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Ultragenyx Pharmaceutical Inc.
Form 10-K
March 27, 2015

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, 2014

OR

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

Commission File No. 001-36276

Ultragenyx Pharmaceutical Inc.

(Exact name of registrant as specified in its charter)

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

Novato, California (Address of principal executive offices)	94949 (Zip Code)
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(415) 483-8800

(Registrant's telephone number, including area code)

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

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

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

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

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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

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

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.

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 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

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

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

DOCUMENTS INCORPORATED BY REFERENCE

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

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CAUTIONARY NOTE REGARDING FORWARD-LOOKING STATEMENTS

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

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

PART I

Item 1. Business

Overview

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

Our current product candidate pipeline has been either in-licensed from academic institutions or derived from partnerships with other pharmaceutical companies. Our strategy is to acquire and retain global commercialization rights to our products to maximize long-term value, where possible. Over time, we intend to build our own commercial organization, which we believe will be of modest size due to the relatively small number of specialists who treat patients with rare and ultra-rare diseases.

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

We were founded in April 2010 by our current President and Chief Executive Officer, Emil Kakkis, M.D., Ph.D., who is the former Chief Medical Officer of BioMarin Pharmaceutical Inc. We have assembled an experienced team with extensive rare disease drug development and commercialization capabilities. Dr. Kakkis and the team at Ultragenyx have been previously involved at other companies in the development and/or commercialization of many therapies approved or in development for rare genetic diseases, including Aldurazyme, Naglazyme, Kuvan, and Vimizim (BioMarin); Lumizyme/Myozyme (Sanofi-Genzyme); and asfotase alpha (Enobia; now Alexion).

Our Strategy

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

- Focus on rare and ultra-rare diseases with significant unmet medical need. There are numerous rare and ultra-rare genetic diseases that currently have no approved drug therapy and for which no therapies are currently in development. Patients suffering from these diseases often have a high unmet medical need with significant morbidity and/or mortality. We are focused on developing and commercializing therapies for multiple such indications with the utmost urgency.
- Focus on diseases and therapies with clear mechanisms of action. We also focus on diseases that have biology and root causes that are well understood. For example, several of our product candidates are replacement therapies for a single deficient enzyme or substrate in the body. We believe that developing drugs that directly impact known disease pathways will increase the probability of success of our development programs.

- Leverage our experience and relationships to in-license promising product candidates. Our management team has strong relationships with key opinion leaders in the genetic field, as well as a history of success in the development and commercialization of therapies for rare and ultra-rare genetic diseases. Accordingly, we enjoy unique access to many in-licensing opportunities. All of our current product candidates are in-licensed from academic institutions or derived from partnerships with other pharmaceutical companies. We believe these parties have agreed to license product candidates to us because they are confident in our drug development capabilities and experience in bringing rare disease therapies to market.
- Develop and commercialize multiple product candidates in parallel. Clinical studies for rare and ultra-rare diseases can often be smaller, fewer in number, and less expensive than those for larger market indications. Development of multiple programs in the genetics field also generates organizational efficiencies and economies of scale. As a result of these efficiencies, we can feasibly develop multiple clinical-stage product candidates in parallel, resulting in a more diversified portfolio that provides multiple opportunities to create value.
- Focus on excellent and rapid clinical and regulatory execution. We believe that building a successful and sustainable rare disease-focused company requires very specific expertise in the areas of patient identification, clinical study design and conduct, and regulatory strategy. We have assembled a team with a successful track record in managing global clinical development activities in an efficient manner, and with multinational experience in obtaining regulatory approvals for rare disease products.

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

Product Candidates

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

The following table summarizes our current product candidate pipeline:

KRN23 (UX023) for the treatment of XLH

KRN23 is a fully human monoclonal antibody administered via subcutaneous injection that is designed to bind and reduce the biological activity of fibroblast growth factor 23, or FGF23, to increase abnormally low phosphate levels in patients with X-linked hypophosphatemia, or XLH. Patients with XLH have low serum phosphate levels due to excessive phosphate loss into the urine, which is directly caused by the effect on kidney function of excess FGF23 production in bone cells. Low phosphate levels lead to poor bone mineralization and a variety of clinical manifestations, including rickets leading to bowing and other skeletal deformities, short stature, bone pain and fractures, and muscle weakness. There is no approved drug therapy or treatment for the underlying cause of XLH. Most patients are managed using frequently dosed oral phosphate replacement and vitamin D therapy, which can lead to significant side effects. Oral phosphate/vitamin D replacement therapy requires extremely close monitoring due to the potential for excessive phosphate levels and secondary increases in calcium, which can result in severe damage to the kidneys from excess calcium phosphate deposits and other complications. Additionally, some patients are unable to tolerate the regimen due to the chalky stool that results from taking large amounts of oral phosphate or the high frequency of dosing required.

