrued Liabilities

Accrued liabilities consist of the following (in thousands):

	December 31, 2014	December 31, 2013
Research and clinical trial expenses	$ 2,703	$ 1,886
Payroll and related expenses	4,205	2,360
Other	667	160
Total accrued liabilities	$ 7,575	$ 4,406

5. License and Research Agreements

Nobelpharma License Agreement

In September 2010, the Company entered into a collaboration and license agreement with Nobelpharma Co., Ltd. (Nobelpharma). Under the terms of this collaboration and license agreement, each party granted the other party a worldwide exclusive license under certain of that party's intellectual property related to the compound identified as N-acetylneuraminic acid, also known as sialic acid, to develop, manufacture, and commercialize products. Nobelpharma's licensed territory includes Japan and certain other Asian countries, and the Company's licensed territory includes the rest of the world.

Under the collaboration and license agreement, the Company paid Nobelpharma $110,500 (10 million Yen) for the license, which was recorded as research and development expense in 2010, and also issued 76,567 shares of common stock to Nobelpharma with a minimal value. The Company is required to pay Nobelpharma annual royalties and earned royalties based on net sales upon product sales commencement. In addition, the Company is required to make certain payments to Nobelpharma based upon achievement of certain development and approval milestones. The remaining total aggregate payments, if all milestones are achieved by Nobelpharma, would be 200 million Yen (approximately $1.7 million based on the exchange rate at December 31, 2014). The Company will pay a high single digit royalty on net sales in the Company's territory and will receive a mid-single digit royalty on net sales in the Nobelpharma territory, excluding Japan, if such product sales are ever achieved. Net sales, as defined in the collaboration and license agreement, represent the net sales of products whereby the licensed compound is the active ingredient. If the products include other active ingredients, the portion of the net sales allocated to the licensed compound would be used in determining the royalty payments.

Saint Louis University License Agreement

In November 2010, the Company entered into a license agreement with Saint Louis University (SLU). Under the terms of this license agreement, SLU granted the Company an exclusive worldwide license to make, have made, use, import, offer for sale, and sell therapeutics related to SLU's beta-glucuronidase product for use in the treatment of human diseases.

Under the license agreement, the Company paid SLU an up-front fee of $10,000, which was recorded as research and development expense in 2010. The Company will be required to make a milestone payment of $100,000 upon approval of a glucuronidase-based enzyme therapy for treatment of MPS 7. Additionally, upon reaching a certain level of cumulative worldwide sales of the product, the Company will be required to pay to SLU a low single-digit royalty on net sales of the licensed products in any country or region, if such product sales are ever achieved.

AAIPharma License Agreement

In March 2011, the Company entered into a license agreement with AAIPharma Services Corp. (AAIPharma). Under the terms of this license agreement, AAI Pharma granted the Company a fully paid-up, royalty-free, exclusive, perpetual, and irrevocable license to research, develop, make, have made, use, import, offer for sale, and sell products incorporating AAIPharma's controlled release matrix solid dose oral tablet. Under the license agreement, the Company will pay a mid-single digit percentage of any sublicense revenue received by Ultragenyx related to the sublicense of AAIPharma technology that had been initially licensed by Ultragenyx.

HIBM Research Group

License Agreement

In April 2012, the Company entered into an exclusive license agreement with HIBM Research Group (HRG). Under the terms of this license agreement, HRG granted the Company an exclusive worldwide license to certain intellectual property related to the treatment of HIBM. Under the license agreement, the Company paid HRG an up-front fee of $25,000 which was recorded as research and development expense during the year ended December 31, 2012. The Company may make future payments that aggregate up to $300,000 and that are contingent upon attainment of various development and approval milestones. Additionally, the Company will pay to HRG a royalty of less than 1% of net sales of the licensed products in the licensed territories, if such product sales are ever achieved.

St. Jude Children's Research Hospital License Agreement

In September 2012, the Company entered into a license agreement with St. Jude Children's Research Hospital (St. Jude). Under the terms of this license agreement, St. Jude granted the Company an exclusive license under certain know-how to research, develop, make, use, offer to sell, import, and otherwise commercialize and exploit St. Jude's protective protein, cathepsin, a protein product to treat, prevent, and/or diagnose galactosialidosis and other monogenetic diseases.

Under the license agreement, the Company paid St. Jude an up-front fee of $10,000 which was recorded as research and development expense during the year ended December 31, 2012. Additionally, the Company will pay to St. Jude a royalty of less than 1% on net sales of the licensed products in the licensed territories, if such product sales are ever achieved.

Baylor Research Institute License Agreement

In September 2012, the Company entered into a license agreement with Baylor Research Institute (BRI). Under the terms of this license agreement, BRI exclusively licensed to the Company certain intellectual property related to triheptanoin for North America. Under the license agreement, the Company paid BRI an up-front fee of $250,000 which was recorded as research and development expense during the year ended December 31, 2012. In June 2013, the Company notified BRI that it was exercising its option pursuant to the agreement to license the rights to triheptanoin in all territories outside of the United States, Canada and Mexico and paid the option exercise fee of $750,000 which was recorded as research and development expense.

The Company may make future payments of up to $10.5 million contingent upon attainment of various development milestones and $7.5 million contingent upon attainment of various sales milestones. Additionally, the Company will pay to BRI a mid-single digit royalty on net sales of the licensed product in the licensed territories, if such product sales are ever achieved.

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). 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 EU, 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 share the costs for development activities in the profit share territory and European territory conducted pursuant to the development plan before the applicable transition date equally with KHK. On the applicable transition date in the relevant territory, KHK will become the lead party and be responsible for these costs. 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 recorded $4.6 million and $402,000 for its share of the costs as research and development expenses for the years ended December 31, 2014 and 2013, respectively. As of December 31, 2014 and 2013, the Company had a receivable in the amount of $1.3 million and $370,000 from KHK and an accrued liability of $35,000 and $435,000, respectively, for this collaboration arrangement.

