Ultragenyx Pharmaceutical Inc.
Form 424B5
July 17, 2015
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Filed Pursuant to Rule 424(b)(5)
Registration No. 333-201838

CALCULATION OF REGISTRATION FEE

Title of Each Class of Securities to be Registered	Amount to be Registered(1)	Proposed Maximum Offering Price Per Share	Proposed Maximum Aggregate Offering Price	Amount of Registration Fee(2)
Common Stock, par value $0.001 per share	2,530,000	$120.00	$303,600,000	$35,278.32

(1) Includes 330,000 shares of common stock, par value $0.001 per share, which may be purchased by the underwriters upon exercise of the underwriters option to purchase additional shares.
(2) Calculated in accordance with Rules 456(b) and 457(r) of the Securities Act of 1933, as amended.

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Prospectus Supplement

(To Prospectus dated February 3, 2015)

2,200,000 shares

Common Stock

We are offering 2,200,000 shares of our common stock.

Our common stock is listed on The NASDAQ Global Select Market under the symbol RARE . The last reported sale price of our common stock on The NASDAQ Global Select Market on July 14, 2015 was $126.77 per share.

We are an emerging growth company, as that term is used in the Jumpstart Our Business Startups Act of 2012, and, as such, have elected to comply with certain reduced public company reporting requirements for this prospectus and certain filings.

Investing in our common stock involves a high degree of risk. See Risk Factors beginning on page S-19.

	Per share	Total
Public offering price	$ 120.00	$ 264,000,000
Underwriting discounts and commissions[1]	$ 6.60	$ 14,520,000
Proceeds to Ultragenyx Pharmaceutical Inc., before expenses	$ 113.40	$ 249,480,000

(1) See Underwriters for additional disclosure regarding underwriting discounts, commissions and estimated offering expenses.

We have granted the underwriters an option for a period of 30 days to purchase up to 330,000 additional shares of our common stock.

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

The underwriters expect to deliver the shares of common stock to purchasers on or about July 21, 2015.

Morgan Stanley **J.P. Morgan** **Cowen and Company**

JMP Securities **Wedbush PacGrow**

July 15, 2015

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Prospectus Supplement

Prospectus

This document is in two parts. The first part is this prospectus supplement, which describes the specific terms of this offering. The second part, the accompanying prospectus, gives more general information, some of which may not apply to this offering. In the event that the description of this offering varies between this prospectus supplement and the accompanying prospectus, you should rely on the information contained in this prospectus supplement. Generally, when we refer to the prospectus, we are referring to this prospectus supplement and the accompanying prospectus combined.

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

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

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PROSPECTUS SUMMARY

The items in the following summary are described in more detail later in this prospectus supplement and the documents incorporated herein by reference. This summary provides an overview of selected information and does not contain all of the information you should consider before buying our common stock. Therefore, you should read the entire prospectus carefully, including the information in our filings with the Securities and Exchange Commission, or SEC, incorporated by reference in this prospectus, before deciding to invest in our common stock. Investors should carefully consider the information set forth under Risk Factors beginning on page S-19 of this prospectus supplement and those identified in our most recent Annual Report on Form 10-K and our subsequent Quarterly Report on Form 10-Q. In this prospectus, unless the context otherwise requires, references to the Company, we, us, our, or Ultragenyx refer to Ultragenyx Pharmaceutical Inc.

Overview

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

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

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

KRN23, or UX023, is an antibody targeting fibroblast growth factor 23, or FGF23, in development for the treatment of X-linked hypophosphatemia, or XLH, a rare genetic disease that impairs bone growth. We are developing KRN23 pursuant to our collaboration with Kyowa Hakko Kirin Co., Ltd., or KHK. KHK has completed one Phase 1 study, one Phase 1/2 study, and one longer-term Phase 1/2 study of KRN23 in adults with XLH. We initiated a Phase 2 pediatric study in July 2014. We are also continuing the clinical development of KRN23 in adults with XLH.

We are also developing KRN23 for the treatment of tumor-induced osteomalacia, or TIO. TIO results from typically benign tumors that produce excess levels of FGF23, which can lead to severe hypophosphatemia, osteomalacia, fractures, fatigue, bone and muscle pain, and muscle weakness. We initiated a Phase 2 study of KRN23 in adult inoperable TIO patients in March 2015.

rhGUS, or UX003, is an enzyme replacement therapy we are developing for the treatment of mucopolysaccharidosis 7, or MPS 7, a rare lysosomal storage disease that often leads to multi-organ

dysfunction, pervasive skeletal disease, and death. We completed enrollment of a Phase 3 clinical study in June 2015.

rhPPCA, or UX004, is an enzyme replacement therapy in preclinical development for galactosialidosis, a rare lysosomal storage disease that can cause multi-system clinical disease similar to MPS 7, including enlarged liver, joint disease, abnormal bone development, short stature, and death. We continue preclinical development of rhPPCA.