In August 2013, we entered into a collaboration agreement with Kyowa Hakko Kirin Co., Ltd., or KHK, to jointly develop and commercialize KRN23 for the treatment of XLH. KHK has conducted one Phase 1 study, one Phase 1/2 study and one longer-term Phase 1/2 study of KRN23 in adults with XLH.

Results from the Phase 1 single dose study in 38 adult XLH patients were presented at the American Society for Bone and Mineral Research, or ASBMR, Annual Meeting in October 2013 and published in the Journal of Clinical Investigation in February 2014. The data demonstrated that KRN23 was well tolerated and increased serum phosphate, or phosphorus. Corresponding changes were observed in renal tubular reabsorption of phosphate. Increases in vitamin D were also observed, suggesting improved intestinal absorption of both phosphate and calcium. Importantly, from a safety perspective, changes were not observed in serum calcium.

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

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

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

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

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

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

In July 2014, we announced the first patient screened and enrolled in the Phase 2 pediatric study of KRN23 in patients with XLH. In late 2014, we completed enrollment of 36 prepubertal patients. The primary objectives of the study are to identify a dose and dosing regimen and to establish the safety profile of treatment with KRN23 in pediatric XLH patients. We will also assess preliminary clinical effects of KRN23 treatment on bone health and deformity as

measured by radiographic assessments, growth, muscle strength, and motor function, as well as markers of bone health and patient-reported outcomes of pain, disability, and quality of life.

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

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

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

KRN23 (UX023) for the treatment of TIO

KRN23 is also intended for the treatment of tumor-induced osteomalacia, or TIO. TIO results from typically benign tumors that produce excess levels of FGF23, which can lead to severe hypophosphatemia, osteomalacia, bone fractures, fatigue, bone and muscle pain, and muscle weakness. There are cases in which resection of the tumor is not feasible or recurrence of the tumor occurs after resection. In patients for whom the tumor is inoperable, the current standard of care consists of oral phosphate and/or vitamin D replacement. The efficacy of this treatment is often limited, as it does not treat the underlying disease and its benefits must be balanced with monitoring for potential risks such as nephrocalcinosis, hypercalciuria, and hyperparathyroidism. We are enrolling patients in an open-label, dose-finding Phase 2 clinical study. Data from the Phase 2 study is expected in late 2015.

This Phase 2 study will evaluate safety and efficacy in approximately six adult inoperable patients. The primary objectives of the study are to establish the dose, and safety profile of treatment with KRN23 in TIO patients. Preliminary clinical effects of KRN23 treatment will be evaluated by radiographic assessments, muscle strength, walking ability, and patient-reported measures of pain, disability, and quality of life. Markers of bone health and changes in serum phosphorus and other biochemical measures will also be followed.

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

rhGUS (UX003) for the treatment of MPS 7

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

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

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

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

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

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

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

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

In addition to the above development plan, we intend to study MPS 7 patients under the age of five years, including potentially younger infants born with hydrops fetalis. Currently, these infants can die within a few months to one year, but enzyme replacement therapy might be able to reduce GAG storage and improve health and survival in these patients.

We are also supplying rhGUS to investigators who are treating patients under emergency investigational new drug, or eIND, applications. Results following 24 weeks of treatment of the first eIND patient were announced in September 2014 and published in *Molecular Genetics and Metabolism* in February 2015. The results indicated that a decline in urinary GAG excretion of 50-70% and a sustained reduction in the size of the enlarged liver and spleen were observed at a dose of 2 mg/kg. The data also showed improved pulmonary function based on reduced carbon dioxide retention. No serious adverse events or infusion-associated reactions were observed through 12 infusions.

rhPPCA (UX004) for the treatment of galactosialidosis

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

Triheptanoin (UX007) for the treatment of LC-FAOD

We are developing triheptanoin for oral administration intended as a substrate replacement therapy for patients with long-chain fatty acid oxidation disorders, or LC-FAOD. Triheptanoin is a medium odd-chain triglyceride of

seven-carbon fatty acids designed to provide substrate replacement for fatty acid metabolism and restore production of energy. Patients with LC-FAOD have a deficiency that impairs the ability to produce energy from fat, which can lead to depletion of glucose in the body, and severe liver, muscle, and heart disease, as well as death. There are currently no approved drugs or treatments specifically for LC-FAOD. The current standard of care for LC-FAOD includes diligent prevention of fasting combined with the use of low-fat/high-carbohydrate diets, carnitine supplementation in some cases, and medium even-chain triglyceride, or MCT, oil supplementation. Despite treatment with the current standard of care, many patients continue to suffer significant morbidity and mortality.