6. Convertible Preferred Stock Warrants and Common Stock Warrants

In connection with the terms of various promissory notes issued by the Company from June 2010 through February 2011, the Company issued warrants in which the number of shares and exercise price were subject to the per share price offered in the Series A convertible preferred stock sale. In February 2011, the Company entered into a convertible note and warrant purchase agreement with William Aliski, a member of the Company's board of directors, in which it borrowed $250,000 from Mr. Aliski. In February 2011, the Company also entered into a convertible note and warrant purchase agreement with John Klock, a former member and former observer of the Company's board of directors, in which it borrowed $1.5 million from Mr. Klock. In June 2011, in connection with its closing of the first round of Series A convertible preferred stock financing, all of the convertible notes were converted into Series A convertible preferred stock, and the Company determined that the warrants were convertible to 1,027,662 shares of Series A convertible preferred stock at an exercise price of $1.034 per share. The warrants are subject to certain anti-dilution provisions, including Series A dividends paid in shares of preferred stock. The Company determined the fair value of the warrants using an option-pricing method to allocate the equity value of the Company to the warrants based on the Company's capital structure. The equity value was estimated using the back-solve method, whereby the equity value was derived from a recent transaction involving the Company's own securities. The fair value ascribed to these warrants upon their issuance was $203,000. The fair value of the warrants was recorded as debt issuance costs and was amortized to interest expense using the effective-interest-rate method over the loan term. In connection with the conversion of the promissory notes into shares of Series A convertible preferred stock in June 2011, the Company recognized all remaining unamortized debt issuance costs. Upon the closing of the Company's IPO in February 2014, the warrants were converted into warrants to purchase common stock. Accordingly, the warrants were reclassified from a liability to permanent equity and were no longer subject to remeasurement.

As of December 31, 2014, outstanding warrants consisted of the following:

Common Stock Warrants:	**Number of Warrants**	**Date Issued**	**Term**	**Exercise Price**
Common stock	83,167	June 2010	10 years	$ 3.006
Common stock	174,651	February 2011	10 years	3.006
Common stock	66,533	June 2011	10 years	3.006
Total common stock warrants	324,351			

As of December 31, 2013, outstanding warrants consisted of the following:

Convertible Preferred Stock Warrants:	**Number of Warrants**	**Date Issued**	**Term**	**Exercise Price**
Series A	241,803	June 2010	10 years	$ 1.034
Series A	592,417	February 2011	10 years	1.034
Series A	193,442	June 2011	10 years	1.034
Total convertible preferred stock warrants	1,027,662			

The fair value of the warrants was estimated to be $6.7 million and $3.4 million as of January 30, 2014 (pricing date of IPO) and December 31, 2013, respectively. The Company recorded $3.3 million, $2.9 million and $302,000 to other expense, net, for the years ended December 31, 2014, 2013 and 2012 respectively, representing the change in fair value of the warrants for the respective period.

7. Common Stock

The Company has reserved sufficient shares of common stock for issuance upon the exercise of stock options and the exercise of warrants. Common stockholders are entitled to dividends if and when declared by the board of directors, subject to the prior rights of the preferred stockholders. As of December 31, 2014, no common stock dividends had been declared by the board of directors.

The Company had reserved shares of common stock, on an as-converted basis, for future issuance as follows:

	December 31, 2014	**December 31, 2013**
Convertible preferred stock	—	19,598,486
Convertible preferred stock warrants	—	353,459
Common stock warrants	324,351	—
Employee stock purchase plan	600,000	—
2011 equity incentive plan	1,960,225	2,228,883
2014 equity incentive plan	810,250	—
Shares available for future stock option grants	1,439,750	799,963
	5,134,576	22,980,791

8. Convertible Preferred Stock

Under the Company's Amended and Restated Certificate of Incorporation, as amended, the Company is authorized to issue two classes of shares: preferred and common stock. The preferred stock is issuable in series, and the Company's board of directors is authorized to determine the rights, preferences and terms of each series. As of December 31, 2014, no shares of preferred stock were outstanding. As of December 31, 2013, convertible preferred stock consisted of the following (in thousands, except share and per share amounts):

	As of December 31, 2013			
Convertible Preferred Stock:	**Shares Authorized**	**Shares Issued and Outstanding**	**Proceeds Net of Issuance Costs**	**Aggregate Liquidation Preference**
Series A	35,377,556	34,349,894	$ 33,623	$ 38,063
Series B	27,081,680	27,081,680	73,929	76,739
Total convertible preferred stock	62,459,236	61,431,574	$ 107,552	$ 114,802

The liquidation preference consists of the liquidation preference on the outstanding shares of the convertible preferred stock and the dividends in arrears on such shares in the amount of $4.0 million as of December 31, 2013.

Significant provisions of the convertible preferred stock were as follows:

Dividends —When and as declared by the Company's board of directors, the holders of the Series A convertible preferred stock (Series A) and the Series B convertible preferred stock (Series B), collectively referred to as "Preferred Stock," are entitled to receive dividends, out of any assets legally available therefor, prior and in preference to the declaration or payment of any dividend on the common stock or other securities and rights convertible of the Company, at the rate of $0.062 per share per annum, payable in the form of cash or property or, upon conversion of the preferred stock to common stock, payable in cash. During 2012, $2,070,000 of preferred stock dividends were declared and paid to holders of Series A in the form of additional shares of Series A. Dividends in arrears as of December 31, 2013 were $4.0 million for both series of preferred stock. In connection with the closing of the IPO in February 2014, all dividends in arrears in the amount of $4.3 million were paid to both series of preferred stock.

Liquidation—In the event of any liquidation, dissolution, or winding up of the Company, either voluntary or involuntary, the holders of Series A and Series B shall be entitled to receive, on a pari passu basis, prior and in preference to any distribution of any of the assets of this Corporation to the holders of common stock by reason of their ownership thereof, an amount per share equal to the sum of $1.034 (the Original Series A Issue Price) for each outstanding share of Series A (subject to adjustment for recapitalizations) and $2.769 (the Original Series B Issue Price) for each outstanding share of Series B (subject to adjustment for recapitalizations) and an amount equal to all declared or accrued but unpaid dividends on such shares.

Redemption—Only the passage of time was required for Series A to become redeemable; accordingly, the Company was accreting the carrying value of Series A to its redemption value over the period from the date of issuance to June 16, 2017 (the earliest redemption date). The Series B was not redeemable. *Conversion* —Each share of preferred stock, at the option of the holder, was convertible into common stock determined by dividing the Original Series A issue price or Original Series B issue price, as applicable, by the conversion price applicable to such share in effect on the date the certificate is surrendered for conversion, subject to certain provisions for adjustment of the conversion price. In connection with the reverse split which was effective on January 17, 2014, all shares of preferred stock were convertible into common stock on a 3.1345-for-one basis. Upon the closing of the IPO, all shares of the preferred stock then outstanding converted into 19,598,486 shares of common stock.