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

- Triheptanoin, or UX007, is a synthetic triglyceride with a specifically designed chemical composition being studied in an international open-label Phase 2 study for the treatment of long-chain fatty acid oxidation disorders, or LC-FAOD. LC-FAOD is a set of rare metabolic diseases that prevent the conversion of fat into energy and can cause low blood sugar, muscle rupture, and heart and liver disease.

- Triheptanoin is also being studied 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.

- Ace-ER (previously known as sialic acid-extended release, or SA-ER), or UX001, is an extended-release form of sialic acid in a Phase 2 extension study for the treatment of GNE myopathy (also known as hereditary inclusion body myopathy), a neuromuscular disorder that causes muscle weakness and wasting. We initiated a Phase 3 study in May 2015, and we intend to file a Marketing Authorization Application, or MAA, seeking conditional approval from the European Medicines Agency, or EMA, for the use of Ace-ER in the treatment of GNE myopathy in the second half of 2015.

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. 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 Strensiq (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 company. The critical components of our business strategy include the following:

Focus on rare and ultra-rare diseases with significant unmet medical need;

Focus on diseases and therapies with clear mechanisms of action;

Leverage our experience and relationships to in-license promising product candidates;

Develop and commercialize multiple product candidates in parallel;

Focus on excellent and rapid clinical and regulatory execution; and

Seek to retain global commercialization rights to product candidates.

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Product Candidates

The following table summarizes our product candidate pipeline:

KRN23 (UX023) for the treatment of XLH

KRN23 is a fully human monoclonal antibody administered via subcutaneous injection that is designed to bind and reduce the biological activity of FGF23 to increase abnormally low phosphate levels in patients with 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 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

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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.

Results from a four-month Phase 1/2 study in 28 adult XLH patients and subsequent twelve-month Phase 1/2 study of KRN23 in 22 patients were presented at the 2014 ICE/ENDO joint meeting of The Endocrine Society and the International Congress on Endocrinology in June 2014 and ASBMR Annual Meeting in September 2014, respectively. The data demonstrated that repeat doses of KRN23 over four months led to increases in serum phosphate, renal tubular reabsorption of phosphate, and serum vitamin D levels over the 16-month period. Increases in bone remodeling markers of bone formation and bone resorption were also observed.

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.

KRN23 was generally safe and well tolerated over the cumulative treatment period. The most common treatment-related adverse events were injection site reaction, arthralgia (joint pain), 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 (kidney stones) 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 are also assessing preliminary clinical effects of KRN23 treatment on bone health and deformity as measured by radiographic assessments, growth, muscle strength, and motor function, as well as markers of bone health and patient-reported outcomes of pain, disability, and quality of life.

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 were divided into three cohorts of escalating starting dose levels of KRN23 with either monthly or biweekly dosing regimens. At the end of the 16-week dose-titration period, patients were allowed to continue to receive dose increases in order to reach the individually-optimized dose of KRN23 on a monthly or biweekly basis for the 48-week treatment period.

In June 2015, we released 16-week data from the Phase 2 pediatric study showing that all patients had increases in serum phosphorus levels from baseline during the 16-week period. At the end of the 16 weeks, 71% of patients receiving monthly dosing reached the normal serum phosphorus range with a mean dose of 0.84 mg/kg per treatment. At the time of the analysis, of the patients who had reached week 22, 9 out of 12 (75%) reached the normal range after further dose titration. In the biweekly dosing group, the proportion of patients reaching the normal serum phosphorus range was 50% at week 16. Of the patients who had reached week 24, 7 out of 9 (78%) reached the normal range after further dose titration. Mean increases were also observed in renal phosphate reabsorption (TmP/GFR) and in serum

1,25 dihydroxy vitamin D levels.

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Per the study protocol, patients discontinued standard of care, or SOC, oral phosphate and Vitamin D therapy after the screening visit, which was two to four weeks prior to the baseline visit. Serum phosphorus levels were measured in 16 patients at screening and baseline. While on SOC, the mean serum phosphorus level at screening in these 16 patients was 2.40 mg/dL and after wash-out from SOC at baseline was 2.26 mg/dL, representing a mean change of 0.14 mg/dL. All 16 patients had an increase from baseline in serum phosphorus after treatment with KRN23 to a mean of 3.09 mg/dL, representing an improvement of 0.83 mg/dL compared to baseline.

