Ultragenyx Pharmaceutical Inc.
Form 10-K
March 24, 2014

UNITED STATES SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

Form 10-K

RANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934
For the fiscal year ended December 31, 2013

OR

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

Commission File No. 001-36276

Ultragenyx Pharmaceutical Inc.

(Exact name of registrant as specified in its charter)

Delaware	27-2546083
(State or other jurisdiction of incorporation or organization)	(I.R.S. Employer Identification No.)
60 Leveroni Court Novato, California	94949
(Address of principal executive offices)	(Zip Code)

(415) 483-8800

(Registrant's telephone number, including area code)

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 ¨ NO R

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 ¨ NO R

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 ¨ 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. R

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 March 14, 2014 was approximately $1,246,786,500, 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. The Company has elected to use March 14, 2014 as the calculation date, as on June 28, 2013 (the last business day of the Company's most recently completed second fiscal quarter) there was no public market for the Company's common stock.

As of March 14, 2014, the Company had 30,035,894 shares of common stock issued and outstanding.

DOCUMENTS INCORPORATED BY REFERENCE

None.

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PART III

PART IV

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. We typically identify these forward-looking statements by the use of forward-looking words such as “expect,” “potential,” “continue,” “may,” “will,” “should,” “could,” “would,” “seek,” “intend,” “plan,” “estimate the negative version of those words or other comparable words. 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.

PART I

Item 1. Business

BUSINESS

Overview

We are a development-stage biopharmaceutical company focused on the identification, acquisition, development, and commercialization of novel products for the treatment of rare and ultra-rare diseases, with an initial focus on serious, debilitating metabolic genetic diseases. We focus on diseases for which the unmet medical need is high, the biology for treatment is clear, and for which there are no approved therapies. Since our inception in 2010, we have in-licensed product candidates for five different diseases that are currently in or have completed Phase 1/2 or Phase 2 clinical studies. 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, Dr. Emil Kakkis, M.D., Ph.D., who is the former Chief Medical Officer of BioMarin Pharmaceutical Inc. We have assembled an experienced team with extensive 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 metabolic 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, 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 metabolic 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 metabolic 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 metabolic 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:

KRN23 (UX023) for the treatment of XLH

KRN23 is a fully human monoclonal antibody administered via subcutaneous injection that is designed to bind and reduce the biological activity of fibroblast growth factor 23, or FGF23, to increase abnormally low phosphate levels in patients with X-linked hypophosphatemia, or XLH. Patients with XLH have low serum phosphate levels due to excessive phosphate loss into the urine, which is directly caused by the effect on kidney function of excess FGF23 production in bone cells. Low phosphate levels lead to poor bone mineralization and a variety of clinical manifestations, including skeletal deformity, bone pain, short stature, gross motor impairment, muscle weakness, and lower than normal bone density. There is no approved drug therapy or treatment for the underlying cause of XLH. Most patients are managed using frequently dosed oral phosphate replacement and/or vitamin D therapy, which is only partially effective at restoring bone physiology and growth and has significant side effects. These therapies require extremely close monitoring due to the potential for excessive spikes in phosphate levels, which can result in severe damage to the kidneys from excess calcium and 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 formed a collaboration with Kyowa Hakko Kirin Co., Ltd., or KHK, to jointly develop and commercialize KRN23 for the treatment of XLH. KHK has conducted one Phase 1 study, one Phase 1/2 study and one Phase 1/2 extension study of KRN23 in adults with XLH. We reviewed safety and efficacy data from the Phase 1/2 studies prior to entering into our collaboration with KHK, and we entered into the collaboration based in part upon our conclusion that these data were supportive of further development (i.e., serum phosphate, renal tubular reabsorption of phosphate, and Vitamin D levels were increased, and the product appeared well tolerated).

Results from the Phase 1 single dose study in 38 adult XLH patients were presented at the American Society for Bone and Mineral Research 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, as well as vitamin D levels. Of the 38 adult XLH patients, 12 received a single subcutaneous injection of KRN23 (at doses of 0.1, 0.3, 0.6, or 1.0 mg/kg), 17 received a single intravenous injection of KRN23 (at doses of 0.003, 0.01, 0.03, 0.1, or 0.3 mg/kg) and 9 received placebo. The effect of KRN23 on the increase in serum phosphate levels was comparable between intravenous and subcutaneous administration; however, time to reach peak effect was slower and duration of effect was greater with subcutaneous administration The demonstrated improvement suggests that significant benefit could be expected. 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. Changes were not observed in serum calcium.

No serious adverse events were reported in the Phase 1 study, although some patients (approximately 83%) experienced non-serious treatment-emergent adverse events. The most common non-serious treatment-emergent adverse events in the study overall were nausea and headache, although no patients in the placebo or subcutaneous treatment arms reported these events. In the subcutaneous arm, two patients (approximately 17%) experienced elevated levels of the enzyme amylase in the blood, and two other patients (approximately 17%) experienced back pain. 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.

We expect that data from the completed Phase 1/2 adult repeat-dose studies will be released in 2014.

Following discussions with multiple regulatory agencies on our pediatric study design, we plan to initiate a Phase 2 pediatric study in 2014 in approximately 30 patients with radiographic evidence of bone disease. Depending on the results of our Phase 2 pediatric study, we intend to conduct a Phase 3 pediatric trial. 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. As a result, pediatric XLH patients may also have the greatest potential for improvement based on 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 also expect to continue to develop KRN23 in adults with XLH and plan to conduct an adult Phase 2b study in parallel with our Phase 3 pediatric trial.

rhGUS (UX003) for the treatment of MPS 7

Recombinant human beta-glucuronidase, or rhGUS, is an intravenous, or IV, enzyme replacement therapy for the treatment of mucopolysaccharidosis 7, or MPS 7, also known as Sly Syndrome. Patients with MPS 7 suffer from severe cellular and organ dysfunction that typically leads to death in the teens or early adulthood. MPS 7 is caused by a deficiency of the lysosomal enzyme beta-glucuronidase, which is required for the breakdown of certain complex carbohydrates known as glycosaminoglycans, or GAGs. The inability to properly break down GAGs leads to their accumulation in many tissues, resulting in a serious multi-system disease. There are currently no approved drug therapies for MPS 7.

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 up to five patients with MPS 7 who are between five and 30 years of age. The initial 12-week treatment period will be followed by a dose-titration period and a long-term extension study. We expect to release interim data from this study during 2014. If these results are supportive, we plan to initiate a pivotal Phase 3 study enrolling at least 12 patients.

We are also supplying rhGUS to an investigator who is treating a single U.S. patient under an emergency investigational new drug, or eIND, application. Results from the treatment of this patient were presented at the Lysosomal Disease Network's 10th Annual World Symposium in February 2014. Preliminary data showed a reduction in lysosomal storage based on reduced excretion of urinary glycosaminoglycans, or urinary GAG, and a reduction in the size of the enlarged liver and spleen. The patient showed an improvement of pulmonary function and no infusion-associated reactions during the first 14 weeks of treatment. The patient's caregivers also reported improved stamina and increased time spent in school.

The European Medicines Agency, or EMA, has agreed that approval under exceptional circumstances could be possible for a proposed 12-patient placebo-controlled pivotal study in this disease with 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. The United States Food and Drug Administration, or FDA, has not yet agreed to the pivotal study plan and would like to see additional data correlating urinary GAG levels with other clinical endpoints, which we are collecting through our Phase 1/2 study.

In addition to the above development plan, we intend to study MPS 7 patients under the age of five years, including younger infants born with hydrops fetalis. Currently, these infants may 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.

rhPPCA (UX004) for the treatment of galactosialidosis

Recombinant human protective protein cathepsin-A, or rhPPCA, which we in-licensed from St. Jude Children's Research Hospital in September 2012, is in preclinical development as an enzyme replacement therapy for galactosialidosis, a rare lysosomal storage disease for which there are no currently approved drug therapies. Similar to MPS patients, patients with galactosialidosis present with both soft tissue storage in the liver, spleen, and other tissues, as well as connective tissue (bone and cartilage) related disease. As with MPS 7, an enzyme deficiency results in accumulation of substrates in the lysosomes, causing skeletal and organ dysfunction, and death. We plan to continue preclinical development of rhPPCA during 2014.

Triheptanoin (UX007) for the treatment of LC-FAOD

We are developing triheptanoin for oral 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 three seven-carbon fatty acids designed to provide substrate replacement for fatty acid metabolism and restore production of energy. Patients with LC-FAOD have a deficiency that impairs the ability to produce energy from fat, which can lead to depletion of 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 relating to triheptanoin from Baylor Research Institute in August 2012. Triheptanoin has been studied clinically for 13 years in approximately 130 human subjects affected by a variety of diseases, including greater than 60 patients with LC-FAOD. Multiple investigator-sponsored open-label studies suggest clinical improvements with triheptanoin treatment, even for patients who were on standard of care. We recently presented a retrospective medical record review study assessing the clinical outcome of triheptanoin treatment on LC-FAOD subjects who have been participating in a compassionate use program at the University of Pittsburgh Medical Center. The data showed that treatment with triheptanoin appeared to reduce the frequency and severity of hospitalizations previously experienced by these patients 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.

Triheptanoin is currently being evaluated in a prospective, interventional, open-label Phase 2 study in approximately 30 severely affected LC-FAOD patients, ages 6 months to 35 years, exhibiting significant clinical manifestations of LC-FAOD despite current therapy. A principal goal of the study is to determine the appropriate clinical endpoints and patient population for testing in potential later-stage pivotal studies. The study will be conducted at approximately eight clinical sites in the United States and Europe. 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. We expect that data from this study will be available in 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 is difficult to comply with and may have limited effectiveness in the treatment of developmental delay and movement disorders. In addition, ketogenic diet can lead to side effects including renal stones. There are currently no antiepileptic drugs approved specifically for patients with Glut 1 DS. In general, Glut 1 DS patients are considered relatively refractory to antiepileptic drugs with only approximately 10% achieving seizure control on antiepileptic drugs alone.

Triheptanoin is intended as a substrate replacement therapy to provide an alternative source of energy to the brain in Glut1 DS patients. Although an open-label investigator-sponsored clinical study is ongoing and the results have not yet been reported, there are anecdotal reports of benefit in terms of reduced seizures and improved development rate in some Glut1 DS subjects taking triheptanoin. In March 2014, we initiated a Phase 2 global, randomized, double-blind, placebo-controlled, parallel-group study of up to 50 patients between three and 17 years of age inclusive, 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. The blinded treatment period will be followed by an open-label extension period in which patients will be treated with triheptanoin through week 52. Patient enrollment may be modified based on an interim analysis. We expect to release data from this trial in 2015.

We also continue to support investigator-sponsored trials studying triheptanoin across multiple indications.

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 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. Top-line results after 48 weeks of treatment showed a modest increase in upper extremity muscle strength composite at the higher dose that was statistically significant versus the decline observed at the lower dose. A positive trend was seen in a patient-reported outcome of functional activity. The results were consistent with the 24-week analysis. SA-ER appears to be well tolerated with no serious adverse events observed to date in either dose group. Data from this study is expected to be presented during 2014. We continue to treat patients in an extension study evaluating an increased daily dosage of sialic acid based on the dose dependence observed at weeks 24 and 48. We anticipate that data from the extension study should be available in late 2014. We also plan to discuss data from this program with regulatory authorities during 2014. In parallel, we are pursuing development of preclinical prodrugs of sialic acid, which may have better absorption into muscle tissue.

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. Enzyme replacement therapy can have an impact on bone and connective tissue disease if patients are 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 medium even-chain triglycerides, or 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 also 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 nutraceutical or 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 in Europe; we are not, however, aware of any ongoing 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 recently completed a Phase 1 clinical study, and we anticipate that it will advance into Phase 2 testing.

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 European Union, 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 twenty percent 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 entire agreement if we do not timely initiate a first pediatric study in XLH. In addition, 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 European Union, 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 also received a right of first negotiation to receive an exclusive license under patents and know-how related to other uses of these products. 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 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 $1.9 million U.S. dollars as of December 31, 2013) 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.

AAI Pharma

In March 2011, we entered into a license agreement with AAIPharma Services Corp., or AAI Pharma. Under the terms of this license agreement, AAI Pharma 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 AAI Pharma'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 AAI Pharma technology. As consideration, we agreed to provide preclinical and clinical data to AAI Pharma. AAI Pharma 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 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 10, 2014, we own 12 pending U.S. patent applications and corresponding patents and patent applications internationally. In addition, as of March 10, 2014, we have licensed 10 issued U.S. patents and 13 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 from the FDA. The patent portfolios for our five leading product candidates as of March 10, 2014 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.

rhGUS

We have no issued patents covering rhGUS but we have filed 1 U.S. application 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, regiment, 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.

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 24 issued patents, including 7 U.S. patents and 8 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 2024 (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.

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 10 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 2034.

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 European Union.

Trademarks

We have filed U.S. trademark applications for ULTRAGENYX and ULTRAGENYX PHARMACEUTICAL.

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 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. The process to produce rhPPCA will only contain commercially available materials.

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 AAI Pharma under our license agreement and accompanying purchase orders with AAI Pharma. We are in the process of identifying 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 investigational new drug application, or 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 a new drug application, or 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 product drug substance and drug product is produced to assess compliance with current Good Manufacturing Practices, or cGMP;

FDA will typically inspect one or more clinical sites to assure compliance with cGPC; 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 current Good Clinical Practices, or cGCPs. 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 institutional review board, or 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 authorization 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 European Union, 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 cGCP, 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 European Union regulatory systems, we must submit a marketing authorization application, or MAA. The content of the NDA or BLA filed in the United States is similar to that required in the European Union, with the exception of, among other things, country-specific document requirements.

For other countries outside of the European Union, 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 European Union, as well as countries outside of the European Union, 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 European Union 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 European Union 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 European Union 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 European Union country of medicinal products that have not yet been authorized in any European Union 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 European Union Member State, in accordance with the national procedures of that country. Following this, further marketing authorizations can be sought from other European Union 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 European Union, 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 European Union 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 European Union, 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 European Union 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 European Union would be sufficient to justify the necessary investment in developing the medicinal product.

In the European Union, 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 European Union, 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 Patient Protection and 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, 2013, we had 59 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 $4.7 million, $12.6 million, and $27.8 million in research and development expense in the years ended December 31, 2011, 2012, and 2013, 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 shall commence on May 1, 2014 and expire on April 30, 2019. The rental term for the current space shall also now 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, which expires in September 2014.

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 $5 million per incident and $5 million in aggregate.

Executive Officers and Key Employees of the Registrant

Information concerning our executive officers and key employees, including their names, ages and certain biographical information can be found in Part III, Item 10 under the caption, “Executive Officers and Key Employees of the Registrant.” 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

RISK FACTORS

Risks Related to Our Financial Condition and Capital Requirements

We are a development-stage company and have a limited operating history on which to assess our business, have incurred significant losses since our inception, and anticipate that we will continue to incur significant losses for the foreseeable future.