9. Stock-Based Awards

2011 Equity Incentive Plan

In 2011, the Company adopted the 2011 Equity Incentive Plan (the 2011 Plan). The 2011 Plan provides for the granting of stock-based awards to employees, directors, and consultants under terms and provisions established by the board of directors. Under the terms of the 2011 Plan, options may be granted at an exercise price not less than fair market value. For employees holding more than 10% of the voting rights of all classes of stock, the exercise prices for incentive stock options must be at least 110% of fair market of the common stock on the grant date, as determined by the board of directors. The terms of options granted under the 2011 Plan may not exceed ten years. Options granted generally vest over a period of four years. Typically, the vesting schedule for option grants to newly hired employees provides that 1/4 of the grant vests upon the first anniversary of the employee's date of hire, with the remainder of the shares vesting monthly thereafter at a rate of 1/48 of the total shares subject to the option. All other employee options typically vest in equal monthly installments over the four-year vesting schedule. In connection with the Company's IPO, no further grants will be made under this plan and all remaining shares available for grant were transferred to the 2014 Incentive Plan.

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 had 2,250,000 shares of common stock available for future issuance at the time of its inception, which included 655,038 shares available under the 2011 Plan, which were transferred to the 2014 Plan upon adoption. The 2014 Plan provides for automatic annual increases in shares available for grant, beginning on January 1, 2015 through January 1, 2024. The 2014 Plan provides for the granting of stock-based awards to employees, directors, and consultants under similar terms, conditions and provisions as the 2011 Plan.

Stock Option Activity

A summary of option activity under the 2011 Plan and the 2014 Plan and related information are as follows:

	Options Outstanding			
	Number of Options	Weighted-Average Exercise Price	Weighted-Average Remaining Contractual Term (Years)	Aggregate Intrinsic Value (In thousands)
Outstanding — December 31, 2011	1,451,580	$ 0.31	9.88	$ —
Shares reserved	—	—		
Options granted	499,278	0.81		
Options exercised	(420,308)	0.31		
Options cancelled	(9,583)	0.31		
Outstanding — December 31, 2012	1,520,967	0.47	9.11	$ 2,038
Options granted	1,267,797	5.80		
Options exercised	(307,366)	0.55		
Options cancelled	(252,515)	1.26		
Outstanding — December 31, 2013	2,228,883	3.41	8.91	$ 19,468
Shares reserved	—	—		
Options granted	932,555	41.12		
Options exercised	(305,090)	2.14		
Options cancelled	(116,873)	8.92		
Outstanding — December 31, 2014	2,739,475	16.15	8.43	$ 79,840
Vested and exercisable — December 31, 2014	802,189	2.65	7.55	$ 33,072
Vested and expected to vest — December 31, 2014	2,666,378	$ 15.86	8.41	$ 78,390

The aggregate intrinsic values of options outstanding, vested and exercisable, and vested and expected to vest were calculated as the difference between the exercise price of the options and the fair value of the Company's common stock as of December 31, 2014. The total intrinsic value of options exercised during the years ended December 31, 2014, 2013 and 2012 was $ 12.1 million, $1.0 million and $211,000, respectively.

The options outstanding and exercisable by exercise price as of December 31, 2014 are as follows:

	Options Outstanding		Options Exercisable		
Exercise Price	**Numbers Outstanding**	**Weighted-Average Remaining Contractual Term (in Years)**	**Number Exercisable**	**Weighted-Average Exercise Price**	**Weighted-Average Remaining Contractual Term (in Years)**
$0.31	667,554	6.88	472,481	$ 0.31	6.88
$0.81 to $1.82	453,552	7.98	136,284	1.33	7.98
$4.07 to $6.86	523,169	8.81	125,181	6.59	8.81
$11.19 to $21.00	315,950	9.01	68,243	14.26	9.01
$33.55 to $34.93	249,500	9.40	—	—	—
$40.37 to $49.15	203,750	9.80	—	—	—
$53.03 to $58.02	326,000	9.43	—	—	—
	2,739,475	8.43	802,189	$ 2.65	7.55

The weighted-average estimated fair value of stock options granted was $26.58, $3.82 and $0.47 per share of the Company's common stock during the years ended December 31, 2014, 2013, and 2012, respectively.

The total estimated fair value of options vested during the years ended December 31, 2014, 2013 and 2012 was $2.0 million, $127,000 and $172,000, respectively.

Restricted Stock Units

In 2014, the Company granted 31,000 Restricted Stock Units (RSUs) under the 2014 Plan to employees with a weighted-average grant date fair value of $53.23. The fair value of the RSUs is determined on the grant date based on the fair value of the Company's common stock. The fair value of the RSUs is recognized as expense ratably over the vesting period of two to four years. The total fair value of shares vested was $264,000 during 2014. As of December 31, 2014, the the total unrecognized compensation expense related to unvested RSUs, net of estimated forfeitures, was $1.4 million, which the Company expects to recognize over an estimated weighted-average period of 2.0 years

Employee Stock Purchase Plan

In January 2014, the Company adopted the 2014 Employee Stock Purchase Plan (the ESPP) which became effective upon the closing of our IPO in February 2014. The Company reserved a total of 600,000 shares of common stock for issuance under the ESPP. Eligible employees may purchase common stock at 85% of the lesser of the fair market value of common stock on the first or last day of the purchase period. The ESPP provides for automatic annual increases in shares available for grant, beginning on January 1, 2015 through January 1, 2024. The Company has not determined the date on which the initial purchase period will commence under the ESPP.

Founder's Stock

In connection with the Series A preferred stock financing, the Company entered into a stock repurchase agreement with the founder on June 16, 2011, whereby 2,552,241 shares of common stock previously owned by the founder were subject to repurchase by the Company at the original issuance price in the event that the founder's employment is terminated either voluntarily or involuntarily. The repurchase rights lapsed over a period of two years from June 16, 2011. The Company calculated the estimated fair value of these restricted shares at the time the restriction was added to the shares as $1,199,000 and recorded this amount as stock-based compensation ratably over the period that the repurchase rights lapsed. Stock-based compensation expense pertaining to the founder's stock was $0, $268,000 and $713,000 during the years ended December 31, 2014, 2013, and 2012, respectively.