No serious adverse events have been reported and there have been no discontinuations from the pediatric Phase 2 study for any reason. The most common adverse events considered to be treatment related were injection site reactions in eight patients (22%), injection site erythema in four patients (11%), and injection site rash, injection site swelling, and limb pain in three patients (8% each). All of these treatment-related adverse events were considered mild in severity. No significant changes were observed in serum calcium, urinary calcium, or serum intact parathyroid hormone (iPTH). No patients had serum phosphorus levels above the upper limit of normal in either dosing group.

In July 2015, we released interim bone treatment data from the first 12 patients in the pediatric Phase 2 study. This interim data showed an improvement in mean rickets score after 40 weeks of treatment with KRN23. Eleven of the first 12 patients enrolled had been on SOC oral phosphate and Vitamin D therapy for an average of six years (3.3 9.4 years) prior to the baseline assessment. The mean rickets score was 1.4 at baseline using the Thacher Rickets Severity Scoring method as evaluated by a blinded expert reader and decreased to 0.6 after 40 weeks of treatment with KRN23, representing a 58% reduction in rickets score. Eight out of 11 patients with rickets at baseline demonstrated an improvement in rickets, of which three patients no longer exhibited radiographic evidence of rickets at week 40. One patient in the biweekly dosing group did not present with radiographic evidence of rickets at baseline and was excluded from the analysis.

Of the 12 patients, 6 received biweekly dosing and 6 received monthly dosing of KRN23. Of the 5 patients with rickets at baseline in the biweekly dosing group, 100% demonstrated improvement in rickets from a mean baseline rickets score of 1.5 to a mean score of 0.3 at week 40, representing an 80% reduction in rickets score. Of the 6 patients in the monthly dosing group, 50% demonstrated improvement in rickets from a mean baseline score of 1.3 to a mean score of 0.8 at week 40, representing a 38% reduction in rickets score. Two patients in the monthly dosing group did not show a change and one patient in the monthly dosing group worsened by 0.5 points.

All 12 patients had increases in serum phosphorus levels from baseline at points during the 40-week treatment period. In the biweekly dosing group (n=6), mean serum phosphorus increased by 0.70 mg/dL, from 2.78 mg/dL at baseline to 3.48 mg/dL, which is in the normal range (3.2 6.1 mg/dL). In the monthly dosing group (n=6), mean serum phosphorus at peak increased by 1.06 mg/dL, from 2.42 mg/dL at baseline to 3.48 mg/dL. The monthly dosing patients showed a decrease to the trough level before the next dose, unlike the biweekly regimen which showed stable phosphate levels. Increases in renal phosphate reabsorption (TmP/GFR) and in serum 1,25 dihydroxy vitamin D levels were observed in all 12 patients.

No serious adverse events have been reported in the study to date and there have been no discontinuations from the study for any reason. For the 12 patients who had reached 40 weeks at the time of the interim analysis, the most common adverse events considered to be treatment related were injection site reactions. All of the treatment-related adverse events were considered mild in severity.

No significant changes were observed in serum calcium, urinary calcium, or serum intact parathyroid hormone (iPTH) in the 12 patients. None of the patients had serum phosphorus levels above the upper limit of normal in either dosing group. Safety data on renal ultrasounds, echocardiograms, or immune response to KRN23 are not yet available.

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Additional data from the pediatric Phase 2 study, including radiographic assessments, through 40 weeks of treatment for 36 patients are expected to be available in the fourth quarter of 2015. We are expanding the pediatric Phase 2 study to enroll approximately 50 patients. The radiographic assessments through 40 weeks for the fully expanded patient group are expected to be available in mid-2016.

Depending on the final results of our Phase 2 pediatric study, we intend to conduct a Phase 3 pediatric study. In our meetings with the United States Food and Drug Administration, or FDA, and EMA, the regulatory agencies 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 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. In discussions with the EMA, the agency indicated that a filing for conditional approval may be possible based on data from the 40-week interim analysis from the pediatric Phase 2 study and from the completed Phase 1/2 and ongoing Phase 2b studies in adults, provided that there is a positive benefit-risk profile and with the obligation to conduct confirmatory studies. We will determine whether to file for conditional approval after we evaluate the pediatric Phase 2 40-week data.