We are a development-stage biopharmaceutical company with a limited operating history. We have incurred net losses in each year since our inception in April 2010, including net losses of $6.8 million, $16.3 million and $35.1 million for the years ended December 31, 2011, 2012 and 2013, respectively. As of December 31, 2013, we had incurred cumulative net losses of $59.6 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, 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. We are in the early stages of clinical development for our product candidates, we have not yet commenced pivotal clinical studies for any product candidate and it may be several years, if ever, before we complete pivotal clinical studies and have a product candidate approved for commercialization. If we obtain regulatory approval to market a product candidate, our future revenue will depend upon the size of any markets in which our product candidates may receive approval, and our ability to achieve sufficient market acceptance, pricing, reimbursement from third-party payors, and adequate market share for our product candidates in those markets. However, even if we obtain adequate market share for our product candidates, because the potential markets in which our product candidates may ultimately receive regulatory approval are very small, 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, acquire, and/or develop other product candidates;
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 revenue and achieve profitability depends on our ability, alone or with strategic collaboration partners, to successfully complete the development of, and obtain the regulatory and marketing approvals necessary to commercialize one or more of our product candidates. We do not anticipate generating revenue from product sales in the near future. Our ability to generate future revenue from product sales depends heavily on our success in many areas, including but not limited to:

- completing research and nonclinical and clinical development of our product candidates;
- obtaining regulatory and marketing approvals for product candidates for which we complete clinical studies;
- developing a sustainable and scalable manufacturing process for any approved product candidates and establishing and maintaining supply and manufacturing relationships with third parties that can conduct the 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;
- addressing any competing technological and market developments;
- identifying, assessing, acquiring and/or developing new product candidates;
- negotiating favorable terms in any collaboration, licensing, or other arrangements into which we may enter;
- maintaining, protecting, and expanding our portfolio of intellectual property rights, including patents, trade secrets, and know-how; and
- attracting, hiring, and retaining qualified personnel.

Even if one or more of the product candidates that we develop is approved for commercial sale, we anticipate incurring significant costs associated with commercializing any approved product candidate. Our expenses could increase beyond expectations if we are required by the U.S. Food and Drug Administration, or the FDA, the European Medicines Agency, or the EMA, or other regulatory agencies, domestic or foreign, to change our manufacturing processes or assays, or to perform clinical, nonclinical, or other types of studies in addition to those that we currently anticipate. In cases where we are successful in obtaining regulatory approvals to market one or more of our product candidates, our revenue will be dependent, in part, upon the size of the markets in the territories for which we gain regulatory approval, the accepted price for the product, the ability to get reimbursement at any price, and whether we own the commercial rights for that territory. If the number of our addressable rare disease patients is not as significant as we estimate, the indication approved by regulatory authorities is narrower than we expect, or the reasonably accepted population for treatment is narrowed by competition, physician choice or treatment guidelines, we may not generate significant revenue from sales of such products, even if approved. For example, the development of KRN23, rhGUS, and triheptanoin for pediatric use is an important part of our current business strategy; if we are unable to obtain regulatory approval for the desired age ranges, our business may suffer. Additionally, if we are not able to generate revenue from the sale of any approved products, we may never become profitable.

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, 2013, our available cash, cash equivalents and short-term investments were $53.4 million. We expect that our existing cash, cash equivalents and short-term investments, including $121.7 million in net proceeds we received from the closing of our initial public offering, or IPO, in February 2014, will be sufficient to fund our current operations into 2016; however, we expect that we will require additional capital to obtain regulatory approval for, and to commercialize, our product candidates. In addition, our operating plans may change as a result of many factors that may currently be unknown to us, and we may need to seek additional funds sooner than planned. Our future funding requirements will depend on many factors, including but not limited to:

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

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

Any additional fundraising efforts may divert our management from their day-to-day activities, which may adversely affect our ability to develop and commercialize our product candidates. In addition, we cannot guarantee that future financing will be available in sufficient amounts or on terms acceptable to us, if at all. Moreover, the terms of any financing may adversely affect the holdings or the rights of our stockholders and the issuance of additional securities, whether equity or debt, by us, or the possibility of such issuance, may cause the market price of our shares to decline. The sale of additional equity or convertible securities would dilute all of our stockholders. The incurrence of indebtedness could result in increased fixed payment obligations and we may be required to agree to certain restrictive covenants, such as limitations on our ability to incur additional debt, limitations on our ability to acquire, sell, or license intellectual property rights, and other operating restrictions that could adversely impact our ability to conduct our business. We could also be required to seek funds through 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, 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 the early stages of development and will require additional clinical development, management of nonclinical, clinical, and manufacturing activities, regulatory approval, obtaining adequate manufacturing supply, building of a commercial organization, and significant marketing efforts before we generate any revenue from product sales. We have five programs that are currently in or have completed Phase 1/2 or Phase 2 clinical studies. None of our product candidates have advanced into a pivotal study and it may be years before such study is initiated, if at all. We are not permitted to market or promote any of our product candidates before we receive regulatory approval from the FDA or comparable foreign regulatory authorities, and we may never receive such regulatory approval for any of our product candidates.

Although certain of our employees have prior experience with submitting marketing applications to the FDA or comparable foreign regulatory authorities, we as a company have not submitted such applications for our product candidates. We cannot be certain that any of our product candidates will be successful in clinical studies or receive regulatory approval. Further, our product candidates may not receive regulatory approval even if they are successful in clinical studies. If we do not receive regulatory approvals for our product candidates, we may not be able to continue

our operations.

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

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

The time required to obtain approval by the FDA and comparable foreign authorities is unpredictable, typically takes many years following the commencement of clinical studies, and depends upon numerous factors. In addition, approval policies, regulations, or the type and amount of clinical data necessary to gain approval may change during the course of a product candidate’s clinical

development and may vary among jurisdictions, which may cause delays in the approval or the decision not to approve an application. We have not obtained regulatory approval for any product candidate, and it is possible that none of our existing product candidates or any product candidates we may seek to develop in the future will ever obtain regulatory approval.

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 a new drug application, or NDA, or biologics license application, or BLA, or other submission or to obtain regulatory approval in the United States or elsewhere;
we may be unable to demonstrate to the FDA or comparable foreign regulatory authorities that a product candidate's risk-benefit ratio for its proposed indication is acceptable;
the FDA or comparable foreign regulatory authorities may fail to approve the manufacturing processes, test procedures and specifications, or facilities of third-party manufacturers with which we contract for clinical and commercial supplies;
As a condition of marketing authorization in the EU, an agreed upon 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 trials or compassionate use studies 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 up to approximately 200 patients in the developed world may suffer from MPS 7, for which rhGUS is being studied;

we estimate that several thousand patients in the United States suffer from LC-FAOD, for which triheptanoin is being studied;
we estimate that several thousand patients in the United States suffer from Glut1 DS, for which triheptanoin is being studied; and
we estimate that about 1,200 to 2,000 patients in the developed world suffer from HIBM, for which SA-ER is being studied.

In addition to the rarity of these diseases, the eligibility criteria of our clinical studies will further limit the pool of available study participants as we will require that patients have specific characteristics that we can measure or to assure their disease is either severe enough or not too advanced to include them in a study. Additionally, the process of finding and diagnosing patients may prove costly. We also may not be able to identify, recruit, and enroll a sufficient number of patients to complete our clinical studies because of the perceived risks and benefits of the product candidate under study, the availability and efficacy of competing therapies and clinical studies, the proximity and availability of clinical study sites for prospective patients, and the patient referral practices of physicians. If patients are unwilling to participate in our studies for any reason, the timeline for recruiting patients, conducting studies, and obtaining regulatory approval of potential products may be delayed.

If we experience delays in the completion of, or termination of, any clinical study of our product candidates, the commercial prospects of our product candidates will be harmed, and our ability to generate product revenue from any of these product candidates could be delayed or prevented. In addition, any delays in completing our clinical studies will increase our costs, slow down our product candidate development and approval process, and jeopardize our ability to commence product sales and generate revenue. Any of these occurrences may harm our business, financial condition, and prospects significantly. In addition, many of the factors that cause, or lead to, a delay in the commencement or completion of clinical studies may also ultimately lead to the denial of regulatory approval of our product candidates.

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

Before obtaining marketing approval from regulatory authorities for the sale of our product candidates, we must conduct extensive clinical studies to demonstrate the safety and efficacy of the product candidates in humans. Clinical testing is expensive, time consuming, and uncertain as to outcome. We cannot guarantee that any clinical studies will be conducted as planned or completed on schedule, if at all. A failure of one or more clinical studies can occur at any stage of testing, and our future clinical studies may not be successful. Events that may prevent successful or timely completion of clinical development include but are not limited to:

inability to generate sufficient preclinical, toxicology, or other in vivo or in vitro data to support the initiation or continuation of human clinical studies or filings for regulatory approval;
delays in reaching a consensus with regulatory agencies on study design;
delays in reaching agreement on acceptable terms with prospective contract research organizations, or CROs, and clinical study sites, the terms of which can be subject to extensive negotiation and may vary significantly among different CROs and clinical study sites;
delays in obtaining required Institutional Review Board, or IRB, approval at each clinical study site;
changes in clinical study design or development strategy resulting in delays related to obtaining approvals from IRBs and/or regulatory agencies to proceed with clinical studies;
failure to gain approval from competent authorities or IRBs to conduct clinical studies in certain countries;
imposition of a clinical hold by regulatory agencies due to a safety concern, 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 trials of our product candidates; and

- delays in manufacturing, testing, releasing, validating, or importing/exporting sufficient stable quantities of our product candidates for use in clinical studies or the inability to do any of the foregoing.

Any inability to successfully complete nonclinical and clinical development could result in additional costs to us or 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. In the completed Phase 1 study, patients treated with KRN23 have experienced nausea, headache, elevated serum amylase, and back pain. Most of these adverse events were mild and no serious adverse events have been observed. Only single-dose Phase 1 data for KRN23 has been reported to date and other side effects may result from repeated dosing and/or longer-term exposure. Patients treated with triheptanoin have experienced drug-related side effects such as cramping, diarrhea, and loose stools. In addition, during a 13-year study of approximately 130 human subjects, including greater than 60 with LC-FAOD, three serious adverse events were classified as possibly related to triheptanoin treatment (muscle cell rupture and elevated creatine kinase reported for two subjects and myoglobinuria in one subject); however, these serious adverse events can be considered typical of the underlying disease. While we have not 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 $5.0 million per incident and $5.0 million in the aggregate, and we are required to maintain product liability insurance pursuant to certain of our license agreements. We believe our product liability insurance coverage is sufficient in light of our current clinical programs; however, we may not be able to maintain insurance coverage at a reasonable cost or in sufficient amounts to protect us against losses due to liability, 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 current Good Manufacturing Practices, or cGMP, regulations. As such, we and our contract manufacturers will be subject to continual review and inspections to assess compliance with cGMP and adherence to commitments made in any NDA, BLA, marketing authorization application, or 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 trials, and surveillance to monitor the safety and efficacy of the product candidate. 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. We could also be asked to conduct post-marketing clinical studies to verify the safety and efficacy of our products in general or in specific patient subsets. If original marketing approval were obtained via the accelerated approval pathway, we could be required to conduct a successful post-marketing clinical study to confirm clinical benefit for our products. An unsuccessful post-marketing study or failure to complete such a study could result in the withdrawal of marketing approval.

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

issue warning letters;
impose civil or criminal penalties;
suspend or withdraw regulatory approval;
suspend any of our ongoing clinical studies;
refuse to approve pending applications or supplements to approved applications submitted by us;

impose restrictions on our operations, including closing our contract manufacturers' facilities; or
seize or detain products, or require a product recall.

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

Risks Related to our Reliance on Third Parties

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

We have relied upon and plan to continue to rely upon third-party CROs to monitor and manage data for our ongoing nonclinical and clinical programs. We rely on these parties for execution of our nonclinical and clinical studies, and control only certain aspects of their activities. Nevertheless, we are responsible for ensuring that each of our studies is conducted in accordance with the applicable protocol, legal, regulatory, and scientific standards and our reliance on the CROs does not relieve us of our regulatory responsibilities. We and our CROs and other vendors are required to comply with cGMP, current good clinical practices, or cGCP, and Good Laboratory Practices, or GLP, which are regulations and guidelines enforced by the FDA, the Competent Authorities of the Member States of the European Economic Area, or EEA, and comparable foreign regulatory authorities for all of our product candidates in development. Regulatory authorities enforce these regulations through periodic inspections of study sponsors, principal investigators, study sites, and other contractors. If we or any of our CROs or vendors fail to comply with applicable regulations, the data generated in our nonclinical and clinical studies may be deemed unreliable and the FDA, EMA, or comparable foreign regulatory authorities may require us to perform additional nonclinical and clinical studies before approving our marketing applications. We cannot assure you that upon inspection by a given regulatory authority, such regulatory authority will determine that any of our clinical studies comply with cGCP regulations or that nonclinical studies comply with GLP regulations. In addition, our clinical studies must be conducted with product produced under cGMP regulations. Our failure to comply with these regulations may require us to repeat clinical or nonclinical studies, which would delay the regulatory approval process.

If any of our relationships with these third-party CROs terminate, we may not be able to enter into arrangements with alternative CROs or do so on commercially reasonable terms. In addition, our CROs are not our employees, and except for remedies available to us under our agreements with such CROs, we cannot control whether or not they devote sufficient time and resources to our on-going nonclinical and clinical programs. If CROs do not successfully carry out their contractual duties or obligations or meet expected deadlines, if they need to be replaced or if the quality or accuracy of the data they obtain is compromised due to the failure to adhere to our protocols, regulatory requirements, or for other reasons, our clinical studies may be extended, delayed, or terminated and we may not be able to obtain regulatory approval for or successfully commercialize our product candidates. CROs may also generate higher costs than anticipated as a result 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.

Switching or adding additional CROs involves additional cost and requires management time and focus. In addition, there is a natural transition period when a new CRO commences work. As a result, delays may occur, which can materially impact our ability to meet our desired clinical development timelines. Though we carefully manage our relationships with our CROs, there can be no assurance that we will not encounter similar challenges or delays in the future or that these delays or challenges will not have a material adverse impact on our business, financial condition, and prospects.

We are dependent on KHK for the supply of clinical and commercial 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 nonclinical and clinical drug supplies. Our business could be harmed if those third parties fail to provide us with sufficient quantities of drug product, or fail to do so at acceptable quality levels or prices.

We do not currently have, nor do we plan to acquire, the infrastructure or capability internally to manufacture our nonclinical and clinical drug supplies for use in the conduct of our clinical studies, and we lack the resources and the capability to manufacture any of our product candidates on a clinical or commercial scale. We rely on our manufacturers to purchase from third-party suppliers the materials necessary to produce our product candidates for our clinical studies. There are a limited number of suppliers for raw materials that we use to manufacture our drugs, 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, natural disasters, power failures, and numerous other factors.

Although we have not experienced any contaminations, equipment failures, or other similar manufacturing problems, any adverse developments affecting manufacturing operations for our product candidates may result in shipment delays, inventory shortages, lot failures, withdrawals or recalls, or other interruptions in the supply of our product candidates. We may also have to take inventory write-offs and incur other charges and expenses for product candidates that fail to meet specifications, undertake costly remediation efforts, or seek more costly manufacturing alternatives.