Stock-Based Compensation Expense

Total stock-based compensation recognized was as follows (in thousands):

	Year Ended December 31,		
	2014	**2013**	**2012**
Research and development	$ 4,116	$ 293	$ 130
General and administrative	1,278	364	761
Total stock-based compensation expense	$ 5,394	$ 657	$ 891

As of December 31, 2014, the total unrecognized compensation expense related to unvested options, net of estimated forfeitures, was $22.5 million, which the Company expects to recognize over an estimated weighted-average period of 3.2 years.

In determining the estimated fair value of the stock-based awards, the Company uses the Black-Scholes option-pricing model and assumptions discussed below. Each of these inputs is subjective and generally requires significant judgment to determine.

Expected Term—The Company's expected term represents the period that the Company's stock-based awards are expected to be outstanding and is determined using the simplified method (based on the mid-point between the vesting date and the end of the contractual term).

Expected Volatility—Prior to the IPO in January 2014, the Company was privately held and did not have any trading history for its common stock; accordingly, the expected volatility was estimated based on the average volatility for comparable publicly traded biopharmaceutical companies over a period equal to the expected term of the stock option grants. When selecting comparable publicly traded biopharmaceutical companies on which it has based its expected stock price volatility, the Company selected companies with comparable characteristics to it, including enterprise value, risk profiles, position within the industry, and with historical share price information sufficient to meet the expected life of the stock-based awards. The historical volatility data was computed using the daily closing prices for the selected companies' shares during the equivalent period of the calculated expected term of the stock-based awards. In 2014, the Company modified its approach by phasing in our own common stock trading history and supplemented the remaining historical information with a blended volatility from the trading history from the common stock of the same set of comparable publicly traded biopharmaceutical companies. The Company will continue to apply this process until a sufficient amount of historical information regarding the volatility of its own stock price becomes available. Sufficient trading history does not yet exist for the Company's common stock, therefore the estimate of expected volatility is based on the volatility of other companies with similar products under development, market, size and other factors.

Risk-Free Interest Rate—The risk-free interest rate is based on the U.S. Treasury zero coupon issues in effect at the time of grant for periods corresponding with the expected term of option.

Expected Dividend—The Company has never paid dividends on its common stock and has no plans to pay dividends on its common stock. Therefore, the Company used an expected dividend yield of zero.

The fair value of stock option awards was estimated at the date of grant using a Black-Scholes option-pricing model with the following weighted-average assumptions:

	Year Ended December 31,		
	2014	2013	2012
Expected term	6.23 years	6.25 years	6.25 years
Expected volatility	70%	74%	67%
Risk-free interest rate	1.9%	0.7% to 1.6%	0.6%
Expected dividend rate	0.0%	0.0%	0.0%

10. Defined Contribution Plan

In March 2013, the Company began to sponsor a 401(k) retirement plan, in which substantially all of its full-time employees are eligible to participate. Eligible participants may contribute a percentage of their annual compensation to this plan, subject to statutory limitations. The Company did not provide any contributions during the year ended December 31, 2014.

11. Income Taxes

The Company did not record a provision or benefit for income taxes during the years ended December 31, 2014, 2013 and 2012. The Company has incurred net operating losses since inception. The Company has not reflected any benefit of such net operating loss carryforwards in the accompanying financial statements. The Company has established a full valuation allowance against its deferred tax assets due to the uncertainty surrounding the realization of such assets.

The effective tax rate of our provision for income taxes differs from the federal statutory rate as follows:

	Year Ended December 31,		
	2014	2013	2012
Federal statutory income tax rate	34.0 %	34.0 %	34.0 %
State income taxes, net of federal benefit	4.6	5.0	6.0
Federal tax credits	6.7	8.2	8.6
Nondeductible permanent items	(1.2)	(2.9)	—
Stock compensation	(1.4)	(0.6)	(1.9)
Change in valuation allowance	(42.7)	(44.6)	(46.0)
Uncertain tax positions	—	0.9	(0.7)
Provision for income taxes	—	—	—

The tax effect of temporary differences that give rise to significant portions of the deferred tax assets is presented below (in thousands):

	Year Ended December 31,	
	2014	2013
Deferred tax assets:		
Net operating loss carryforwards	$ 32,500	$ 16,352
Tax credits	16,737	8,692
Stock options	1,058	—
Accruals and reserves	476	591
Fixed assets and intangibles	455	65
Other	113	—
Total deferred tax assets	51,339	25,700
Valuation allowance	(51,339)	(25,700)
Net deferred tax assets	$ —	$ —

Additionally, the future utilization of the net operating loss carryforwards and tax credits to offset future taxable income may be subject to an annual limitation, pursuant to Internal Revenue Code Section 382, as a result of ownership changes that may have occurred previously or that could occur in the future. A Section 382 analysis to determine the limitation of the net operating loss carryforwards has not been performed. Until this analysis has been performed, the deferred tax assets for net operating losses of $725,000 generated through December 31, 2014 have been removed from the deferred tax asset schedule and a corresponding decrease to the valuation allowance has been recorded. This represents the amount estimated to expire before utilization, assuming a change in ownership has occurred. The Company recorded unrecognized tax benefits for uncertainty in income taxes. Due to the existence of the valuation allowance, future changes in unrecognized tax benefits will not impact the effective tax rate. The valuation allowance increased by $25.6 million and $15.6 million during the year ended December 31, 2014 and 2013, respectively.

As of December 31, 2014 and 2013, the Company had approximately $89.0 million and $39.4 million of federal net operating loss carryforwards available to reduce future taxable income that will begin to expire in 2030 for federal tax purposes. As of December 31, 2014 and 2013, the Company had approximately $90.1 million and $50.8 million of state NOL carryforwards available to reduce future taxable income that will begin to expire in 2030 for state tax purposes.

As of December 31, 2014 and 2013, the Company also had research and development tax credit carryforwards of approximately $986,000 and $464,000 for federal purposes and $1.6 million and $586,000 for state purposes, respectively, available to offset future taxable income. If not utilized, the federal carryforwards will expire in various amounts beginning in 2030, and the state credits can be carried forward indefinitely.

On January 2, 2013, the American Taxpayer Relief Act of 2012 (the Act) was passed in to law. The Act included a retroactive extension of the U.S. research credit for 2012. Since the effects of the tax law changes are recognized in the first period the Company recognized $12,000 of additional research credits as a discrete item during 2013. The tax effects of the research credits will be offset by a valuation allowance and will not impact the financial statements.