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

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

Triheptanoin (UX007) for the treatment of Glut1 DS

We are also developing triheptanoin for patients with glucose transporter type-1 deficiency syndrome, or Glut1 DS. Glut1 DS is caused by a mutation affecting the gene that codes for Glut1, which is a protein that transports glucose from the blood into the brain. Because glucose is the primary source of energy for the brain, Glut1 DS results in a chronic state of brain energy deficiency and is characterized by seizures, developmental delay, and movement disorder. There are currently no approved drugs specific to Glut1 DS. The current standard of care for Glut1 DS is the ketogenic diet, an extreme high-fat (70-80% of daily calories as fat)/low-carbohydrate diet, which generates ketone bodies as an alternative energy source to glucose, and one or more antiepileptic drugs. The ketogenic diet can be effective in reducing seizures but compliance can be difficult, and the diet has demonstrated limited effectiveness in the treatment of developmental delay and movement disorders. In addition, ketogenic diet can lead to side effects including renal stones. In general, Glut1 DS patients are considered relatively refractory to antiepileptic drugs with only approximately 8% achieving seizure control on antiepileptic drugs alone. There are currently no antiepileptic drugs approved specifically for patients with Glut1 DS.

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

In March 2014, we initiated a Phase 2 global, randomized, double-blind, placebo-controlled, parallel-group clinical trial that may enroll up to 40 patients who are currently not fully compliant with ketogenic diet and continue to have seizures. The primary efficacy objective is the reduction in frequency of seizures compared to placebo following a 6-week baseline period and subsequent 8-week placebo-controlled treatment period. Other efficacy objectives include cognitive function and movement disorder. The blinded treatment period will be followed by an open-label extension period in which patients will be treated with triheptanoin through week 52. Based on recently published results and in order to accelerate enrollment, we have amended the enrollment criteria to also include patients with only absence seizures. We expect to release interim data from this study in the second half of 2015. We are exploring additional studies in patients with additional disease manifestations and diet regimens based on investigator feedback.

SA-ER (UX001) for the treatment of HIBM

We are developing an extended-release, oral formulation of sialic acid, or SA-ER, for the treatment of hereditary inclusion body myopathy, or HIBM, which is also known as GNE myopathy. HIBM is characterized by severe progressive muscular myopathy, or disease in which muscle fibers do not function properly, with onset typically in the late teens or twenties. Patients with HIBM have a genetic defect in the gene coding for a particular enzyme that is involved in the first step in the biosynthesis of sialic acid. Therefore, HIBM patients have a sialic acid deficiency,

which interferes with muscle function, leading to myopathy and atrophy. Patients typically lose major muscle function within ten to 20 years of diagnosis. There is no approved drug therapy for HIBM.

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

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

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

We recently completed an End-of-Phase 2 meeting with the FDA regarding a potential randomized placebo-controlled 48-week single pivotal study of SA-ER in HIBM patients. The FDA agreed with the proposed Phase 3 study design, including the primary endpoint of a composite of upper extremity muscle strength, with supportive secondary endpoint data from a patient-reported outcome, both of which were studied in the Phase 2 study. We plan to initiate the Phase 3 trial, which we anticipate will include approximately 80 patients, during the second half of 2015.

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

Competition

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

The acquisition or licensing of pharmaceutical products is also very competitive, and a number of more established companies, which have acknowledged strategies to license or acquire products, may have competitive advantages as may other emerging companies taking similar or different approaches to product acquisitions. These established

companies may have a competitive advantage over us due to their size, cash flows, and institutional experience.

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

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

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

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

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

License Agreements

Kyowa Hakko Kirin

In August 2013, we entered into a collaboration and license agreement with Kyowa Hakko Kirin Co., Ltd., or KHK, pursuant to which we and KHK will collaborate on the development and commercialization of certain products containing KRN23, an antibody directed towards FGF23, in the field of orphan diseases in the United States and Canada, or the profit share territory, and in the EU, Switzerland, and Turkey, or the European territory, and we will have the right to develop and commercialize such products in the field of orphan diseases in Mexico and Central and South America, or Latin America. Under the agreement, we also have a right of first negotiation with KHK to receive a license to develop and commercialize products in any non-diagnostic field, or in the field of orphan drugs outside of the profit share territory, the European territory, and Latin America.

In the field of orphan diseases, and except for studies conducted by KHK, we will be the lead party for development activities in the profit share territory and in the European territory until, with respect to the profit share territory, the fifth anniversary of the first commercial sale in the United States in the first indication and, with respect to the European territory, the date on which marketing approval for a licensed product for the first indication is obtained in the European territory on a country-by-country basis; each such date is referred to herein as the applicable transition date. We will share the costs for development activities in the profit share territory and European territory conducted pursuant to the development plan before the applicable transition date equally with KHK. On the applicable transition

date in the relevant territory, KHK will become the lead party and be responsible for these costs. However, we will continue to share the costs of the studies commenced prior to the applicable transition date equally with KHK. While we are the lead development party in the profit share territory, we must use commercially reasonable efforts to conduct development activities in at least one orphan disease indication other than XLH, as mutually agreed upon by KHK and us.

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

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

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

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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, Eur; (Full Title of the Plan) Dated: June 25, 2009 By:

/s/ Philip A. Brown

Vice President, Human Resources