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

The drug substance and drug product for KRN23 are made by KHK pursuant to our license and collaboration agreement with KHK. The drug substance and drug product for rhGUS are manufactured by Rentschler Biotechnologie GmbH under a development and clinical supply agreement and accompanying purchase orders. The pharmaceutical-grade drug substance for triheptanoin is manufactured by Cremer Oleo GmbH & Co. KG, or Cremer, pursuant to our supply agreement with Cremer, and the drug product for triheptanoin is prepared by Haupt Pharma AG pursuant to purchase orders. The drug substance for SA-ER is manufactured by Sanyo Fine Co., Ltd. under our license agreement and accompanying purchase orders with Nobelpharma Co., Ltd., and the drug product for SA-ER is manufactured by AAIPharma Services Corp., or AAIPharma, pursuant to our license agreement and accompanying purchase orders with AAIPharma. We do not currently have any other suppliers for the drug substance or drug product of our product candidates and, although we believe that there are alternate sources of supply that could satisfy our clinical and commercial requirements, we cannot 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 cGMP. These regulations govern manufacturing processes and procedures (including record keeping) and the implementation and operation of quality systems to control and assure the quality of investigational products and products approved for sale. Poor control of production processes can lead to the introduction of contaminants or to inadvertent changes in the properties or stability of our product candidates that may not be detectable in final product testing. We, our collaborators, or our contract manufacturers must supply all necessary documentation in support of an NDA, BLA, MAA, or other application for regulatory approval, on a timely basis and must adhere to GLP, cGMP, 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 trial of triheptanoin in LC-FAOD will enroll 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 at 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 do not 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 cGMP 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 of 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 B. Braun may be evaluating whether or not 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 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, none of the current intellectual property relating to rhGUS covers composition of matter, and 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 rhGUS and/or rhPPCA, subject to any regulatory exclusivities. With respect to triheptanoin, although some of the patents relating to triheptanoin cover aspects of composition of matter, it is possible that a competitor could develop the same or similar molecule. 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 our other product candidates for which we have not conducted freedom to operate analyses. 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 Biologics Price Competition and Innovation Act of 2009 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. This data exclusivity 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 Biologics Price Competition and Innovation Act of 2009 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 trials, 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 European Union, 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 a life-threatening or chronically debilitating condition affecting not more than five in 10,000 persons in the European Union. 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 European Union would be sufficient to justify the necessary investment in developing the drug or biological product or where there is 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 trial 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 European Union, 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 KRN23 in the United States, and 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. 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, 2013, we had 59 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 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 Securities and Exchange Commission, or 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 our current 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 will be required to perform system and process evaluation and testing of our internal controls over financial reporting to allow management to report, commencing in our annual report on Form 10-K for the year ending December 31, 2014, on the effectiveness of our internal controls over financial reporting, if then 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 Patient Protection and 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;
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;
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;
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 plan to maintain sales representatives and conduct physician and patient association outreach activities, as well as clinical trials, outside of the United States. 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. We priced our initial public offering at $21.00 per share on January 30, 2014 and, since then, our common stock has reached a high of $69.77 per share. 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 14, 2014, our executive officers, directors, five percent stockholders, and their affiliates beneficially owned approximately 48% 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 emerging growth company 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 as of the following calendar year-end. 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 lock-up and other legal restrictions on resale discussed in this report lapse, the market price of our common stock could decline. As of March 14, 2014, we had a total of 30,035,894 shares of common stock issued and outstanding. After the lock-up agreements pertaining to our initial public offering expire on July 29, 2014, up to an additional 23.4 million shares of common stock will be eligible for sale in the public market, of which approximately 9.3 million shares are held by directors, executive officers and other affiliates and will be subject to the manner of sale, volume limitations, and public reporting requirements of Rule 144 under the Securities Act of 1933, as amended, or the Securities Act. J.P. Morgan Securities LLC and Morgan Stanley & Co. LLC, however, may, in their sole discretion, permit our officers, directors, and other stockholders who are subject to these lock-up agreements to sell shares prior to the expiration of the lock-up agreements.

In addition, as of March 14, 2014, approximately 5.5 million shares of common stock that are either subject to outstanding options, reserved for future issuance under our equity incentive plans, 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, the lock-up agreements, 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.

The holders of approximately 19.6 million shares of our common stock, or 20.0 million including the shares underlying outstanding warrants, will be entitled to rights with respect to the registration of their shares under the Securities Act, subject to the lock-up agreements described above. Registration of these shares under the Securities Act would result in the shares becoming freely tradable without restriction under the Securities Act, except for shares purchased by affiliates. Any sales of securities by these stockholders could have a material adverse effect on the market price of our common stock.

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 (beginning January 1, 2015) of each year 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. We may experience ownership changes in the future as a result of subsequent shifts in our stock ownership. As a result, if we earn net taxable income, 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 shall commence on May 1, 2014 and expire on April 30, 2019. The rental term for the current space shall also now 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, which expires in September 2014.

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 table sets 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 14, 2014.

	Fiscal 2014	
	High	Low
First Quarter (January 31, 2014 through March 14, 2014)	$69.77	$35.15

As of March 14, 2014, we had approximately 62 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. We have not paid any dividends on our common stock since our inception and do not expect to pay dividends on our common stock in the foreseeable future.

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

In the three years preceding the filing of this Annual Report on Form 10-K, we or our California corporation predecessor have issued the following securities that were not registered under the Securities Act. Issuances made prior to June 2011 were made by Ultragenyx Pharmaceutical Inc., a California corporation. The share numbers under the heading “Common Stock Purchase Agreements” below reflect (i) that, in connection with our reincorporation from California to Delaware in June 2011, each outstanding share of common stock was converted into 80 shares of the new Delaware corporation and (ii) the 1-for-3.1345 reverse stock split we implemented on January 17, 2014.

Common Stock Purchase Agreements

On February 11, 2011, we issued 26,288 shares of common stock for consideration of $0.00039 per share, for an aggregate purchase price of $10.30 to William E. Aliski. Mr. Aliski is one of our directors.

On February 28, 2011, we issued 26,288 shares of common stock for consideration of $0.00039 per share, for an aggregate purchase price of $10.30 to Jonathan K. Wright.

On March 11, 2011, we issued 42,545 shares of common stock for consideration of $0.00039 per share, for an aggregate purchase price of $16.67 to William E. Aliski. Mr. Aliski is one of our directors.

On March 28, 2011, we issued 26,288 shares of common stock for consideration of $0.0039 per share, for an aggregate purchase price of $103.00 to Steven Jungles. Mr. Jungles is our Senior Vice President, Technical Operations.

On April 6, 2011, we issued 288,403 shares of common stock for consideration of $0.00039 per share, for an aggregate purchase price of $113.00 to John Klock.

We claimed exemption from registration under the Securities Act for the sale and issuance of these shares of common stock by virtue of Section 4(a)(2) and/or Regulation D promulgated thereunder as transactions not involving any public offering. All of the purchasers of the shares of common stock for which we relied on Section 4(a)(2) and/or Regulation D represented that they were accredited investors as defined under the Securities Act. We claimed such exemption on the basis that (a) the purchasers in each case represented that they intended to acquire the securities for investment only and not with a view to the distribution thereof and that they either received adequate information about the registrant or had access, through employment or other relationships, to such information and (b) appropriate legends were affixed to the stock certificates issued in such transactions.

Convertible Notes and Series A Convertible Preferred Stock Warrants

On February 15, 2011, we entered into a Note and Warrant Purchase Agreement with the John and Cynthia Klock Trust. Pursuant to the Note and Warrant Purchase Agreement, we issued a convertible promissory note in the amount of $1.5 million to the John and Cynthia Klock Trust and also issued to the trust a warrant to purchase up to 507,786 shares of our Series A convertible preferred stock. In connection with dividends that were paid in shares of Series A convertible preferred stock in August 2012 and December 2012, the number of shares of Series A convertible preferred stock issuable upon exercise of this warrant was increased to 547,445 shares of Series A convertible preferred stock. In connection with the automatic conversion of the Series A convertible preferred stock into common stock upon the closing of our initial public offering, this warrant is currently exercisable for 174,651 shares of common stock.

On February 23, 2011, we entered into a Note and Warrant Purchase Agreement with William Aliski, one of our directors. Pursuant to the Note and Warrant Purchase Agreement, we issued a convertible promissory note in the amount of $250,000 to Mr. Aliski and also issued him a warrant to purchase up to 84,631 shares of our Series A convertible preferred stock. In connection with dividends that were paid in shares of Series A convertible preferred stock in August 2012 and December 2012, the number of shares of Series A convertible preferred stock issuable upon exercise of this warrant was increased to 91,241 shares of Series A convertible preferred stock. In connection with the automatic conversion of the Series A convertible preferred stock into common stock upon the closing of our initial public offering, this warrant is currently exercisable for 29,108 shares of common stock.

On June 14, 2011, we entered into a Note and Warrant Purchase Agreement with Emil D. Kakkis, our President and Chief Executive Officer and one of our directors. Pursuant to the Note and Warrant Purchase Agreement, we issued a convertible promissory note in the amount of $300,000 to Dr. Kakkis and also issued him a warrant to purchase up to 72,541 shares of our Series A convertible preferred stock. In connection with dividends that were paid in shares of Series A convertible preferred stock in August 2012 and December 2012, the number of shares of Series A convertible preferred stock issuable upon exercise of this warrant was increased to 78,206 shares of Series A convertible preferred stock. In connection with the automatic conversion of the Series A convertible preferred stock into common stock upon the closing of our initial public offering, this warrant is currently exercisable for 24,950 shares of common stock.

On June 14, 2011, we entered into a second Note and Warrant Purchase Agreement with Emil D. Kakkis, our President and Chief Executive Officer and one of our directors. Pursuant to the Note and Warrant Purchase Agreement, we issued a convertible promissory note in the amount of $500,000 to Dr. Kakkis and also issued him a warrant to purchase up to 120,901 shares of our Series A convertible preferred stock. In connection with dividends that were paid in shares of Series A convertible preferred stock in August 2012 and December 2012, the number of shares of Series A convertible preferred stock issuable upon exercise of this warrant was increased to 130,344 shares of Series A convertible preferred stock. In connection with the automatic conversion of the Series A convertible preferred stock into common stock upon the closing of our initial public offering, this warrant is currently exercisable for 41,583 shares of common stock.

We claimed exemption from registration under the Securities Act for the sale and issuance of these securities by virtue of Section 4(a)(2) and/or Regulation D promulgated thereunder as transactions not involving any public offering. All of the purchasers of unregistered securities for which we relied on Section 4(a)(2) and/or Regulation D represented that they were accredited investors as defined under the Securities Act. We claimed such exemption on the basis that (a) the purchasers in each case represented that they

intended to acquire the securities for investment only and not with a view to the distribution thereof and that they either received adequate information about the registrant or had access, through employment or other relationships, to such information and (b) appropriate legends were affixed to the stock certificates issued in such transactions.

Series A Convertible Preferred Stock Financing

On June 16, 2011, we sold an aggregate of 18,052,464 shares of our Series A convertible preferred stock to eight investors at a purchase price of $1.034 per share, for an aggregate purchase price of approximately $15.0 million in cash and $3.7 million in converted bridge notes. On July 16, 2012, we sold, pursuant to a second tranche closing, an aggregate of 14,604,895 shares of our Series A convertible preferred stock to six investors at a purchase price of $1.034 per share, for an aggregate purchase price of $15.1 million in cash. We claimed exemption from registration under the Securities Act for the sale and issuance of these securities by virtue of Section 4(a)(2) and/or Regulation D promulgated thereunder as transactions not involving any public offering. All of the purchasers of unregistered securities for which we relied on Section 4(a)(2) and/or Regulation D represented that they were accredited investors as defined under the Securities Act. We claimed such exemption on the basis that (a) the purchasers in each case represented that they intended to acquire the securities for investment only and not with a view to the distribution thereof and that they either received adequate information about the registrant or had access, through employment or other relationships, to such information and (b) appropriate legends were affixed to the stock certificates issued in such transactions.

Series A Paid-in-Kind Dividends

On August 16, 2012, we issued an aggregate of 1,193,088 shares of our Series A convertible preferred stock to holders of our Series A convertible preferred stock in accordance with Article IV.B.1.(a) of our Certificate of Incorporation that was filed with the Secretary of State of the State of Delaware on June 13, 2011. We claimed exemption from registration under the Securities Act for the sale and issuance of these securities by virtue of Section 4(a)(2) and/or Regulation D promulgated thereunder as transactions not involving any public offering.

On December 14, 2012, we issued an aggregate of 499,447 shares of our Series A convertible preferred stock to holders of our Series A convertible preferred stock in accordance with Article IV.B.1.(a) of our Certificate of Incorporation that was filed with the Secretary of State of the State of Delaware on June 13, 2011. We claimed exemption from registration under the Securities Act for the sale and issuance of these securities by virtue of Section 4(a)(2) and/or Regulation D promulgated thereunder as transactions not involving any public offering.

Series B Convertible Preferred Stock Financing

On December 18, 2012, we sold an aggregate of 27,081,680 shares of our Series B convertible preferred stock to 34 investors at a purchase price of $2.7694 per share, for an aggregate purchase price of approximately $75 million in cash. We claimed exemption from registration under the Securities Act for the sale and issuance of these securities by virtue of Section 4(a)(2) and/or Regulation D promulgated thereunder as transactions not involving any public offering. All of the purchasers of unregistered securities for which we relied on Section 4(a)(2) and/or Regulation D represented that they were accredited investors as defined under the Securities Act. We claimed such exemption on the basis that (a) the purchasers in each case represented that they intended to acquire the securities for investment only and not with a view to the distribution thereof and that they either received adequate information about the registrant or had access, through employment or other relationships, to such information and (b) appropriate legends were affixed to the stock certificates issued in such transactions.

Stock Options

From November 17, 2011 through December 31, 2013, we granted stock options to employees under our 2011 Equity Incentive Plan, as amended, covering an aggregate of 3,218,659 shares of common stock, at a weighted-average average exercise price of $2.55 per share. Of these, options covering an aggregate of 262,134 shares were cancelled without being exercised and we sold an aggregate of 727,682 shares of common stock to employees for cash consideration in the aggregate amount of $0.3 million upon the exercise of stock options.

We claimed exemption from registration under the Securities Act for these sales and issuances under Section 4(a)(2) of the Securities Act in that such sales and issuances did not involve a public offering or under Rule 701 promulgated under the Securities Act, in that they were offered and sold either pursuant to written compensatory plans or pursuant to a written contract relating to compensation, as provided by Rule 701.