As of December 31, 2014 and 2013, the Company had an Orphan Drug Credit of approximately $21.9 million and $11.6 million for federal tax purposes available to offset future regular and alternative minimum tax. If not utilized, the Orphan Drug Credit will expire in various amounts beginning in 2026.

A reconciliation of the Company's unrecognized tax benefits for the years ended December 31, 2014 and 2013 is as follows (in thousands):

	December 31,		
	2014	2013	2012
Balance at beginning of year	$ 3,725	$ 1,551	$ 324
Additions based on tax positions related to current year	3,550	2,169	1,227
Additions (reductions) for tax positions of prior years	—	5	—
Balance at end of year	$ 7,275	$ 3,725	$ 1,551

The entire amount of the unrecognized tax benefits would not impact the Company's effective tax rate if recognized. The Company has elected to include interest and penalties as a component of tax expense. During the years ended December 31, 2014 and 2013, the Company did not recognize accrued interest and penalties related to unrecognized tax benefits. The Company does not anticipate that the amount of existing unrecognized tax benefits will significantly increase or decrease during the next 12 months.

The Company files income tax returns in the U.S. federal and California tax jurisdictions. The federal and state income tax returns from inception to December 31, 2014 remain subject to examination.

12. Commitments and Contingencies

Facilities

In July 2011, the Company entered into a lease agreement for office facilities in Novato, California, which provided for a tenant improvement allowance of up to $376,000. The lease commenced in March of 2012. This noncancelable operating lease expires five years after the commencement date. At the end of the lease term, the Company has the option to extend the lease for two additional consecutive terms of five years each. In July 2011, the Company signed an addendum to the lease agreement to add warehouse space to the arrangement. As provided in the lease agreement, monthly lease payments are subject to an annual increase based upon a CPI adjustment with a minimum increase of three percent and a maximum increase of six percent per year. In February 2014, the Company signed an addendum to the lease agreement to lease the remainder of the office and warehouse space of the building and extend the term of the leased space for an additional five years from the date of the addendum, as provided under the original agreement. The addendum provided for a tenant improvement allowance of up to $369,000.

In September 2010, the Company entered into a license and service agreement for a lab facility in Novato, California. The term commenced in September 2010. In September 2012 and August 2014, the Company entered into amendments to increase the size of the lab facility and extend the term. The term of the lease under the September 2014 amendment expires five years after the amendment date and can be extended for three one-year periods after the amendment term, and either party may terminate the agreement with one year's prior notice without cause.

As of December 31, 2014, the aggregate future minimum lease payments under the noncancelable operating lease arrangements are as follows (in thousands):

Year Ending December 31,	
2015	$ 1,173
2016	1,305
2017	1,335
2018	1,366
2019	560
Thereafter	—
	$ 5,739

*- Includes additional lease payments under the lease amendment entered into in March 2015, as detailed in Note 14 "Subsequent Events"

The Company recognizes rent expense on a straight-line basis over the noncancelable term of its operating lease. Rent expense was $572,000, $285,000 and $265,000 during the years ended December 31, 2014, 2013 and 2012, respectively.

Under the terms of the lease agreement and the addendum of its Novato office facility, the Company provided the lessor with a irrevocable letter of credit. The lessor shall be entitled to draw on the letter of credit in the event of any uncured default by the Company under the terms of the lease. Provided there has been no default on the lease, the Company may reduce the amount of the letter of credit by $119,000 on each anniversary date effective May 1, 2014. As of December 31, 2014, the current amount of restricted cash and amount of the irrevocable letter of credit in connection with the lease agreement was $594,000.

Other Commitments

The Company has various manufacturing, clinical, research, and other contracts with vendors in the conduct of the normal course of its business. All contracts are terminable, with varying provisions regarding termination. If a contract with a specific vendor were to be terminated, the Company would only be obligated for the products or services that the Company had received at the time the termination became effective.

Contingencies

While there are no legal proceedings the Company is aware of, the Company may become party to various claims and complaints arising in the ordinary course of business. Management does not believe that any ultimate liability resulting from any of these claims will have a material adverse effect on its results of operations, financial position, or liquidity. However, management cannot give any assurance regarding the ultimate outcome of these claims, and their resolution could be material to operating results for any particular period, depending upon the level of income for the period.

Guarantees and Indemnifications

The Company indemnifies each of its directors and officers for certain events or occurrences, subject to certain limits, while the director is or was serving at the Company's request in such capacity, as permitted under Delaware law and in accordance with its certificate of incorporation and bylaws. The term of the indemnification period lasts as long as a director may be subject to any proceeding arising out of acts or omissions of such director in such capacity. The maximum amount of potential future indemnification is unlimited; however, the Company currently holds director liability insurance. This insurance allows the transfer of risk associated with the Company's exposure and may enable it to recover a portion of any future amounts paid. The Company believes that the fair value of these indemnification obligations is minimal. Accordingly, it has not recognized any liabilities relating to these obligations for any period presented.

13. Net Loss per Share Attributable to Common Stockholders

The following table sets forth the computation of the basic and diluted net loss per share attributable to common stockholders during the years ended December 31, 2014, 2013 and 2012 (in thousands, except share and per share data):

	Year Ended December 31,		
	2014	2013	2012
Numerator:			
Net loss	$ (59,802)	$ (35,070)	$ (16,334)
Accretion and dividends on convertible preferred stock	(4,808)	(15,219)	(3,227)
Net loss attributable to common stockholders	$ (64,610)	$ (50,289)	$ (19,561)
Denominator:			
Weighted-average common shares outstanding	28,755,758	3,583,522	3,118,798
Less: weighted-average unvested common shares subject to repurchase	—	(201,033)	(1,741,591)
Weighted-average shares used to compute net loss per share attributable to common stockholders, basic and diluted	28,755,758	3,382,489	1,377,207
Net loss per share attributable to common stockholders, basic and diluted	$ (2.25)	$ (14.87)	$ (14.20)

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

	Year Ended December 31,		
	2014	2013	2012
Convertible preferred stock	1,610,834	19,598,486	8,354,772
Stock options to purchase common stock	2,572,729	1,666,036	1,563,217
Unvested restricted stock units	9,715	—	—
Common stock subject to repurchase	—	201,033	1,741,591
Convertible preferred stock warrants	29,051	353,459	353,459
Common stock warrants	318,666	—	—
	4,540,995	21,819,014	12,013,039

14. Subsequent Events

Underwritten Public Offering

In February 2015, we completed an underwritten public offering in which we sold 3,450,000 shares of our common stock, which included 450,000 shares purchased by the underwriters pursuant to an option granted to them in connection with the offering, at a public offering price of $54.00 per share. The total proceeds that the Company received from the offering were approximately $175.1 million, net of underwriting discounts and commissions of approximately $11.2 million. After deducting offering expenses payable of approximately $0.6 million, net proceeds were $174.5 million.