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 are also continuing to develop KRN23 in adults with XLH. We initiated a long-term, open-label Phase 2b extension study of KRN23 in adult XLH patients who had previously participated in the studies conducted by KHK. Based on discussions with the FDA and EMA, we plan to initiate a Phase 3 randomized, double-blind, placebo-controlled study in approximately 120 adult XLH patients and a Phase 3 open-label bone biopsy study in approximately ten adult XLH patients in the second half of 2015. The planned primary endpoint for the larger study will be serum phosphorus levels at 24 weeks. We expect that the Brief Pain Inventory patient-reported outcome will be a key secondary endpoint.

In July 2015, we announced that the FDA has granted Fast Track Designation to the KRN23 program in XLH. Fast Track Designation is intended to facilitate the development and expedite the review of drugs for serious and life-threatening conditions that have the potential to address an unmet medical need. The designation allows for more frequent interaction with the FDA review team. It also enables eligibility for priority review and the potential for a rolling review of the Biologics License Application, when and if filed. However, priority review designation does not change the scientific or medical standard for approval or the quality of evidence necessary to support approval.

Potential market opportunity

Based on incidence and prevalence rates published in a Danish epidemiologic study and surveys of physicians in the United States, we estimate that there are approximately 3,000 cases of XLH in pediatric patients in the United States. Further, there are an estimated 9,000 cases of XLH in adult patients in the United States. However, we expect that many of these adult patients may not seek treatment if their bone disease is not too severe.

KRN23 (UX023) for the treatment of TIO

We are also developing KRN23 for the treatment of TIO. TIO results from typically benign tumors that produce excess levels of FGF23, which can lead to severe hypophosphatemia, osteomalacia, bone fractures, fatigue, bone and muscle pain, and muscle weakness. There are cases in which resection of the tumor is not feasible or recurrence of the

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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 are expected in late 2015 or early 2016.

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.

Potential market opportunity

We estimate that there are between 500 and 1,000 patients with TIO in the United States, and that approximately half of all cases are inoperable.

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 Annual Symposium and showed a decline in urinary 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%.

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

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

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

In 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 of birth, 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 and other expanded access programs. Results following 24 weeks of treatment of the first eIND patient were announced in September 2014 and published in Molecular Genetics and Metabolism in February 2015.

Potential market opportunity

Through our ongoing survey work with metabolic clinics, we have identified approximately 100 potential MPS 7 patients worldwide to date. Based on our experiences with other MPS diseases, we expect that, over time,

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more patients will be identified during patient identification efforts globally, potentially resulting in up to approximately 200 patients in the developed world.

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 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 oil supplementation. Despite treatment with the current standard of care, many patients continue to suffer significant morbidity and mortality.

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

Triheptanoin is currently being evaluated in a prospective, interventional, open-label Phase 2 study in 29 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.

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Potential market opportunity

Based upon data from the National Newborn Screening Information System, we estimate that there are approximately 2,000 to 3,500 LC-FAOD patients in the United States, depending on the assumed mortality rate.

It is unclear how many of these patients are currently diagnosed because the availability of newborn screening in all 50 states in the United States is a relatively new development. Furthermore, until additional clinical development of triheptanoin is conducted, it is not clear which subsets of diagnosed patients would be considered by clinicians to be good candidates for triheptanoin treatment. Outside of the United States, where newborn screening is not consistently done, estimates of the prevalence of LC-FAOD are more uncertain.

Triheptanoin (UX007) for the treatment of Glut1 DS

We are also developing triheptanoin for patients with Glut1 DS. Glut1 DS is caused by a mutation affecting the gene that codes for Glut1, which is a protein that transports glucose from the blood into the brain. Because glucose is the primary source of energy for the brain, Glut1 DS results in a chronic state of brain energy deficiency and is characterized by seizures, developmental delay, and movement disorder. There are currently no approved drugs specific to Glut1 DS. The current standard of care for Glut1 DS is the ketogenic diet, an extreme high-fat (70-80% of daily calories as fat)/low-carbohydrate diet, which generates ketone bodies as an alternative energy source to glucose, and one or more antiepileptic drugs. The ketogenic diet can be effective in reducing seizures but compliance can be difficult, and the 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 study 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 six-week baseline period and subsequent eight-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. Enrollment in the study has been slower than we originally anticipated due to the rare nature of the disease as well as the inclusion criteria of the study; the study is enrolling patients who are not currently on or compliant with the ketogenic diet and who have a minimum baseline seizure rate. 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. Subject to the final enrollment target and the rate of enrollment in the study, 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.