Issuer’s Purchases of Equity Securities

None

Item 6. Selected Financial Data

The selected statements of operations data for the years ended December 31, 2011, 2012 and 2013 and the selected balance sheet data as of December 31, 2011, 2012 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,		
	2011	2012	2013
	(in thousands, except share and per share amounts)		
Statements of Operations Data:			
Operating expenses:			
Research and development	$4,717	$12,641	$27,829
General and administrative	1,844	3,344	4,451
Total operating expenses	6,561	15,985	32,280
Loss from operations	(6,561)	(15,985)	(32,280)
Interest income	4	1	216
Interest expense	(270)	-	-
Other expense	(22)	(350)	(3,006)
Net loss	$(6,849)	$(16,334)	$(35,070)
Net loss attributable to common stockholders[(1)]	$(7,466)	$(19,561)	$(50,289)
Net loss per share attributable to common stockholders, basic and diluted	$(4.62)	$(14.20)	$(14.87)
Shares used to compute net loss per share attributable to common stockholders, basic and diluted	1,617,384	1,377,207	3,382,489

(1) See Notes 2 and 15 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,		
	2011	2012	2013
	(in thousands)		
Balance Sheets Data:			
Cash, cash equivalents and short-term investments	$10,645	$86,190	$53,377
Working capital	9,954	83,257	49,304
Total assets	12,129	88,316	59,649
Convertible preferred stock warrant liability	216	518	3,419
Convertible preferred stock	18,604	111,387	124,930
Deficit accumulated during the development stage	(8,155)	(27,058)	(74,836)
Total stockholders' deficit	(7,961)	(27,047)	(74,821)

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 wel 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 development-stage biopharmaceutical company focused on the identification, acquisition, development, and commercialization of novel products for the treatment of rare and ultra-rare diseases, with an initial focus on serious, debilitating metabolic genetic diseases. We focus on diseases for which the unmet medical need is high, the biology for treatment is clear, and for which there are no approved therapies. Since our inception in 2010, we have in-licensed potential treatments for five different diseases that are currently in or have completed Phase 1/2 or Phase 2 clinical studies. 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 X-linked hypophosphatemia, or XLH, a rare genetic disease that impairs bone growth. We are developing KRN23 pursuant to our collaboration with Kyowa Hakko Kirin Co., Ltd., or KHK. KHK has completed one Phase 1 study, one Phase 1/2 study, and one Phase 1/2 extension study of KRN23 in adults with XLH. We plan to initiate a Phase 2 pediatric study in 2014. We also expect to continue the clinical development of KRN23 in adults with XLH.
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 1/2 clinical study in MPS 7 in December 2013.
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 plan to continue preclinical development of rhPPCA during 2014.
Our substrate replacement therapy pipeline includes the following product candidates in development for three diseases:

Triheptanoin, or UX007, is synthetic oil with a specifically designed chemical composition being studied in an international open-label Phase 2 study for the treatment of long-chain fatty acid oxidation disorders, or LC-FAOD. This 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 glucose transporter type-1 deficiency syndrome, or Glut1 DS, a rare metabolic disease of brain energy deficiency that is characterized by seizures, developmental delay, and movement disorder. In addition,
SA-ER, or UX001, is an extended-release form of sialic acid in a Phase 2 extension study for the treatment of hereditary inclusion body myopathy, or HIBM, a neuromuscular disorder that causes muscle weakness and wasting. We reported 24-week data from our completed Phase 2 study in HIBM in July 2013 and reported top-line 48-week data in December 2013. We continue to treat the patients from the Phase 2 study in an extension study and anticipate that data from the extension study will be available in late 2014.
We are considered a development-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 $6.8 million, $16.3 million and $35.1 million for the years ended December 31, 2011, 2012, and 2013. As of December 31, 2013 we had incurred cumulative net losses of $59.6 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 revenue from any product candidates that we develop until we obtain regulatory approval 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.

Interest expense

Interest expense consists of interest on outstanding borrowings under convertible promissory notes. We had no outstanding debt as of December 31, 2011 and thereafter as our convertible promissory notes and related accrued interest were converted into shares of Series A convertible preferred stock in 2011.

Other expense

Other expense primarily consists of gains and losses resulting from the remeasurement of our convertible preferred stock warrant liability. We have 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 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. To date, there have been no material differences from our accrued estimated expenses to the actual clinical trial expenses.

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.

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. We will continue to apply this process until a sufficient amount of historical information regarding the volatility of our own stock price becomes available.

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.

For the years ended December 31, 2011, 2012, and 2013 stock-based compensation expense was $0.3 million, $0.9 million and $0.7 million, respectively. As of December 31, 2013, we had $4.8 million of total unrecognized stock-based compensation costs, net of estimated forfeitures, which we expect to recognize over a weighted-average period of 2.7 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, 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 price on the option grant date.

Contemporaneous Valuations

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 to assist our board of directors in estimating the fair value of our common stock at subsequent grant dates.

June 2012 and December 2012 Contemporaneous Valuations. The June 2012 and December 2012 valuations used the Back-Solve Method of the option-pricing method, or OPM, which derives the implied equity value for one type of equity security from a contemporaneous transaction involving another equity security. The June 2012 valuation, which was completed in July 2012, was based on the price of Series A convertible preferred stock that we sold to investors in July 2012. The December 2012 valuation was based on the price of Series B convertible preferred stock that we sold in December 2012. In both valuations, the contemporaneous transaction occurred in close proximity and involved third-party investors. Given the arm's-length nature of these financings, the close proximity of the Series A and Series B convertible preferred stock financings to the respective valuation dates, and the fair value hierarchy as described in FASB Accounting Standards Codification Topic 820, Fair Value, we believe the per share issuance prices of the Series A and Series B convertible preferred stock provide an indication of our equity value, as well as the fair value of common stock, as of June 30, 2012 and December 31, 2012, respectively.

The OPM treats common stock and preferred stock as call options on the total equity value of a company, with exercise prices based on the liquidation preference of the preferred stock. Under this method, the common stock has value only if the funds available for distribution to the stockholders exceed the value of the liquidation preference at the time of a liquidity event such as a merger, sale, or IPO, assuming the enterprise has funds available to make a liquidation preference meaningful and collectible by the stockholders. The common stock is modeled as a call option on the underlying equity value at a predetermined exercise price. In the model, the exercise price is based on a comparison with the total equity value, rather than, as in the case of a regular call option, a comparison with a per share stock price. The OPM uses the Black-Scholes option-pricing model to price the call option. This model defines the securities' fair values as functions of the current fair value of a company and uses assumptions such as the anticipated timing of a potential liquidity event and the estimated volatility of the equity securities.

For purposes of the June 2012 valuation, we estimated the time to liquidity as 1.5 years based on then-current plans and estimates of our board of directors and management regarding a liquidity event. The volatility assumption was based on an analysis of guideline companies' historical equity volatility factors for a period of 1.5 years, which is the term assumption. Based on this analysis of the guideline companies, a volatility assumption of 67% was selected and utilized. The risk-free rate was estimated as the interpolated 1.5 year U.S. Treasury yield. A discount for lack of marketability of 31% was then applied to the value indicated in our common stock. Based on these factors, the third party valuation concluded that our common stock had an estimated fair value of $0.81 per share as of June 30, 2012.

For purposes of the December 2012 valuation, we estimated the time to liquidity as 2.0 years based on then-current plans and estimates of our board of directors and management regarding a liquidity event. The time to liquidity increased from 1.5 years from June 2012 to 2.0 years in December 2012 due to the completion of the Series B convertible preferred stock financing in December 2012, which provided us with the funds to be able to have a liquidity event at a later date. The volatility assumption was based on an analysis of guideline companies' historical equity volatility factors for a period of 2.0 years, which is the term assumption. Based on this analysis of the guideline companies, a volatility assumption of 75% was selected and utilized. The risk-free rate was estimated as the interpolated 2.0 year U.S. Treasury yield. A discount for lack of marketability of 40% was then applied to the value indicated in our common stock. Based on these factors, the third-party valuation concluded that our common stock had an estimated fair value of $1.82 per share as of December 31, 2012.

June 2013 Contemporaneous Valuation. For purposes of the June 2013 valuation, a hybrid method was used to determine our equity value, which is a hybrid between the probability-weighted return methodology, or PWERM, and the OPM. The PWERM is a scenario-based analysis that estimates the value per share based on the probability-weighted present value of expected future investment returns, considering each of the possible outcomes available to us, as well as the economic and control rights of each share class. In the hybrid method, the OPM is used to estimate the allocation of value within one or more of PWERM scenarios. The hybrid method can be a useful alternative to explicitly modeling all PWERM scenarios in situations when the company has transparency into one or more near-term exits but is unsure about what will occur if the current plans fall through. The hybrid model was selected at this time for the reasons described below relating to our plans for a potential IPO.

The OPM was used to allocate the equity value to the various securities under two scenarios. The first scenario assumed we would complete an IPO within 12 months and the second scenario assumed we would remain private beyond 12 months with a potential sale or merger in 2.0 years. The estimated time to liquidity was 1.0 year and 2.0 years based on timing of a liquidity event in the two scenarios. Based on an analysis of the guideline companies, a volatility assumption of 75% was selected and utilized for both scenarios. The risk-free rate was estimated based on the applicable U.S. Treasury yield. A discount for lack of marketability of 20% and 35% was applied to the value indicated in our common stock under the first scenario and the second scenario, respectively. As of June 30, 2013 our board of directors had not authorized our management to begin preparations for a potential IPO. The board made this decision in late July, and that is when we initiated our preparation process. The increased probability of an IPO was

retroactively taken into consideration in the June 30, 2013 valuation, which is a critical factor contributing to the increase in the fair value of our common stock as of that date. Based on these factors, the third-party valuation concluded that our common stock had an estimated fair value of $4.07 per share as of June 30, 2013.

September 2013 Contemporaneous Valuation. For purposes of the September 2013 valuation, a hybrid method was used to determine our equity value, which is consistent with the method used in the June 2013 valuation.

The OPM was used to allocate the equity value to the various securities under two scenarios. The first scenario assumed we would complete an IPO within six months and the second scenario assumed we would remain private beyond 12 months with a potential sale or merger in 1.5 years. We estimated a probability of 60% for the first scenario and 40% for the second scenario compared to a 50% weighting for each in the June 2013 valuation. The increase in the probability of an IPO was because, at the July 2013 meeting of our board of directors, preparations for a potential IPO were authorized, we subsequently selected a banking syndicate, and on September 6, 2013 an organizational meeting was held in order to begin the IPO process. The estimated time to liquidity was six months and 1.5 years based on timing of a liquidity event in the two scenarios. Based on an analysis of the guideline companies, a volatility assumption of 75% was selected and utilized for both scenarios. The risk-free rate was estimated based on the applicable U.S. Treasury yield. A discount for lack of marketability of 10% and 30% was applied to the value indicated in our common stock under the first scenario and the second scenario, respectively. In addition, in July 2013, we announced that we would initiate development of triheptanoin for a new indication, Glut1 DS, which was incorporated into the valuation. In August 2013, we entered into a collaboration agreement with KHK, which was also incorporated into the valuation. Based on these factors, the third-party valuation concluded that our common stock had an estimated fair value of $6.86 per share as of September 30, 2013.

November 2013 Contemporaneous Valuation. For purposes of the November 2013 valuation, a hybrid method was used to determine our equity value, which is consistent with the method used in the June 2013 and September 2013 valuations.

The OPM was used to allocate the equity value to the various securities under two scenarios. The first scenario assumed we would complete an IPO within three months and the second scenario assumed we would remain private beyond 12 months with a potential sale or merger in 1.5 years. We estimated a probability of 75% for the first scenario and 25% for the second scenario compared to 60% and 40%, respectively, in the September 2013 valuation. The increase in the probability of an IPO was due to the progress we have made since September 2013 in preparing for a potential IPO and in our development programs. In December 2013, we announced the dosing of the first patient in a Phase 1/2 study of rhGUS for MPS 7, our IND for triheptanoin for the treatment of Glut1 DS went into effect, and we released topline results from a 48-week Phase 2 clinical study of SA-ER showing apparent activity at the higher dose level. These developments were anticipated and taken into consideration in the November 2013 valuation. The estimated time to liquidity was three months and 1.5 years based on timing of a liquidity event in the two scenarios. Based on an analysis of the guideline companies, a volatility assumption of 70% was selected and utilized for both scenarios. The risk-free rate was estimated based on the applicable U.S. Treasury yield. A discount for lack of marketability of 5% and 30% was applied to the value indicated in our common stock under the first scenario and the second scenario, respectively. Based on these factors, the third-party valuation concluded that our common stock had an estimated fair value of $11.19 per share as of November 30, 2013.

December 2013 Value. For purposes of the December 31, 2013 estimated value of our common stock, we evaluated a number of qualitative and quantitative factors including the increase in the probability of an IPO due to progress in our development programs that was made since November 30, 2013 and the decrease in the estimated time to liquidity. Based on these factors, we concluded that our common stock had an estimated fair value of $12.14 per share as of December 31, 2013 for purposes of determining stock-based compensation disclosures.

Stock Option Grants

Information regarding our stock option grants along with the estimated fair value per share of the underlying common stock, for stock options granted since January 1, 2012 is summarized in the table below:

Grant date	Number of common shares underlying options granted	Exercise price per common share	Estimated fair value per share of common stock
August 2, 2012	451,425	$ 0.81	$ 0.81
September 13, 2012	28,712	0.81	0.81
October 25, 2012	19,141	0.81	0.81
March 21, 2013	82,944	1.82	1.82
April 25, 2013	79,757	1.82	1.82
May 23, 2013	285,530	1.82	1.82
August 15, 2013	54,234	4.07	4.07
November 1, 2013	519,683	6.86	6.86
December 19, 2013	245,649	$ 11.19	$ 11.19

The intrinsic value of all outstanding options as of December 31, 2013 was $19.5 million.

The estimated fair value per share of the common stock in the table above represents the determination by our board of directors of the fair value of our common stock as of the date of the grant, as discussed below.

Stock Options Granted in August, September, and October 2012. Our board of directors granted stock options on August 2, 2012, September 13, 2012, and October 25, 2012, each having an exercise price of $0.81 per share. In establishing this exercise price, our board of directors considered input from management, the results of our June 30, 2012 third-party valuation, and the objective and subjective criteria discussed above, as well as the following: (i) in September 2012, we obtained the rights to rhPPCA and in-licensed North American rights to triheptanoin; (ii) triheptanoin had primarily been studied in academic settings with data available only from uncontrolled clinical studies or in anecdotal form; and (iii) rhPPCA has only ever been studied in mice and in vitro, and we have made very limited investments in the development of this compound to date. As each of these compounds was speculative, early stage, and would require significant funds and risk on our part to advance, our board of directors did not believe that these events increased our equity value.

In the judgment of our board of directors, there were no internal or external developments that would indicate that the fair value of our common stock would have increased from June 30, 2012. As a result, our board of directors concluded that the fair value of our common stock at each of these grant dates was $0.81 per share.

Stock Options Granted in March, April, and May 2013. Our board of directors granted stock options on March 21, 2013, April 25, 2013, and May 23, 2013, each having an exercise price of $1.82 per share. In establishing this exercise price, our board of directors considered input from management, the results of our December 31, 2012 third-party valuation, the objective and subjective criteria discussed above as well as the following: (i) a toxicology study for rhGUS, a retrospective study for triheptanoin, and the Phase 2 study for SA-ER were all ongoing during this time period, but no results had yet been generated; and (ii) these studies were all either underway or already contemplated at the time of the financing upon which the December 31, 2012 valuation was based. Given the lack of clarity around a future liquidity event, and the lack of any significant clinical data in the first five months of 2013, in the judgment of our board of directors, there were no internal or external developments that would indicate that the fair value of our common stock had increased from December 31, 2012. As a result, our board of directors concluded that the fair value of our common stock at each of these grant dates was $1.82 per share.

Stock Options Granted in August 2013. Our board of directors granted stock options on August 15, 2013, each having an exercise price of $4.07 per share. In establishing this exercise price, our board of directors considered input from management, the results of our June 30, 2013 third-party valuation, the objective and subjective criteria discussed above as well as the following: (i) the probability of an IPO was already taken into consideration in the June 30, 2013 valuation and there was no change in probability as of August 15, 2013; (ii) the interim analysis of the 24-week data in our study of SA-ER showed only modest efficacy; (iii) although we had announced development of triheptanoin for Glut1 DS between June 30, 2013 and August 15, 2013, no clinical development activity had yet commenced as of the latter date; and (iv) our acquisition of ex-U.S. rights to triheptanoin, which was announced in July 2013, was already taken into consideration in the valuation as of June 30, 2013. As a result, our board of directors concluded that the fair value of our common stock at this grant date was $4.07 per share.

Stock Options Granted in November 2013. Our board of directors granted stock options on November 1, 2013, each having an exercise price of $6.86 per share. In establishing this exercise price, our board of directors considered input from management, the results of our September 30, 2013 third-party valuation, and the objective and subjective criteria discussed above. The board of directors considered the increase in the probability of an IPO from 50% as of June 30, 2013 to 60% as of September 30, 2013 and also concluded that no further change in this probability had taken place as of November 1, 2013. In the judgment of our board of directors, there were no internal or external developments that would indicate the fair value of our common stock would have increased from September 30, 2013. As a result, our board of directors concluded that the fair value of our common stock at this grant date was $6.86 per share.