Lease Amendment

On March 9, 2015, the Company entered into an amendment to its existing lease to obtain an additional office building with warehouse space. The amendment to this noncancelable lease commences on May 1, 2015 and co-terminates with the existing lease on April 30, 2019. At the end of the amended lease term, the Company has the option to extend the entire lease for two additional consecutive terms of five years. As specified in the amendment, the Company also increased the existing irrevocable letter of credit required by the lease by $287,000 for a total of $762,000 after giving effect for the scheduled April 2015 reduction of $119,000. Provided there has been no default on the lease, the Company may reduce the amount of the letter of credit by approximately $191,000 on each anniversary of the lease amendment commencement date. The amendment also provides for an additional tenant improvement allowance of up to $287,000. In addition, the Company is required to enter into a separate irrevocable letter of credit, for approved budgeted improvements.

15. Quarterly Financial Data (unaudited)

The following table presents certain unaudited quarterly financial information. This information has been prepared on the same basis as the audited financial statements and includes all adjustments (consisting only of normal recurring adjustments) necessary to present fairly the unaudited quarterly results of operations set forth herein. Net loss per share for all periods presented has been retroactively adjusted to reflect the 1-for-3.1345 reverse stock split effected on January 17, 2014.

(in thousands, except share and per share data)

	2014			
	March 31,	June 30,	September 30,	December 31,
Operating expenses	$ 10,339	$ 13,661	$ 15,835	$ 16,943
Net loss	(13,630)	(13,585)	(15,849)	(16,738)
Net loss attributable to common stockholders	(18,438)	(13,585)	(15,849)	(16,738)
Net loss per share applicable to common stockholders, basic and diluted	$ (0.85)	$ (0.45)	$ (0.50)	$ (0.52)
	2013			
	March 31,	**June 30,**	**September 30,**	**December 31,**
Operating expenses	$ 6,747	$ 8,247	$ 7,761	$ 9,525
Net loss	(6,735)	(8,590)	(8,428)	(11,317)
Net loss attributable to common stockholders	(8,205)	(10,829)	(12,590)	(18,665)
Net loss per share applicable to common stockholders, basic and diluted	$ (2.84)	$ (3.32)	$ (3.48)	$ (4.98)

Subsequent to the filing of its Form 10-Q for the third quarter of 2014, the Company determined that the reclassification of deferred offering costs, related to its initial public offering in February 2014, from other assets to additional paid-in capital, was not appropriately reflected in the Statements of Cash Flows for the three, six and nine months ended March 31, 2014, June 30, 2014, and September 30, 2014. The Company assessed the materiality of this error, based on quantitative and qualitative factors, and concluded that it was not material to the previously issued interim financial statements taken as a whole. As such, it has corrected its Statement of Cash Flows for the year ended December 31, 2014 and will do so for the three, six and nine months ended March 31, 2014, June 30, 2014, and September 30, 2014, in its Form 10-Q filings during 2015. The revisions had no impact on net cash used in investing activities, net increase in cash and cash equivalents, or net loss per share in any period. The following table reflects the revisions to the Statements of Cash Flows (in thousands):

	2014					
	Three Months Ended March 31,		Six Months Ended June 30,		Nine Months Ended September 30,	
	Previously Reported	As Adjusted	Previously Reported	As Adjusted	Previously Reported	As Adjusted
Net cash used in operating activities	$ (8,336)	$ (10,621)	$ (18,865)	$ (21,150)	$ (29,895)	$ (32,180)
Net cash provided by financing activities	121,754	124,039	121,764	124,049	182,274	184,559

Exhibit Index

Exhibit Number	Exhibit Description	Incorporated by Reference Form	Date	Number	Filed Herewith
3.1	Amended and Restated Certificate of Incorporation	8-K	2/5/2014	3.1	
3.2	Amended and Restated Bylaws	8-K	2/5/2014	3.2	
4.1	Reference is made to Exhibits 3.1 and 3.2				
4.2	Form of Common Stock Certificate	S-1	11/8/2013	4.2	
4.3	Warrant, dated as of June 30, 2010, issued to Emil D. Kakkis, M.D., Ph.D.	S-1	11/8/2013	4.3	
4.4	Warrant, dated as of February 15, 2011, issued to the John and Cynthia Klock Charitable Trust	S-1	11/8/2013	4.4	
4.5	Warrant, dated as of June 14, 2011, issued to Emil D. Kakkis, M.D., Ph.D.	S-1	11/8/2013	4.6	
4.6	Warrant, dated as of June 14, 2011, issued to Emil D. Kakkis, M.D., Ph.D.	S-1	11/8/2013	4.7	
4.7	Amended and Restated Investors' Rights Agreement, dated as of December 18, 2012, among the Registrant and the investors named therein	S-1	11/8/2013	4.8	
10.1†	Collaboration and License Agreement, dated as of August 29, 2013, between the Registrant and Kyowa Hakko Kirin Co., Ltd.	S-1	12/23/2013	10.1	
10.2†	License Agreement, dated as of March 1, 2011, between the Registrant and AAIPharma Services Corp.	S-1	12/23/2013	10.2	
10.3†	License Agreement, dated as of September 20, 2012, between the Registrant and Baylor Research Institute	S-1	12/23/2013	10.3	
10.4†	Amendment to the License Agreement, dated as of March 22, 2013, between the Registrant and Baylor Research Institute	S-1	11/8/2013	10.4	
10.5†	Exclusive License Agreement, dated as of April 23, 2012, between the Registrant and HIBM Research Group	S-1	11/8/2013	10.5	
10.6†	Collaboration and License Agreement, dated as of September 30, 2010, between the Registrant and Nobelpharma Co., Ltd.	S-1	12/23/2013	10.6	
10.7†	License Agreement, dated as of September 1, 2012, between the Registrant and St. Jude Children's Research Hospital	S-1	12/23/2013	10.7	
10.8†	Exclusive License Agreement, dated as of November 22, 2010, between the Registrant and Saint Louis University	S-1	12/23/2013	10.8	
10.9†	Supply Agreement, dated as of November 19, 2012, between the Registrant and CREMER OLEO GmbH & Co KG	S-1	12/23/2013	10.9	
10.10†	Development and Clinical Supply Agreement, dated as of August 31, 2012, between the Registrant and Rentschler Biotechnologie GmbH	S-1	11/8/2013	10.10	
10.11#	2011 Equity Incentive Plan (including forms of Stock Option Grant Notice and Stock Option Agreement thereunder)	S-1	11/8/2013	10.11	
10.12#	Amendment to the 2011 Equity Incentive Plan	S-1	11/8/2013	10.12	
10.13#	2014 Incentive Plan	S-1	1/17/2014	10.13	
10.14#	Form of Incentive Stock Option Agreement	S-1	1/17/2014	10.14	
10.15#	Form of Non Statutory Stock Option Agreement (Employees)	S-1	1/17/2014	10.15	
10.16#	Form of Non-Statutory Stock Option Agreement (Directors)	S-1	1/17/2014	10.16	
10.17#	Form of Restricted Stock Unit Agreement (Employees)	S-1	1/17/2014	10.17	
10.18#	Form of Restricted Stock Unit Agreement (Directors)	S-1	1/17/2014	10.18	