Stock Options Granted in December 2013. Our board of directors granted stock options on December 19, 2013, each having an exercise price of $11.19 per share. In establishing this exercise price, our board of directors considered input from management, the results of our November 30, 2013 third-party valuation, and the objective and subjective criteria discussed above. The board of directors considered the increase in the probability of an IPO from 60% as of September 30, 2013 to 75% as of November 30, 2013 and also determined that there were no internal or external developments that would indicate the fair value of our common stock would have increased from November 30, 2013, as all developments in December had been anticipated and taken into consideration at that date. As a result, our board of directors concluded that the fair value of our common stock at this grant date was $11.19 per share.

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, 2013, our total deferred tax assets were $25.5 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 Review 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, 2012 and 2013

Research and Development Expenses (dollars in thousands)

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

*not meaningful

Research and development expenses increased $15.2 million for the twelve months 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 preclinical and research costs for various other potential product candidates.

General and Administrative Expenses (dollars in thousands)

	Year Ended December 31,		Dollar	%
	2012	2013	Change	Change
General and administrative	$3,344	$4,451	$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	%
	2012	2013	Change	Change
Interest income	$ 1	$ 216	$ 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	%
	2012	2013	Change	Change
Other expense, net	$350	$3,006	$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.

Comparison of Years Ended December 31, 2011 and 2012

Research and Development Expenses (dollars in thousands)

	Year Ended December 31,		Dollar	%
	2011	2012	Change	Change
Development candidate:				
rhGUS	$438	$3,198	$2,760	630%
rhPPCA	7	172	165	2357%
Triheptanoin (LC-FAOD)	-	546	546	*
Triheptanoin (Glut 1 DS)	-	-	-	*
SA-ER	3,570	6,840	3,270	92%
Preclinical and other research costs	702	1,885	1,183	169%
Total research and development expenses	$4,717	$12,641	$7,924	168%

*not meaningful

Research and development expenses increased $7.9 million, or 168%, for the year ended December 31, 2012 compared to the same period in 2011.

The increase in research and development expenses above is primarily due to:

for rhGUS, an increase of $2.8 million related to the development and manufacturing costs associated with supplying rhGUS for our various clinical studies;
for triheptanoin, an increase of $0.5 million related to the increase in clinical activities, as well as $0.3 million paid to BRI to license the rights to triheptanoin;
for SA-ER, an increase of $3.3 million related to the development and manufacturing costs for our various clinical studies, increase in personnel costs, and the costs for our Phase 2 clinical study; and
an increase of $1.2 million in preclinical and other research costs for various other potential product candidates.

General and Administrative Expenses (dollars in thousands)

	Year Ended December 31,		Dollar	%
	2011	2012	Change	Change
General and administrative	$1,844	$3,344	$1,500	81%

General and administrative expenses increased $1.5 million for the year ended December 31, 2012 compared to the same period in 2011. 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	%
	2011	2012	Change	Change
Interest income	$ 4	$ 1	$ (3)	-75%

There was no significant change in interest income for the year ended December 31, 2012 compared to the same period in 2011.

Interest Expense (dollars in thousands)

	Year Ended December 31, 2011	2012	Dollar Change	% Change
Interest expense	$ 270	$ -	$ (270)	-100%

Interest expense decreased $0.3 million for the year ended December 31, 2012 compared to the same period in 2011. The decrease is due to the conversion of the outstanding convertible promissory notes and related accrued interest into shares of our Series A convertible preferred stock in June 2011.

Other Expense, net (dollars in thousands)

	Year Ended December 31, 2011	2012	Dollar Change	% Change
Other expense, net	$ 22	$ 350	$ 328	1491%

Other expense, net increased $0.3 million for the year ended December 31, 2012 compared to the same period in 2011. This was primarily due to the $0.3 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. As of December 31, 2013, we had $53.4 million in available cash, cash equivalents, and short-term investments and had incurred cumulative net losses of $59.6 million. Our cash, cash equivalents and short-term investments are held in a variety of interest-bearing accounts, including corporate debt securities and money market accounts. Cash in excess of immediate requirements is invested with a view toward liquidity and capital preservation, and we seek to minimize the potential effects of concentration and credit risk.

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 its common stock were declared effective by the 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 paid to the preferred stockholders, 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. In addition all of our outstanding warrants that were exercisable to purchase shares convertible preferred stock became exercisable to purchase shares of our common stock. The warrants will no longer be subject to remeasurement and were reclassified from a liability to permanent equity.

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

	Year Ended December 31,		
	2011	2012	2013
Cash used in operating activities	$(5,825)	$(12,504)	$(31,200)
Cash used in investing activities	(924)	(1,191)	(47,734)
Cash provided by financing activities	17,329	89,240	171
Net increase (decrease) in cash and cash equivalents	$10,580	$75,545	$(78,763)

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, 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 operating activities for the year ended December 31, 2011 was $5.8 million and reflected a net loss of $6.8 million, offset by non-cash charges of $0.3 million for interest expense related to the convertible promissory notes and $0.3 million for stock-based compensation. Cash used in operating activities also reflected an increase in accounts payable and accrued and other liabilities of $0.7 million as we continued to increase our research and development activities and the timing of payments made to our vendors, which was partially offset by an increase in prepaid expenses and other current assets of $0.2 million.

Cash Used in Investing Activities

Cash used in investing activities for the year ended December 31, 2013 was $47.7 million and 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 used in investing activities for the year ended December 31, 2011 was $0.9 million and was related to purchases of property and equipment of $0.5 million and an increase in restricted cash of $0.4 million.

Cash Flows Provided by Financing Activities

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.

Cash provided by financing activities for the year ended December 31, 2011 was $17.3 million and related to net proceeds from the issuance of $14.9 million of convertible preferred stock and $2.4 million of promissory notes.

Funding Requirements

We believe that our existing capital resources, including net proceeds we received from the closing of our IPO in February 2014, will be sufficient to meet to fund our current operations into 2016. 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, 2013 (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	$527	$1,330	$1,411	$241	$3,509

*—Includes additional lease payments under the lease amendment entered into in February 2014

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 February 2013, the Financial Accounting Standards Board issued Accounting Standards Update No. 2013-02, or ASU 2013-02, Reporting of Amounts Reclassified Out of Accumulated Other Comprehensive Income. ASU 2013-02 requires reporting and disclosure about changes in accumulated other comprehensive income balances and reclassifications out of accumulated other comprehensive income. We adopted this guidance as of January 1, 2013 on a prospective basis, and this adoption did not have an impact 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

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, 2013, we had cash, cash equivalents, and short-term investments totaling $53.4 million consisting of bank deposits, money market funds, 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, 2013. 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 does not include a report of management's assessment regarding internal control over financial reporting or an attestation report of the company's registered public accounting firm due to a transition period established by the rules of the Securities and Exchange Commission for newly public companies.

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, 2013, that has materially affected, or is reasonably likely to materially affect our internal control over financial reporting.

Item 9B. Other Information

On February 28, 2014, the Compensation Committee of the Board of Directors of the Company approved annual increases in the base salaries of our named executive officers, as set forth below and described in "Item 11. Executive Compensation."

Name	Title	New Salary
Emil D. Kakkis, M.D., Ph.D.	President and Chief Executive Officer	$ 500,000

Thomas Kassberg	Chief Business Officer and Senior Vice President	$	350,000
Shalini Sharp	Chief Financial Officer and Senior Vice President	$	350,000

Effective March 24, 2014, Theodore A. Huizenga, 43, who has served as our Corporate Controller since January 2014, was appointed our Principal Accounting Officer. Prior to joining us, Mr. Huizenga served as Controller of Crescendo Bioscience from August 2013 until January 2014. Prior to Crescendo Bioscience, Mr. Huizenga was employed by RDV Corporation, where he served as Director of Finance – Investment Group from January 2008 through December 2012 and as Corporate Controller from September 2003 through December 2007. Mr. Huizenga previously was a Manager in the Audit and Assurance Practice with PricewaterhouseCoopers LLP from January 1998 to September 2003. Mr. Huizenga has a B.S. in Accounting from Calvin College and is a Certified Public Accountant.

The Company did not enter into any material compensatory plan contract or arrangement, or any material amendment thereto, with Mr. Huizenga in connection with his appointment as Principal Accounting Officer. Mr. Huizenga is not a party to any transaction required to be disclosed pursuant to Item 404(a) of Regulation S-K.

On March 24, 2014, the amount of annual cash bonus awards for fiscal 2013 for our named executive officers became calculable, as set forth below and described in “Item 11. Executive Compensation.”

Name	Title	New Salary	
Emil D. Kakkis, M.D., Ph.D.	President and Chief Executive Officer	$	140,910
Thomas Kassberg	Chief Business Officer and Senior Vice President	$	114,345
Shalini Sharp	Chief Financial Officer and Senior Vice President	$	110,206

PART III

Item 10. Directors, Executive Officers and Corporate Governance

Information About Our Board of Directors

The number of directors currently authorized to serve on our Board is six, and the terms of office of the directors are divided into three classes: Class I, whose term will expire at the annual meeting of stockholders to be held in 2014; Class II, whose term will expire at the annual meeting of stockholders to be held in 2015; and Class III, whose term will expire at the annual meeting of stockholders to be held in 2016.

Certain information regarding each of our directors, including his age as of March 14, 2014, experience, qualifications, attributes and skills that led the Board of Directors (the "Board") to conclude that the individual should serve on the Board and his principal occupation and directorships during the past five years, is set forth below:

Name	Age	Position	Director Since	Year Current Term Expires	Current Director Class
Emil D. Kakkis, M.D., Ph.D.	53	President and Chief Executive Officer	2010	2014	I
Eran Nadav, Ph.D.	44	Chairman of the Board	2011	2015	II
William Aliski	66	Director	2011	2016	III
Matthew K. Fust	49	Director	2014	2016	III
Clay B. Siegall, Ph.D.	53	Director	2014	2015	II
Mårten Steen, M.D., Ph.D.	38	Director	2011	2014	I

Emil D. Kakkis, M.D., Ph.D. is our founder and has served as our President and Chief Executive Officer and as a member of our Board since inception in April 2010. Prior to Ultragenyx, Dr. Kakkis served from September 1998 to February 2009 in various executive capacities, and ultimately as Chief Medical Officer, at BioMarin Pharmaceutical Inc., a biopharmaceutical company. Dr. Kakkis also serves as President and Founder of EveryLife Foundation for Rare Diseases, a non-profit organization he started in 2009 to accelerate biotechnology innovation for rare diseases. Dr. Kakkis is board certified in both Pediatrics and Medical Genetics. He holds a B.A. in Biology from Pomona College and received combined M.D. and Ph.D. degrees from the UCLA School of Medicine's Medical Scientist Training Program where he received the Bogen prize for his research. We believe that Dr. Kakkis possesses specific expert knowledge of genetics and rare diseases that qualifies him to serve on our Board, including his leadership, management, and operational experience in the life sciences sector.

Eran Nadav, Ph.D. has served as a member of our Board since June 2011 and has served as our Chairman of the board since January 2012. Dr. Nadav is a Managing Director at TPG Biotech®, the life science venture investment arm of TPG, a global private investment firm. Dr. Nadav joined TPG in 2007 with a focus on global pharmaceuticals and biotechnology investments. Prior to TPG, Dr. Nadav served as Business Development Director at Eisai, a pharmaceutical company, from September 2003 to August 2007 and also as a manager at Johnson & Johnson Development Corporation, the venture capital arm of Johnson & Johnson, a healthcare company, from November 1999 until July 2002. Dr. Nadav served on the board of directors of Eden Springs Ltd., a European provider of

drinking water solutions for the workplace, from July 2010 until August 2011. Since June 2013 he has been serving on the board of directors of MacroGenics, Inc., a biopharmaceutical company. Dr. Nadav received a B.Sc. magna cum laude in Life Sciences, an M.Sc. magna cum laude and Ph.D. in Biochemistry, as well as an M.B.A., from Tel Aviv University. We believe that Dr. Nadav is qualified to serve on our Board due to his experience in the venture capital industry and his years of analyzing development opportunities in the life sciences sector.

William Aliski has served as a member of our Board since January 2011. Mr. Aliski served as a commercial consultant for early stage orphan disease companies, including Enobia Pharma, from September 2011 until March 2012. Before that, Mr. Aliski served as Senior Vice President and Chief Commercial Officer of FoldRx Pharmaceuticals, a rare disease company that is now a wholly-owned subsidiary of Pfizer Inc., from June 2009 until March 2011, as Director of Simon Kucher Partners, a global consulting firm, from January 2008 until June 2009 and as General Manager of BioMarin Europe at BioMarin Pharmaceuticals Inc. from December 2005 until January 2008. Mr. Aliski received a B.S. in Economics and a Master of Social Planning from Boston College and an M.P.A. from the Kennedy School of Government at Harvard University. We believe that Mr. Aliski is qualified to serve on our Board due to his extensive experience in the life sciences industry, membership of various boards of directors, and his leadership and management experience.

Matthew K. Fust has served as a member of our Board since January 2014. Mr. Fust served as Executive Vice President of Onyx Pharmaceuticals, Inc., a biopharmaceutical company, from January 2009 until January 2014. Onyx Pharmaceuticals, Inc. was acquired by Amgen, Inc. in October 2013. From May 2003 to December 2008, Mr. Fust served as Chief Financial Officer at Jazz Pharmaceuticals, Inc., a specialty pharmaceutical company. From 2002 to 2003, Mr. Fust served as Chief Financial Officer at Perlegen Sciences, a biopharmaceutical company. Previously, he was Senior Vice President and Chief Financial Officer at ALZA Corporation, a pharmaceutical company, where he was an executive from 1996 until 2002. From 1991 until 1996, Mr. Fust was a manager in the healthcare strategy practice at Andersen Consulting. Mr. Fust serves on the Board of Directors of Sunesis Pharmaceuticals, Inc. and

MacroGenics, Inc., both, biopharmaceutical companies. Mr. Fust received a B.A. from the University of Minnesota and an M.B.A. from the Stanford Graduate School of Business. We believe that Mr. Fust is qualified to serve on our Board due to his extensive experience in the life sciences industry, his leadership and management experience, and his service as a director of another public biopharmaceutical company.

Clay B. Siegall, Ph.D. has served as a member of our Board since January 2014. Dr. Siegall currently serves as President and Chief Executive Officer and Chairman of the Board of Seattle Genetics, Inc., a biotechnology company. Dr. Siegall co-founded Seattle Genetics in 1998. Prior to Seattle Genetics, Dr. Siegall worked for the Bristol-Myers Squibb Pharmaceutical Research Institute from 1991 to 1997 and the National Cancer Institute, National Institutes of Health from 1988 to 1991. In addition to Seattle Genetics, Dr. Siegall serves as a director of Alder BioPharmaceuticals, Inc., a privately-held biotechnology company and Mirna Therapeutics, Inc., a privately-held biotechnology company. Dr. Siegall received a B.S. in Zoology from the University of Maryland and a Ph.D. in Genetics from George Washington University. We believe that Dr. Siegall is qualified to serve on our Board due to his extensive experience in the life sciences industry and his leadership and management experience.

Mårten Steen, M.D., Ph.D. has served as a member of our Board since June 2011. Dr. Steen has served as a Partner at HealthCap, a private equity firm, since March 2010. Prior to HealthCap, Dr. Steen served as Associate Director at Merck Serono, a biopharmaceutical company, from February 2008 until March 2010. Dr. Steen received a B.Sc. in Business Administration, an M.D. and a Ph.D. in Clinical Chemistry from Lund University. We believe that Dr. Steen is qualified to serve on our Board due to his medical and scientific background as well as his experience in the venture capital industry.

Information About Our Executive Officers and Key Employees

The names of our executive officers and other key employees and their ages as of March 14, 2014 are set forth below. Officers are elected annually by the Board and hold office until their respective successors are qualified and appointed or until their earlier death, resignation, removal or disqualification.

Name	Age	Position
Executive Officers		
Emil D. Kakkis, M.D., Ph.D.	53	President and Chief Executive Officer, Director
Thomas Kassberg	53	Chief Business Officer and Senior Vice President
Shalini Sharp	39	Chief Financial Officer and Senior Vice President
Key Employees		
Steven Jungles	48	Senior Vice President, Technical Operations
Michael P. Cohrs, Ph. D.	52	Vice President of Quality
John Ditton	49	Vice President, Commercial Planning
Tony Koutsoukos, Ph.D.	53	Vice President, Biometrics
Cordelia Leonard, RAC	53	Vice President, Regulatory Affairs and Quality Assurance
Javier San Martin, M.D.	48	Vice President, Clinical Development
Vimal Srivastava	48	Vice President, Program Development
Michael Vellard, Ph.D.	52	Vice President, Research
Spencer Guthrie	38	Senior Director, Clinical Operations
Alison Skrinar, Ph.D.	44	Senior Director, Clinical Sciences
Theodore A. Huizenga	43	Corporate Controller and Principal Accounting Officer

Executive Officers

Biographical information for Dr. Kakkis is set forth above under the heading “Information About Our Board of Directors.”

Thomas Kassberg has served as our Chief Business Officer and Senior Vice President since November 2011. Prior to Ultragenyx, Mr. Kassberg worked as Vice President of Business Development at Corium International, Inc., a biotechnology company, from July 2010 until October 2011. Prior to his work at Corium International, Inc., Mr. Kassberg worked as an independent consultant in Corporate Development and Business Strategy and consulted with a number of companies from March 2009 to June 2010, including Corium International, Inc. and Rib-X Pharmaceuticals, Inc., a pharmaceutical company focused on the development of novel antibiotics. Before becoming a consultant, Mr. Kassberg worked at Proteolix, Inc., a biotechnology company subsequently acquired by Onyx Pharmaceuticals, from January 2008 until February 2009, where he served as Senior Vice President of Corporate Development. Mr. Kassberg holds a B.A. in Business Administration from Gustavus Adolphus College and an M.B.A. from Northwestern University.

Shalini Sharp has served as our Chief Financial Officer and Senior Vice President since May 2012. Prior to Ultragenyx, Ms. Sharp served in various executive capacities, and ultimately as Chief Financial Officer, of Agenus Inc., a biotechnology company, from August 2003 until May 2012. Prior to Agenus, Ms. Sharp held strategic planning and corporate finance roles and ultimately served as chief of staff to the chairman of the board at Elan Pharmaceuticals, a biotechnology company, from August 1998 to August 1999 and September 2001 to August 2003. Prior to Elan, Ms. Sharp was a management consultant at McKinsey & Company and an investment banker at Goldman Sachs, specializing in pharmaceuticals and medical devices. Ms. Sharp has also served as a board member of Agenus since May 2012. Ms. Sharp holds a B.A. and an M.B.A. from Harvard University.

Key Employees

Steven Jungles has served as our Senior Vice President, Technical Operations since August 2011. Prior to Ultragenyx, Mr. Jungles worked as Vice President, Supply Chain at BioMarin Pharmaceutical Inc., a biopharmaceutical company, from June 1999 to July 2011, was Associate Director of Operations at Harvard Gene Therapy Initiative from June 1997 until June 1999, and worked at Somatix Therapy Corporation, a research and development company in the field of gene therapy that was acquired by Cell Genesys, Inc., from March 1993 to May 1997. Mr. Jungles holds a B.S. in Biology from the University of Iowa.

Michael P. Cohrs, Ph.D. has served as our Vice President of Quality since December 2013 and is responsible for overseeing our GMP, GLP, GCP, and Clinical Assay departments. Prior to Ultragenyx, Dr. Cohrs served as Senior Director of Quality Assurance/Quality Control at Medicines 360, a pharmaceutical company, from October 2012 through November 2013 and previously served as the Director of Quality Assurance at Medicines 360 from September 2009 through October 2012. Prior to Medicines 360, Dr. Cohrs served as the Director of Quality Assurance at Sunesis Pharmaceuticals Inc., a pharmaceutical company, from June 2007 to June 2008. Dr. Cohrs has also held increasingly responsible positions at a number of large pharmaceutical and small start-up companies, first in Quality Control and then in Quality Assurance, including Aventis Behring, Genetics Institute, Chiron, and InterMune. Dr. Cohrs has also contributed to numerous regulatory submissions resulting in several product approvals in both the United States and Europe. Dr. Cohrs received his Ph.D. in Organic Chemistry from Washington University and an M.B.A. in International Business from the University of Chicago.

John Ditton has served as our Vice President, Commercial Planning since April 2011. Prior to Ultragenyx, Mr. Ditton was the Chief Operating Officer at EveryLife Foundation for Rare Diseases, from January 2009 to April 2011. Prior to working at the EveryLife Foundation, Mr. Ditton served as the Vice President of Marketing at Diamics, Inc., a maker of cancer diagnostics, from October 2006 to December 2008 and Director of Global Marketing at BioMarin Pharmaceutical Inc., a biopharmaceutical company, from March 2004 to March 2006. Mr. Ditton holds an M.B.A. from the University of Tasmania.

Tony Koutsoukos, Ph.D. has served as our Vice President of Biometrics since October 2013. Prior to Ultragenyx, Mr. Koutsoukos worked as Vice President of Biometrics at Allos Therapeutics, a biopharmaceutical company, from September 2007 to March 2013, which was acquired by Spectrum Pharmaceuticals. He was also Director of Biostatistics at Amgen Inc., a biotechnology company, from May 2002 to September 2007. Prior to Amgen, Mr. Koutsoukos spent three years at Quintiles, a contract research company, as a Director of Biostatistics. His experience also includes five years at the FDA, Center for Drugs Evaluation and Research (CDER) division and approximately four years at the National Cancer Institute, Biometric Research Branch, CTEP, DCT. Dr. Koutsoukos received his Ph.D. and M.A., both in Mathematical Statistics from the University of Maryland, College Park.

Cordelia Leonard has served as our Vice President, Regulatory Affairs and Quality Assurance since July 2011. Prior to Ultragenyx, Ms. Leonard was Senior Director, Regulatory Affairs at BioMarin Pharmaceutical Inc., a biopharmaceutical company, from October 2003 until July 2011. Prior to BioMarin, Ms. Leonard was the Manager,

Regulatory Affairs at Cerus Corporation, a biomedical products company, from May 1999 until October 2003. Ms. Leonard received bachelor degrees in Chemistry and Biological Science from the University of California, Irvine and holds both U.S. and EU Regulatory Affairs Certifications.

Javier San Martin, M.D. has served as our Vice President, Clinical Development since December 2013. Prior to Ultragenyx, Dr. San Martin served as Senior Vice President of Clinical Development at Alder Biopharmaceuticals Inc., a pharmaceutical company, from January 2012 through May 2013. Prior to Alder, Dr. San Martin served as Executive Director and Global Development Leader at Amgen, Inc., a biotechnology company, from March 2006 to September 2011. Prior to Amgen, Dr. San Martin served as Medical Advisor at Eli Lilly and Company, a pharmaceutical company, from June 1998 to February 2006. Dr. San Martin received his M.D. from the University of Buenos Aires Medical School and completed his residence in internal medicine at CEMIC University of Buenos Aires.

Vimal Srivastava has served as our Vice President, Program Development since August 2011. Before joining Ultragenyx, Mr. Srivastava was Senior Director, Portfolio and Project Management at Elan/Janssen Alzheimer Immunotherapy, a biotechnology company, from January 2008 until August 2011. He was also Director, Global Program Manager, Diabetes at Amgen Inc., a biotechnology company, from September 2005 to January 2008 and Director, Program Management at BioMarin Pharmaceutical Inc., a biopharmaceutical company, from March 2003 to September 2005. Mr. Srivastava holds a B.S. in Pharmacy from Banaras Hindu University, an M.S. in Medicinal Chemistry from St. John’s University and an M.A.S. in Management from Johns Hopkins University.

Michael Vellard, Ph.D. has served as our Vice President, Research since May 2013. Prior to joining Ultragenyx, Dr. Vellard worked as Head of Lysosomal Biology at BioMarin Pharmaceutical Inc., a biopharmaceutical company, from October 1999 to May 2013. He was a postdoctoral fellow in the pediatric department at UCLA Harbor Medical Center from September 1992 to June 1995. Dr. Vellard received his B.S. in Natural and Life Sciences and M.S. in Molecular and Cellular Genetics from the University of Lyon I, France. He obtained his Ph.D. in Virology from the Pasteur and Curie Institutes (Universities Paris VI, VII and XI), France.

Spencer Guthrie has served as our Senior Director, Clinical Operations since June 2012. Prior to Ultragenyx, Mr. Guthrie worked as Director of Clinical Operations and Project Team Leader at Elan Pharmaceuticals, a biotechnology company, and Janssen Alzheimer's Immunotherapy from September 2007 to June 2012. Prior to that, Mr. Guthrie spent nine years with increasing responsibilities at Genentech in Clinical Operations and Market Planning. At Genentech, he worked on several innovative clinical programs, IND and BLA filings with Rituxan, Avastin, and Lucentis, including work on orphan indications. Mr. Guthrie also spent two years at ICON Clinical Research and a year at NASA's space science lab. Mr. Guthrie received his B.A. in Neuroscience from Vanderbilt University, an M.B.A. from the University of California, Irvine and he is certified as a Project Management Professional.

Alison Skrinar, Ph.D. has served as our Senior Director, Clinical Sciences since March 2012. Prior to joining Ultragenyx, Dr. Skrinar worked as the Senior Director of Clinical Outcomes and Regulatory Affairs from February 2009 to February 2012 at Enobia Pharma, Inc., a private clinical stage orphan company focused on the development of an enzyme replacement therapy for hypophosphastasia, which was acquired by Alexion in 2012. Prior to Enobia Pharma, Dr. Skrinar was the Senior Director of Clinical Outcomes at Genzyme Corporation, a biotechnology company, from May 2001 until January 2009. In her nearly 15 years in the biotechnology industry, Dr. Skrinar has worked exclusively on the clinical development and regulatory approval of ultra-orphan drugs. Dr. Skrinar received a B.B.A. from Emory University and a Ph.D. and a Master of Public Health degree from the University of Alabama.

Theodore A. Huizenga has served as our Corporate Controller since January 2014 and was appointed our Principal Accounting Officer in March 2014. Prior to joining us, Mr. Huizenga served as Controller of Crescendo Bioscience from August 2013 until January 2014. Prior to Crescendo Bioscience, Mr. Huizenga was employed by RDV Corporation, where he served as Director of Finance – Investment Group from January 2008 through December 2012 and as Corporate Controller from September 2003 through December 2007. Mr. Huizenga previously was a Manager in the Audit and Assurance Practice with PricewaterhouseCoopers LLP from January 1998 to September 2003. Mr. Huizenga has a B.S. in Accounting from Calvin College and is a Certified Public Accountant.

Section 16(a) Beneficial Ownership Reporting Compliance

Under Section 16(a) of the Exchange Act and SEC rules, our directors, executive officers and beneficial owners of more than 10% of any class of equity security are required to file periodic reports of their ownership, and changes in that ownership, with the SEC. Because we did not become subject to the reporting requirements of Section 16(a) of the Exchange Act until January 2014, there were no such applicable SEC filings for the fiscal year ended December 31, 2013.

Code of Business Conduct and Ethics

We have adopted a code of business conduct and ethics that applies to all of our employees, officers, and directors, including those officers responsible for financial reporting. Our code of business conduct and ethics is available on our website at www.ultragenyx.com. We intend to disclose any amendments to the code, or any waivers of its requirements, on our website. You may also request a printed copy of our code of ethics, without charge, by writing to us at 60 Leveroni Court, Novato, California 94949, Attn: Investor Relations.

Limitation on Liability and Indemnification Matters

Our amended and restated certificate of incorporation contains provisions that limit the liability of our directors for monetary damages to the fullest extent permitted by Delaware law. Consequently, our directors will not be personally liable to us or our stockholders for monetary damages for any breach of fiduciary duties as directors, except liability for:

- any breach of the director's duty of loyalty to us or our stockholders;
- any act or omission not in good faith or that involves intentional misconduct or a knowing violation of law;
- unlawful payments of dividends or unlawful stock repurchases or redemptions as provided in Section 174 of the Delaware General Corporation Law; or
- any transaction from which the director derived an improper personal benefit.

Our amended and restated certificate of incorporation provides that we are required to indemnify our directors and officers to the fullest extent permitted by Delaware law and also provides that we are obligated to advance expenses incurred by a director or officer in advance of the final disposition of any action or proceeding, and permit us to secure insurance on behalf of any officer, director, trustee, employee or other agent for any liability arising out of his or her actions in that capacity regardless of whether we would otherwise be permitted to indemnify him or her under Delaware law.

We have entered and expect to continue to enter into agreements to indemnify our directors, executive officers and other employees as determined by our board of directors. With specified exceptions, these agreements provide for indemnification for related expenses including, among other things, attorneys' fees, judgments, fines and settlement amounts incurred by any of these individuals in any action or proceeding. We believe that these indemnification agreements and the provisions in our amended and restated certificate of incorporation are necessary to attract and retain qualified directors and officers. We also maintain directors' and officers' liability insurance.

The limitation of liability and indemnification provisions in our amended and restated certificate of incorporation may discourage stockholders from bringing a lawsuit against our directors and officers for breach of their fiduciary duty. They may also reduce the likelihood of derivative litigation against our directors and officers, even though an action, if successful, might benefit us and our stockholders. Further, a stockholder's investment may be adversely affected to the extent that we pay the costs of settlement and damage. To the extent the indemnification for liabilities arising under the Securities Act may be permitted to our directors, officers and controlling persons pursuant to the foregoing provisions, or otherwise, we have been advised that, in the opinion of the SEC, such indemnification is against public policy as expressed in the Securities Act and is, therefore, unenforceable. At present, there is no pending litigation or proceeding involving any of our directors, officers or employees for which indemnification is sought, and we are not aware of any threatened litigation that may result in claims for indemnification.

Corporate Governance

Our Audit Committee consists of Eran Nadav, Matthew Fust and Mårten Steen, with Matthew Fust serving as chairman of the committee. Our Board has determined that each member of the Audit Committee meets the independence requirements of Rule 10A-3 under the Exchange Act and the applicable listing standards of NASDAQ. Our Board has determined that Matthew Fust is an "audit committee financial expert" within the meaning of the SEC regulations and applicable listing standards of NASDAQ.

Our Compensation Committee consists of Eran Nadav, William Aliski, and Clay Siegall, with Eran Nadav serving as chairman of the committee. Our Board has determined each member of the Compensation Committee is "independent" as defined under the applicable listing standards of NASDAQ.

Our Nominating and Corporate Governance Committee consists of Matthew Fust, Eran Nadav and Mårten Steen, with Matthew Fust serving as chairman of the committee. Our board of directors has determined that each member of the nominating and corporate governance committee is "independent" as defined under the applicable listing standards of NASDAQ.