Exhibit Number	Exhibit Description	Incorporated by Reference			Filed Herewith
		Form	Date	Number	
10.19#	2014 Employee Stock Purchase Plan	S-1	1/17/2014	10.19	
10.20#	Executive Employment Agreement, dated as of June 15, 2011, between the Registrant and Emil D. Kakkis, M.D., Ph.D.	S-1	11/8/2013	10.18	
10.21#	Offer Letter, dated as of October 31, 2011, between the Registrant and Thomas Kassberg	S-1	11/8/2013	10.19	
10.22#	Offer Letter, dated as of March 12, 2012, between the Registrant and Shalini Sharp	S-1	11/8/2013	10.20	
10.23#	Form of Indemnification Agreement	10-K	3/24/2014	10.23	
10.24	Standard Lease, dated as of July 5, 2011, between the Registrant and Condiotti Enterprises, Inc.	S-1	11/8/2013	10.22	
10.25	License and Services Agreement, dated as of September 24, 2010, between the Registrant and The Buck Institute for Age Research	S-1	11/8/2013	10.23	
10.26	Amendment No. 1 to License and Services Agreement, dated as of September 4, 2012, between the Registrant and The Buck Institute for Research on Aging	S-1	11/8/2013	10.24	
10.27#	Corporate Bonus Plan	S-1	1/17/2014	10.27	
10.28	Addendum #3 to the Lease, effective as of February 12, 2014, by and between the Registrant and Condiotti Enterprises, Inc.	8-K	2/25/2014	10.1	
10.29	First Amendment to License Agreement, effective as of March 1, 2014, by and between the Registrant and St. Jude Children's Research Hospital	10-Q	8/11/2014	10.1	
10.30	Amendment No. 1 to Executive Employment Agreement, dated August 8, 2014, by and between the Registrant and Emil D. Kakkis, M.D., Ph.D.	10-Q	8/11/2014	10.2	
10.31	Amendment No. 1 to Offer of Employment, dated as of August 8, 2014, by and between Ultragenyx Pharmaceutical Inc. and Thomas Kassberg	10-Q	8/11/2014	10.3	
10.32	Amendment No. 1 to Offer of Employment, dated as of August 8, 2014, by and between Ultragenyx Pharmaceutical Inc. and Shalini Sharp	10-Q	8/11/2014	10.4	
10.33	Amendment No. 2 to License and Services Agreement, effective as of September 15, 2014, by and between the Registrant and The Buck Institute for Research on Aging	10-Q	11/10/2014	10.1	
10.34	Amendment 1 to the Development and Clinical Supply Agreement, effective as of November 4, 2014, by and between the Registrant and Rentschler Biotechnologie GmbH				X
23.1	Consent of Independent Registered Public Accounting Firm				X
24.1	Power of Attorney (included on the signature page of this report)				
31.1	Certification of Chief Executive Officer of the Registrant, as required by Rule 13a-14(a) or Rule 15d-14(a) of the Securities Exchange Act of 1934, as amended, as adopted pursuant to Section 302 of the Sarbanes-Oxley Act of 2002				X
31.2	Certification of Chief Financial Officer of the Registrant, as required by Rule 13a-14(a) or Rule 15d-14(a) of the Securities Exchange Act of 1934, as amended, as adopted pursuant to Section 302 of the Sarbanes-Oxley Act of 2002				X
32.1*	Certification by the Chief Executive Officer and Chief Financial Officer, as required by Rule 13a-14(b) or Rule 15d-14(b) and Section 1350 of Chapter 36 of Title 18 of the United States Code (18 U.S.C. §1350)				X

Exhibit Number	Exhibit Description	Incorporated by Reference Form	Date	Number	Filed Herewith
101.INS	XBRL Instance Document				X
101.SCH	XBRL Taxonomy Extension Schema Document				X
101.CAL	XBRL Taxonomy Extension Calculation Linkbase Document				X
101.DEF	XBRL Taxonomy Extension Definition Linkbase Document				X
101.LAB	XBRL Taxonomy Extension Labels Linkbase Document				X
101.PRE	XBRL Taxonomy Extension Presentation Linkbase Document				X

† Confidential treatment has been granted with respect to certain portions (indicated by asterisks) of this exhibit. Omitted portions have been filed separately with the SEC.

# Indicates management contract or compensatory plan.

* The certification attached as Exhibit 32.1 that accompanies this Annual Report on Form 10-K is not deemed filed with the SEC and is not to be incorporated by reference into any filing of Registrant under the Securities Act of 1933, as amended, or the Securities Exchange Act of 1934, as amended, whether made before or after the date of this Form 10-K, irrespective of any general incorporation language contained in such filing.

Exhibit 10.34

Amendment 1 ("this Amendment")
to the Development and Clinical Supply Agreement
with the Contract Number: E86A1D4C-B3F9

Between

Ultragenyx Pharmaceutical Inc.
60 Leveroni Court, Novato, CA 94949, USA
("Ultragenyx")

and

Rentschler Biotechnologie GmbH,
Erwin-Rentschler-Str. 21, 88471 Laupheim, Germany
("Rentschler")

Rentschler and/or Ultragenyx are hereinafter referred to as "Party" or "Parties".