Compensation Committee Interlocks and Insider Participation

None of the members of our Compensation Committee has at any time during the prior three years been one of our officers or employees. None of our executive officers currently serves, or in the past fiscal year has served, as a member of the board of directors or compensation committee of any entity that has one or more executive officers serving on our Board or Compensation Committee. For a description of transactions between us and members of our Compensation Committee, please see "Item 13. Certain Relationships and Related Transactions and Director Independence" below.

Compensation Committee Report

As an emerging growth company, the Company is not required to include a Compensation Discussion and Analysis section in this Annual Report on Form 10-K.

Item 11. Executive Compensation

The following is a summary of the compensation arrangements of our named executive officers. Actual compensation programs that we may adopt may differ materially from currently planned programs as summarized in this discussion. As an “emerging growth company” as defined in the JOBS Act, we are not required to include a Compensation Discussion and Analysis section and have elected to comply with the scaled disclosure requirements applicable to emerging growth companies.

Summary Compensation Table

The following table sets forth the compensation earned during the years ended December 31, 2013 and 2012 to our chief executive officer and our next two highest-paid executive officers. We refer to these officers as our named executive officers.

Name and Principal Position	Year	Salary	Bonus	Option Awards[1]	Nonequity Incentive Plan Compensation[2]	All Other Compensation	Total
Emil D. Kakkis, M.D., Ph.D.	2013	$306,034	$–	$ 218,873	$ 140,910	$ 19,721	$685,538
President and Chief Executive Officer	2012	$300,172	$–	$–	$ 92,125	$ 9,056 [3]	$401,353
Thomas Kassberg	2013	$289,419	$–	$ 182,394	$ 114,345	$ 20,352	$606,510
Chief Business Officer and Senior Vice President	2012	$272,041	$–	$–	$ 81,813	$ 15,640 [4]	$369,494
Shalini Sharp[5]	2013	$278,440	$ 30,000	$ 182,394	$ 110,206	$ 24,193	$625,233
Chief Financial Officer and Senior Vice President	2012	$148,669	$–	$ 90,042	$ 51,560	$ 13,228 [4]	$303,499

(1) The amounts reported in this column represent the grant date fair value of the stock options granted to our named executive officers during 2013 and 2012, respectively, as computed in accordance with Accounting Standards Codification, or ASC, Topic 718, not including any estimates of forfeitures. The assumptions used in calculating the grant date fair value of the stock options reported in this column are set forth in the notes to our financial statements included elsewhere in this annual report. Note that the amounts reported in this column reflect the accounting cost for these stock options, and do not correspond to the actual economic value that may be received by the named executive officers from the options.

(2) Amounts for fiscal 2013 represent cash bonuses earned in fiscal 2013, and paid during 2014, based on achievement of performance goals and other factors deemed relevant by our Board. Amounts for fiscal 2012 represent cash bonuses earned in 2012, and paid during 2013, based on achievement of performance goals and other factors deemed relevant by our Board.

(3) Amounts reported in this column consist of medical, dental, vision and life/accidental death & dismemberment and key person life insurance premiums paid by us.

(4) Amounts reported in this column consist of medical, dental, vision and life/accidental death & dismemberment premiums paid by us.

(5) Ms. Sharp commenced employment with us in May 2012.

Narrative Disclosure to Summary Compensation Table

Employment Arrangements with Our Named Executive Officers

Emil D. Kakkis, M.D., Ph.D., President and Chief Executive Officer. We entered into an executive employment agreement with Dr. Kakkis in June 2011 for the position of President and Chief Executive Officer. Dr. Kakkis currently receives a base salary of $500,000, which is subject to adjustment at the discretion of the Board or the Compensation Committee. Dr. Kakkis is also eligible for an annual performance bonus of up to 35% of his base salary, payable based on his individual performance evaluated against certain goals mutually agreed upon and our overall performance, as determined by the Board. Dr. Kakkis is also eligible to participate in our employee benefit plans, subject to the terms of those plans. Pursuant to the terms of the executive employment agreement, the

employment of Dr. Kakkis is at will; we may terminate his employment at any time, without advance notice, for any reason or for no reason at all and Dr. Kakkis may terminate his employment at any time, upon four weeks' prior written notice, for any reason or for no reason at all.

Thomas Kassberg, Chief Business Officer and Senior Vice President. We entered into an offer letter in October 2011 with Thomas Kassberg for the position of Chief Business Officer and Senior Vice President. Mr. Kassberg currently receives a base salary of $350,000, which is subject to adjustment at the discretion of the Board or the Compensation Committee. Mr. Kassberg is also eligible for an annual performance bonus of up to 30% of his base salary, payable based on his individual performance evaluated against certain goals mutually agreed upon and our overall performance, as determined by the Chief Executive Officer in consultation with the Board. Additionally, pursuant to the terms of the offer letter, Mr. Kassberg received an option to purchase 202,584 shares of our common stock in connection with his hiring. Mr. Kassberg is eligible to participate in our employee benefit plans, subject to the terms of those plans. Pursuant to the terms of the offer letter, Mr. Kassberg's employment is at will and may be terminated either by us or by him, with or without advance notice, for any reason or for no reason at all.

Shalini Sharp, Chief Financial Officer and Senior Vice President. We entered into an offer letter in March 2012 with Shalini Sharp for the position of Chief Financial Officer and Senior Vice President. Ms. Sharp currently receives a base salary of $350,000, which is subject to adjustment at the discretion of the Board or the Compensation Committee. Ms. Sharp is also eligible for an annual performance bonus of up to 30% of her base salary, payable based on her individual performance evaluated against certain goals mutually agreed upon and our overall performance, as determined by the Chief Executive Officer in consultation with the Board. Additionally, pursuant to the terms of the offer letter, Ms. Sharp received an option to purchase 191,418 shares of our common stock

in connection with her hiring. Ms. Sharp is eligible to participate in our employee benefit plans, subject to the terms of those plans. Pursuant to the terms of the offer letter, Ms. Sharp's employment is at will and may be terminated either by us or by her, with or without advance notice, for any reason or for no reason at all.

Each of these employment arrangements also contain provisions that provide for certain payments and benefits in the event of an involuntary termination of employment. In addition, the named executive officers may be entitled to accelerated vesting of their outstanding and unvested awards in certain circumstances. The information below describes certain compensation that may become due and payable as a result of certain events.

Involuntary Termination of Employment

Pursuant to their employment arrangements, each named executive officer is eligible to receive certain payments and benefits in the event of certain qualifying terminations, including termination of his or her employment by us without "cause" (as defined below) or resignation of his or her employment with "good reason" or because of a "constructive termination" (each, as defined below). Upon the timely execution of a general release of claims, each named executive officer is eligible to receive the following payments and benefits:

- if Dr. Kakkis is terminated by us other than for cause or because of death or disability, he shall be entitled to receive six months of base salary continuation;
- if Dr. Kakkis resigns his employment with us for good reason following a "change in control" (as defined below) within six months of the event constituting good reason and after providing us with 20 days to cure the good reason, then he shall be entitled to receive 12 months of base salary continuation; and
- if Mr. Kassberg or Ms. Sharp is terminated by us without cause or resigns employment with us due to a constructive termination, each executive will be entitled to: (i) extend the exercise period applicable to any options then held such that the executive has 12 months from termination to exercise any of the vested shares, provided that in no event shall the exercise period be extended beyond the expiration date of any options then held; and (ii) six months of base salary continuation.

Deemed Liquidation Event

Pursuant to the offer letter with Mr. Kassberg, in addition to the severance benefits described above, in the event (i) we consummate a "deemed liquidation event" (as defined in our certificate of incorporation), which includes certain mergers or material asset sales, as well as any dissolution, liquidation, or winding down of the Company, (ii) Mr. Kassberg is employed by us on the date of the deemed liquidation event, and (iii) Mr. Kassberg is terminated by us without cause or resigns his employment with us due to a constructive termination within 12 months after the deemed liquidation event, the vesting of Mr. Kassberg's November 17, 2011 option to purchase 202,584 shares of our common stock shall accelerate with respect to 50% of the then-unvested shares subject to such option and any other equity held by Mr. Kassberg shall accelerate with respect to 100% of the then-unvested shares.

Pursuant to the offer letter with Ms. Sharp, in the event (i) we consummate a deemed liquidation event, (ii) Ms. Sharp is employed by us on the date of the deemed liquidation event, and (iii) Ms. Sharp is terminated without cause or resigns due to a constructive termination within 12 months of the deemed liquidation event, the vesting of all options held by Ms. Sharp as of the date of the deemed liquidation event shall accelerate with respect to 50% of the then-unvested shares.

Definitions

For purposes of Dr. Kakkis's employment agreement, "cause" means his:

- commission of a felony or any crime involving dishonesty, breach of trust, or physical harm to any person;

willful engagement in conduct that is in bad faith and materially injurious to us, including but not limited to misappropriation of trade secrets, fraud, or embezzlement;

material breach of his employment agreement that is not cured within 10 days after written notice to him from us; or

willful refusal to implement or follow a lawful policy or directive of ours, which breach is not cured within 10 days after written notice to him from us.

For purposes of each of the offer letters with Mr. Kassberg and Ms. Sharp, “cause” means the named executive officer’s:

gross negligence in carrying out, or material failure to carry out, his or her duties for us (including, without limitation, failure to cooperate in any company investigation), after notice from the Board and a reasonable opportunity to cure (if deemed curable);

breach of his or her fiduciary duties to us, after notice from the Board and a reasonable opportunity to cure (if deemed curable);

conviction of, or plea of guilty or no contest to, any felony;

any act of fraud or embezzlement with respect to his or her obligations to us or otherwise relating to our business;
material violation of any of our policies;
material breach of any agreement entered into with us; or
unauthorized use or disclosure of confidential information or trade secrets of ours or of our affiliates.

For purposes of Dr. Kakkis's employment agreement, "good reason" means any of the following events if (i) we effect the event without the consent of Dr. Kakkis and (ii) such event occurs after a change in control:

a change in his position with us that materially reduces his level of responsibility;
a material reduction in his base salary, except for reductions that are comparable to reductions generally applicable to similarly situated executives of ours; or
a relocation of his principal place of employment by more than 50 miles.

For purposes of Dr. Kakkis's employment agreement, "change in control" means a change in ownership or control of us effected through a merger, consolidation, or acquisition by any person or related group of persons (other than an acquisition by us or by an employee benefit plan sponsored by us or by a person or persons that directly or indirectly control, is controlled by, or is under common control with, us) of beneficial ownership of securities possessing more than 50% of the total combined voting power of our outstanding securities.

For purposes of each of the offer letters with Mr. Kassberg and Ms. Sharp, "constructive termination" means the occurrence of any of the following events without the named executive officer's consent if (i) the executive provides us with written objection (or notice) to the event or condition within 30 days following the occurrence of the event or condition, (ii) we do not reverse or otherwise cure the event within 30 days of receiving such written objection, and (iii) the executive resigns his or her employment with us within 30 days following the expiration of that cure period:

a material reduction or change in the executive's job duties, responsibilities and requirements from the executive's job duties, responsibilities and requirements immediately prior to such reduction or change, taking into account the differences in job title and duties that are normally occasioned by reason of an acquisition of one company by another;
a material reduction of the executive's base salary (other than an equal, across-the-board reduction in the compensation of all similarly-situated employees of ours or the surviving entity that is approved by the Board); or
a requirement that the executive relocate to a principal office that increases his or her one-way commute by more than 50 miles relative to the executive's immediately preceding principal office.

Terms and Conditions of Annual Bonuses

Our Board has adopted a corporate bonus plan, or the bonus plan, that provides for cash bonus payments based upon the attainment of performance targets established by our Compensation Committee. The payment targets will be related to corporate, financial, and operational measures or objectives, or corporate performance goals, as well as individual performance objectives.

Our Compensation Committee may select corporate performance goals from among the following: sales; revenue; assets; expenses; earnings from operations, earnings before or after deduction for all or any portion of interest, taxes, depreciation, amortization, incentives, service fees or extraordinary or special items, whether or not on a continuing operations or an aggregate or per share basis; net income or net income per common share (basic or diluted); return on equity, investment, capital or assets; one or more operating ratios; borrowing levels, leverage ratios or credit rating; market share; capital expenditures; cash flow, free cash flow, cash flow return on investment, or net cash provided by operations; stock price, dividends or total stockholder return; development of new technologies or products; sales of particular products or services; economic value created or added; operating margin or profit margin; customer acquisition or retention; raising or refinancing of capital; successful hiring of key individuals; resolution of significant litigation; acquisitions and divestitures (in whole or in part); joint ventures and strategic alliances; spin-offs, split-ups and the like; reorganizations; recapitalizations, restructurings, financings (issuance of debt or equity) or refinancings; or strategic business criteria, consisting of one or more objectives based on the following goals: meeting specified

market penetration or value added, product development or introduction (including, without limitation, any clinical trial accomplishments, regulatory or other filings or approvals, or other product development milestones), geographic business expansion, cost targets, cost reductions or savings, customer satisfaction, operating efficiency, acquisition or retention, employee satisfaction, information technology, corporate development (including, without limitation, licenses, innovation, research or establishment of third party collaborations), manufacturing or process development, legal compliance or risk reduction, patent application or issuance goals, or goals relating to acquisitions or divestitures (in whole or in part), joint ventures or strategic alliances, any of which may be measured in absolute terms, as compared to any incremental increase, in terms of growth, as compared to results of a peer group, against the market as a whole, compared to applicable market indices and/or measured on a pre-tax or post-tax basis.

Each executive officer who is selected to participate in the bonus plan will have a target bonus opportunity set for each performance period. The bonus formulas will be adopted in each performance period by the Compensation Committee and communicated to each executive. The corporate performance goals will be measured at the end of each performance period after our financial reports have been published or such other appropriate time as the Compensation Committee determines. If the corporate performance goals and individual performance objectives are met, payments will be made following the end of each performance

period. Subject to the rights contained in any agreement between the executive officer and the company, an executive officer must be employed by the company on the bonus payment date to be eligible to receive a bonus payment. The bonus plan also permits the compensation committee to approve additional bonuses in its sole discretion.

Equity Compensation

Outstanding Equity Awards at December 31, 2013

The following table sets forth information concerning the outstanding equity awards held by each of the named executive officers as of December 31, 2013.

	Option awards			
Name	Number of securities underlying unexercised option (#) exercisable	Number of securities underlying unexercised options (#) unexercisable	Option exercise price $	Option expiration date
Emil D. Kakkis, M.D., Ph.D.[1]	—	47,854	$ 6.86	10/31/2023
Thomas Kassberg[2]	12,661	97,071	$ 0.31	11/16/2021
	—	39,878	6.86	10/31/2023
Shalini Sharp[3]	11,963	115,648	$ 0.81	8/1/2022
	—	39,878	6.86	10/31/2023

(1) Represents an option to purchase 47,854 shares of our common stock granted on November 1, 2013. The shares underlying this option vest as follows: 25% vest on November 1, 2014, with the remainder of the shares vesting in equal monthly installments over the following three years through November 1, 2017, subject to the holder's continued service to us through each such vesting date.

(2) Represents an option to purchase 202,584 shares of our common stock granted on November 17, 2011. The shares underlying this option vest as follows: 25% vest on November 15, 2012, with the remainder of the shares vesting in equal monthly installments over the following three years through November 15, 2015, subject to the holder's continued service to us through each such vesting date. Vesting of 50% of the unvested shares shall accelerate in connection with a deemed liquidation event pursuant to the terms of Mr. Kassberg's offer letter dated October 31, 2011, as more fully described above under the section entitled "—Narrative Disclosure to Summary Compensation Table—Deemed Liquidation Event." Mr. Kassberg exercised 50,646 options on November 28, 2012 and 42,204 options on September 27, 2013.

Represents an option to purchase 39,878 shares of our common stock granted on November 1, 2013. The shares underlying this option vest as follows: 25% vest on November 1, 2014, with the remainder of the shares vesting in equal monthly installments over the following three years through November 1, 2017, subject to the holder's continued service to us through each such vesting date.

(3) Represents an option to purchase 191,418 shares of our common stock granted on August 2, 2012. The shares underlying this option vest as follows: 25% vest on May 21, 2013, with the remainder of the shares vesting in equal monthly installments over the following three years through May 21, 2016, subject to the holder's continued service

to us through each such vesting date. Vesting of 50% of the unvested shares shall accelerate in connection with a deemed liquidation event pursuant to the terms of Ms. Sharp's offer letter dated March 12, 2012, as more fully described above under the section entitled "—Narrative Disclosure to Summary Compensation Table—Deemed Liquidation Event." Ms. Sharp exercised 47,854 options on May 30, 2013, 7,975 options on July 24, 2013, and 7,975 options on September 26, 2013.

Represents an option to purchase 39,878 shares of our common stock granted on November 1, 2013. The shares underlying this option vest as follows: 25% vest on November 1, 2014, with the remainder of the shares vesting in equal monthly installments over the following three years through November 1, 2017, subject to the holder's continued service to us through each such vesting date.

Director Compensation

Dr. Kakkis, our president and chief executive officer, receives no compensation for his service as a director. None of our non-employee directors received compensation for their service on the Board or otherwise during fiscal 2013.

Our Board has adopted a non-employee director compensation policy that is designed to provide a total compensation package that enables us to attract and retain, on a long-term basis, high caliber non-employee directors. Under the policy, all non-employee directors will be paid cash compensation during fiscal 2014 and thereafter as set forth below:

	Annual Retainer
Board of Directors:	
All non-employee members	$ 35,000
Audit Committee:	
Chairman	$ 15,000
Non-Chairman members	$ 7,500
Compensation Committee:	
Chairman	$ 10,000
Non-Chairman members	$ 5,000
Nominating and Corporate Governance Committee:	
Chairman	$ 6,000
Non-Chairman members	$ 3,000

Under the non-employee director compensation policy, each non-employee director who is initially appointed or elected to the Board will receive an option grant to purchase up to 17,500 shares of our common stock under our stock option plan on the date he or she first becomes a non-employee director, which will vest annually over a three-year period, subject to the holder's continued service to us through each such vesting date. In addition, on the date of the annual meeting of stockholders, each continuing non-employee director will be eligible to receive an annual option grant to purchase up to 7,500 shares of our common stock, which will vest in full upon the first anniversary of the date of grant, subject to the holder's continued service to us through such vesting date. All of the foregoing options will be granted at fair market value on the date of grant.

Compensation Risk Assessment

We believe that our executive compensation program does not encourage excessive or unnecessary risk taking. This is primarily due to the fact that our compensation programs are designed to encourage our executive officers and other employees to remain focused on both short-term and long-term strategic goals, in particular in connection with our pay-for-performance compensation philosophy. As a result, we do not believe that our compensation programs are reasonably likely to have a material adverse effect on us.

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

The following table sets forth information relating to the beneficial ownership of our common stock as of March 14, 2014, by:

- each person, or group of affiliated persons, known by us to beneficially own more than 5% of our outstanding shares of common stock;
- each of our directors;
- each of our named executive officers; and
- all current directors and executive officers as a group.

The number of shares beneficially owned by each entity, person, director or executive officer is determined in accordance with the rules of the SEC, and the information is not necessarily indicative of beneficial ownership for any other purpose. Under such rules, beneficial ownership includes any shares over which the individual has sole or shared voting power or investment power as well as any shares that the individual has the right to acquire within 60 days of March 14, 2014 through the exercise of any stock option, warrants or other rights. Except as otherwise indicated, and subject to applicable community property laws, the persons named in the table have sole voting and investment power with respect to all shares of common stock held by that person.

The percentage of shares beneficially owned is computed on the basis of 30,035,894 shares of our common stock outstanding as of March 14, 2014. Shares of our common stock that a person has the right to acquire within 60 days of March 14, 2014 are deemed outstanding for purposes of computing the percentage ownership of the person holding such rights, but are not deemed outstanding for purposes of computing the percentage ownership of any other person, except with respect to the percentage ownership of all directors and executive officers as a group. Unless otherwise indicated below, the address for each beneficial owner listed is c/o Ultragenyx Pharmaceutical Inc., at 60 Leveroni Court, Novato, California 94949.

Name and Address of Beneficial Owner	Beneficial Ownership (1) Number of Shares	% of Total
5% or Greater Stockholders:		
TPG Biotechnology Partners III, L.P.(1)	3,085,240	10.3%
Beacon Bioventures Fund II Limited Partnership(2)	3,260,240	10.9%
HealthCap VI, L.P.(3)	2,742,436	9.1%
Adage Capital Partners, L.P.(4)	1,867,713	6.2%
Directors (including our Director Nominees) and Named Executive Officers:		
Eran Nadav, Ph.D.(5)	1,458	*
Mårten Steen, M.D., Ph.D.(6)	1,458	*
William Aliski(7)	67,469	*
Matthew K. Fust(8)	6,458	*
Clay B. Siegall, Ph.D.(9)	1,458	*
Emil D. Kakkis, M.D., Ph.D.(10)	3,326,181	11.0%
Thomas Kassberg(11)	155,348	*
Shalini Sharp(12)	96,221	*
All executive officers and directors as a group(13) (8 persons)	3,656,051	12.1%

* Indicates beneficial ownership of less than 1% of the total outstanding common stock.

(1) Based on information set forth in a Form 4 filed with the SEC by TPG Group Holdings (SBS) Advisors, Inc. on February 7, 2014. TPG Biotechnology Partners III, L.P. is a Delaware limited partnership, whose general partner is TPG Biotechnology GenPar III, L.P., a Delaware limited partnership, whose general partner is TPG Biotechnology GenPar III Advisors, LLC, a Delaware limited liability company, whose sole member is TPG Holdings I, L.P., a Delaware limited partnership, whose general partner is TPG Holdings I-A, LLC, a Delaware limited liability company, whose sole member is TPG Group Holdings (SBS), L.P., a Delaware limited partnership, whose general partner is TPG Group Holdings (SBS) Advisors, Inc., or Group Advisors, a Delaware corporation. Messrs. David Bonderman and James G. Coulter are officers, directors and sole shareholders of Group Advisors and may therefore be deemed to be the beneficial owners of the shares held by TPG Biotechnology Partners III, L.P. The address for Messrs. Bonderman and Coulter is c/o TPG Capital, L.P., 301 Commerce Street, Suite 3300, Fort Worth, TX 76102.

(2) Based on information set forth in a Schedule 13G filed with the SEC by FMR LLC on February 14, 2014. Beacon Bioventures Advisors Fund II Limited Partnership is the general partner of Beacon Bioventures Fund II Limited Partnership. Beacon Bioventures Advisors Fund II Limited Partnership is solely managed by Northern Neck Investors LLC, its general partner and investment manager. Northern Neck Investors LLC is owned by the shareholders and certain employees of FMR LLC. Northern Neck Investors LLC is managed on a day-to-day basis by its President, Paul L. Mucci, and as such Mr. Mucci may be deemed to share voting and dispositive power with respect to all shares held by Beacon Bioventures Fund II Limited Partnership. Each of the individuals and entities listed above expressly disclaims beneficial ownership of the securities listed above except to the extent of any pecuniary interest therein. The address for each of the individuals and entities listed above is 100 Summer Street R7B, Boston, Massachusetts 02110.

(3) HealthCap VI GP SA, L.L.C. (“HCSA”) is the sole general partner of HealthCap VI, L.P. HCSA has voting and dispositive power over the shares held by HealthCap VI, L.P. HCSA disclaims beneficial ownership of such shares, except to the extent of its pecuniary interest therein. Francois Kaiser, Dag Richter, and Daniel Schafer, the members of the board of HCSA, share voting and dispositive power over the shares held by HealthCap VI, L.P.

and may be deemed to have indirect beneficial ownership of the shares held by such entities. The members of the board of HCSA disclaim beneficial ownership of shares held by HealthCap VI, L.P. except to the extent of any pecuniary interest therein. The address of HealthCap VI, L.P. is c/o HealthCap VI GP SA, 18, Avenue d Ouchy, 1006 Lausanne, Switzerland.

(4) Adage Capital Partners, GP, LLC ("ACPGP"), serves as the general partner of Adage Capital Partners, L.P., a Delaware limited partnership (the "Fund") and as such has discretion over the portfolio of securities beneficially owned by the Fund. Adage Capital Advisors, LLC, a Delaware limited liability company ("ACA"), is managing member of ACPGP and directs ACPGP's operations. Robert Atchinson and Phillip Gross are the managing members of ACPGP and ACA and general partners of the Fund. Robert Atchinson and Phillip Gross disclaim beneficial ownership of the reported securities except to the extent of their pecuniary interest therein. The address of Adage Capital Partners, L.P. is 200 Clarendon Street, 52nd Floor, Boston, MA 02116.

(5) Consists of 1,458 shares of common stock issuable upon the exercise of stock options within 60 days of March 14, 2014.

(6) Consists of 1,458 shares of common stock issuable upon the exercise of stock options within 60 days of March 14, 2014.

(7) Consists of (a) 36,903 shares of common stock, (b) 29,108 shares of common stock that may be acquired pursuant to the exercise of a warrant held by Mr. Aliski and (c) 1,458 shares of common stock issuable upon the exercise of stock options within 60 days of March 14, 2014.
(8) Consists of (a) 5,000 shares of common stock and (b) 1,458 shares of common stock issuable upon the exercise of stock options within 60 days of March 14, 2014.
(9) 1,458 shares of common stock issuable upon the exercise of stock options within 60 days of March 14, 2014.
(10) Consists of (a) 2,552,241 shares of common stock held by the Emil Kakkis and Jenny Soriano Living Trust, dated June 18, 2009, (b) 624,240 shares of common stock held by Dr. Kakkis and (c) 149,700 shares of common stock that may be acquired pursuant to the exercise of warrants held by Dr. Kakkis. Dr. Kakkis shares voting and dispositive power over the 2,552,241 shares of common stock held by the Emil Kakkis and Jenny Soriano Living Trust, dated June 18, 2009; each of Dr. Kakkis and Dr. Soriano is a trustee of such trust. Dr. Kakkis has sole voting and dispositive power over the 624,240 shares of common stock held by him and the 149,700 shares of common stock that may be acquired pursuant to the exercise of warrants held by Dr. Kakkis.
(11) Consists of (a) 125,804 shares of common stock and (b) 29,544 shares of common stock issuable upon the exercise of stock options within 60 days of March 14, 2014.
(12) Consists of (a) 84,255 shares of common stock and (b) 11,966 shares of common stock issuable upon the exercise of stock options within 60 days of March 14, 2014.
(13) Consists of (a) 3,428,443 shares held by our directors and officers, (b) 178,808 shares of common stock that may be acquired pursuant to the exercise of warrants by our certain of our directors and officers, and (c) 48,800 shares of common stock issuable upon the exercise of stock options within 60 days of March 14, 2014 held by our officers.

Equity Compensation Plan Information

The table below discloses information as of December 31, 2013 with respect to our equity compensation plans that have been approved by stockholders and equity compensation plans that have not been approved by stockholders.

Plan Category	Number of Securities to be Issued upon Exercise of Outstanding Options	Weighted-Average Exercise Price of Outstanding Options	Number of Securities Remaining Available for Future Issuance under Equity Compensation Plans (Excluding Securities Reflected in Column (a))
Equity compensation plans approved by security holders:			
2011 Equity Incentive Plan, as amended	2,222,839	$ 3.41	799,963
Equity compensation plans not approved by security holders	-	-	-
Total	2,222,839	$ 3.41	799,963

Item 13. Certain Relationships and Related Transactions and Director Independence

Related-Party Transactions

Since January 1, 2013, other than participation in our IPO by certain greater than 5% holders and entering into indemnification agreements with each of our executive officers and directors, we have not become a party to any transactions with any "related parties," which are generally considered to be our directors and executive officers, nominees for director, holders of 5% or more of our outstanding common stock and members of their immediate families, in which the amount involved exceeds $120,000.

Participation in our IPO

In connection with our IPO, the underwriters allocated shares of our common stock in the offering to certain of our greater than 5% holders on the same terms as the other shares that were offered and sold in our IPO. These allocations included allocations of 240,000 shares to Adage Capital Partners, L.P. and 175,000 shares to Beacon Bioventures Fund II Limited Partnership. All of these shares were sold at $21.00, which was the IPO price.

Indemnification Agreements and Directors' and Officers' Liability Insurance

We have entered into indemnification agreements with each of our directors and executive officers. These agreements, among other things, require us to indemnify each director and executive officer to the fullest extent permitted by Delaware law, including indemnification of expenses such as attorneys' fees, judgments, penalties fines and settlement amounts incurred by the director or executive officer in any action or proceeding, including any action or proceeding by or in right of us, arising out of the person's services as a director or executive officer.

Procedures for Related Party Transactions

We have adopted a related person transaction approval policy that governs the review, approval and/or ratification of related person transactions. Pursuant to this policy, if we want to enter into a transaction with a related person or an affiliate or immediate family member of a related person, our Chief Financial Officer will review the proposed transaction to determine, based on applicable NASDAQ and SEC rules, if such transaction qualifies as a related person transaction. If the Chief Financial Officer determines that the proposed transaction is a related person transaction, then the proposed transaction shall be submitted to the Audit Committee for pre-approval at the next regular or special Audit Committee meeting; if the Chief Financial Officer, in consultation with the Chief Executive Officer, determines that it is not practicable to wait until the next meeting of the Audit Committee, then the Chief Financial Officer shall submit the proposed transaction to the chairperson of the Audit Committee. In the event that our Chief Executive Officer or Chief Financial Officer becomes aware of a related person transaction that has not been previously approved or previously ratified under our related person transaction approval policy, the transaction, if pending or ongoing, will be promptly submitted to the Audit Committee or the chairperson of the Audit Committee for consideration. If the transaction is already completed, the Audit Committee or the chairperson of the Audit Committee shall evaluate the transaction to determine if rescission of the transaction and/or any disciplinary action is appropriate.

Board Independence

Our Board currently consists of six members. Our Board has determined that all of our directors, other than Dr. Kakkis, qualify as "independent" directors in accordance with the NASDAQ listing requirements. Dr. Kakkis is not considered independent because he is an employee of Ultragenyx. The NASDAQ independence definition includes a series of objective tests, such as that the director is not, and has not been for at least three years, one of our employees and that neither the director nor any of his family members has engaged in various types of business dealings with us. In addition, as required by NASDAQ rules, our Board has made a subjective determination as to each independent director and director nominee that no relationships exist, which, in the opinion of our Board, would interfere with the exercise of independent judgment in carrying out the responsibilities of a director. In making these determinations, our Board reviewed and discussed information provided by the directors, director nominees, and us with regard to each director's and director nominee's business and personal activities and relationships as they may relate to us and our management. There are no family relationships among any of our directors or executive officers.

Item 14. Principal Accounting Fees and Services

The following table shows the fees paid or accrued by us for the audit and other services provided by Ernst & Young LLP for fiscal 2012 and 2013.

	2012	2013
Audit fees[1]	$18,000	$1,264,000
Audit-related fees	-	-
Tax fees[2]	-	8,000
All other fees[3]	-	