The Parties amend their Development and Clinical Supply Agreement with the Contract Number: E86A1D4C-B3F9, effective as of 31 August 2012, ("the Agreement") as follows:

1. Section 2.4 is changed and reads as follows:

If (1) Ultragenyx cancels or postpones the Services concerning Drug Product for a rea son within Ultragenyx's control and not the result of Rentschler's policies, or (2) other deviations to the respective timelines stated in **Schedule Two** are caused by reasons within Ultragenyx's control and not the result of Rentschler's policies, then in either case, Rentschler is entitled to require that Ultragenyx pay the following reimbursement for the unused production facilities:

Cancellation period prior to the beginning of the Drug Product manufacturing	Exit fee (percentage of total fees for the Drug Product manufacturing)
More than 13 weeks	No exit fee
12- 9 weeks	30%
8 - 5 weeks	60%
4 - 3 weeks	90%
2 weeks and less	100%

Rentschler shall use commercially reasonable efforts to mitigate any losses or damages it may incur due to Ultragenyx's cancellation or postponement regarding the Drug Product. If Rentschler mitigates such losses or damages so that it incurs no damage or significantly less damage as a result of the cancellation or postponement in the provision of materials or information, Ultragenyx must only reimburse Rentschler for the unmitigated costs of the cancellation or postponement. This in particular applies if Rentschler can use the production time for another order.

For clarity, if Ultragenyx notifies Rentschler of a cancellation or postponement prior to the thirteenth week before the production time, then the foregoing reimbursement shall not be owed to Rentschler; provided, however, that any actual expenses for activities performed by Rentschler with regard to the cancelled or postponed batch (e.g. preparation of manufacturing documentation) shall be borne by Ultragenyx and may be invoiced by Rentschler to Ultragenyx.

2. No change or modification of this Amendment shall be valid or binding upon the Parties unless such change or modification is in writing and duly executed by the Parties.

3. Except as specifically set forth herein, all other terms and conditions of the Agreement shall remain unchanged and in full force and effect. In the event of a conflict between the provisions of this Amendment and the provisions of the Agreement, the provisions of this Amendment shall control.

4. This Amendment comes into force immediately after both parties have signed this Amendment. This Amendment may be executed by facsimile or Adobe™ Portable Document Format (PDF) sent by electronic mail and in one or more counterparts each of which will be deemed an original, but all of which together shall constitute one and the same instrument. It shall form an integral part of the Agreement.

Signed on behalf of
Rentschler Biotechnologie GmbH

Date:	23 OKT. 2014	Date:	23/10/14
Signature:	/s/ Dr. Klaus Schoepe	Signature:	/s/ Thomas Lottner
Printed Name:	Dr. Klaus Schoepe	Printed Name:	Thomas Lottner
Position:	VP Project Management	Position:	VP Commercial Management

Signed on behalf of
Ultragenyx Pharmaceutical Inc.

If second signature is required:

Date:	4 Nov 2014	Date:	
Signature:	/s/ Steven Jungles	Signature:	
Printed Name:	Steven Jungles	Printed Name:	
Position:	SVP Tech ops	Position:	

Exhibit 23.1

CONSENT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

We consent to the incorporation by reference in the following Registration Statements:

(1) Registration Statement (Form S-3ASR No. 333-201838) of Ultragenyx Pharmaceutical Inc., and

(2) Registration Statement (Form S-8 No. 333-201843 and 333-194773) pertaining to the 2011 Equity Incentive Plan, as amended, 2014 Incentive Plan and 2014 Employee Stock Purchase Plan of Ultragenyx Pharmaceutical Inc.; of our report dated March 27, 2015, with respect to the financial statements of Ultragenyx Pharmaceutical Inc. included in this Annual Report (Form 10-K) of Ultragenyx Pharmaceutical Inc. for the year ended December 31, 2014.

/S/ ERNST & YOUNG LLP

Redwood City, California

March 27, 2015

Exhibit 31.1

CERTIFICATION PURSUANT TO SECTION 302 OF THE SARBANES-OXLEY ACT OF 2002

I, Emil D. Kakkis, certify that:

1. I have reviewed this Annual Report on Form 10-K of Ultragenyx Pharmaceutical Inc.;
2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;
3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;
4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) for the registrant and have:
    a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;
    b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;
    c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and
    d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and
5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of registrant's Board of Directors (or persons performing the equivalent functions):
    a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and
    b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Dated: March 27, 2015

/s/ Emil D Kakkis

Emil D. Kakkis, M.D., Ph.D.
President and Chief Executive Officer
(Principal Executive Officer)

Exhibit 31.2

CERTIFICATION PURSUANT TO SECTION 302 OF THE SARBANES-OXLEY ACT OF 2002

I, Shalini Sharp, certify that:

1. I have reviewed this Annual Report on Form 10-K of Ultragenyx Pharmaceutical Inc.;
2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;
3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;
4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) for the registrant and have:
   a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;
   b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;
   c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and
   d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and
5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of registrant's Board of Directors (or persons performing the equivalent functions):
   a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and
   b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Dated: March 27, 2015

/s/ Shalini Sharp
Shalini Sharp
Chief Financial Officer and Senior Vice President
(Principal Financial Officer)

Exhibit 32.1

**CERTIFICATION PURSUANT TO SECTION 906 OF
THE SARBANES-OXLEY ACT OF 2002 (18 U.S.C. SECTION 1350)**

In connection with the accompanying Quarterly Report of Ultragenyx Pharmaceutical Inc. (the “Company”) on Form 10-K for the year ended December 31, 2014 (the “Report”), I, Emil D. Kakkis, M.D., Ph.D., as President and Chief Executive Officer of the Company, and Shalini Sharp, as Chief Financial Officer and Senior Vice President of the Company, certify, pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, that:

(1) The Report fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934; and

(2) The information contained in the Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

Dated: March 27, 2015	/s/ Emil D. Kakkis Emil D. Kakkis, M.D., Ph.D. President and Chief Executive Officer (Principal Executive Officer)
Dated: March 27, 2015	/s/ Shalini Sharp Shalini Sharp Chief Financial Officer and Senior Vice President (Principal Financial Officer)