In April 2015, positive data from an investigator-sponsored study of triheptanoin for the treatment of movement disorders associated with Glut1 DS were presented at the American Academy of Neurology Annual Meeting. The data showed a statistically significant 90% reduction in movement disorder events after treatment with triheptanoin ($p=0.028$) and a statistically significant increase in events after withdrawal from treatment with triheptanoin

(p=0.043). Based on the study results, we intend to initiate a company-sponsored clinical study of

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triheptanoin in the Glut1 DS movement disorder phenotype and we expect to discuss the details of final study design with the FDA in the second half of 2015.

Potential market opportunity

While a comprehensive genetic analysis of birth incidence has not been conducted, published literature suggests a range of 3,000 to 7,000 Glut1 DS patients in the United States based on evaluations of generalized or absence seizures. The increasing recognition of alternative or variable motor forms of the disease suggests that older patients may be discovered over time. Given that the disease can be inherited as an autosomal dominant disease, the discovery of one patient may be used to identify other affected relatives in some cases, which can be important in marketing of the product.

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

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

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

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

We continued to treat these patients in an extension study evaluating an increased daily dosage of sialic acid based on the dose dependence observed at weeks 24 and 48. Interim data from the extension study were presented at the International Congress of the World Muscle Society, or WMS, in October 2014. In the first part

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of the extension study, all 46 patients who completed the 48-week Phase 2 study crossed over to six grams for a variable period of time that was on average 24 weeks. In the second part of the extension study, all 46 patients and 13 treatment-naïve patients received 12 grams of Ace-ER for 24 weeks. The results presented at WMS 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 Ace-ER treatment. The higher dose appeared to be generally safe and well tolerated with no drug-related serious adverse events, but the rate of mild to moderate gastrointestinal adverse events did appear to be greater with this dose. Throughout the approximately two-year study period, treatment with Ace-ER appeared to slow the progression of upper extremity disease when compared to the 24-week placebo group extrapolated out to two years.

We initiated a randomized, double-blind, placebo-controlled 48-week pivotal Phase 3 study of Ace-ER in approximately 80 patients with GNE myopathy in May 2015. The FDA agreed with the Phase 3 study design, including the primary endpoint of a composite of upper extremity muscle strength, with supportive secondary endpoint data from a patient-reported outcome, both of which were studied in the Phase 2 study. Data from the Phase 3 study are expected in the second half of 2016.

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

Potential market opportunity

GNE Myopathy is expected to occur in one in every 1,600 persons of Persian Jewish descent. Patients have also been identified in Asian Indian, European, Chinese, Japanese, Korean, and Middle Eastern populations. To better understand the patient population, we conducted an initial survey of 420 myopathy clinics in the United States, and the extrapolated results suggest a patient population of approximately 2,000 worldwide.

Risks Associated with Our Business

Our ability to implement our business strategy is subject to numerous risks that you should be aware of before making an investment decision. These risks are described more fully in the section entitled Risk Factors immediately following this prospectus summary and our most recent Annual Report on Form 10-K and our subsequent Quarterly Report on Form 10-Q, incorporated by reference herein. These risks include, among others:

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

- We are heavily dependent upon the success of our product candidates, some of which are in the early stages of clinical development, and we cannot provide any assurance that any of our product candidates will receive regulatory approval;

Because the target patient populations of our product candidates are small, and the addressable patient populations potentially even smaller, we must be able to successfully identify patients and acquire a significant market share to achieve profitability and growth;

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

The insurance coverage and reimbursement status of newly-approved products is uncertain and 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;

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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; and

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

Our Corporate Information

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

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

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THE OFFERING

Common stock offered by us	2,200,000 shares
Underwriters option to purchase additional shares	We have granted the underwriters a 30-day option to purchase up to an additional 330,000 shares of our common stock.
Common stock to be outstanding after this offering	37,812,019 shares (38,142,019 shares if the underwriters exercise their option to purchase additional shares in full)
Use of proceeds	We estimate that the net proceeds to us from this offering will be approximately $249.2 million, or approximately $286.6 million if the underwriters exercise their option to purchase additional shares in full, after deducting the underwriting discounts and commissions and estimated offering expenses payable by us at the public offering price of $120.00 per share. We intend to use the net proceeds of the offering to accelerate commercial launch preparation for Ace-ER, rhGUS, and KRN23 in the U.S. and other markets. We may also use a portion of the net proceeds to in-license, acquire, or invest in additional businesses, technologies, products, or assets, though we currently have no specific agreements, commitments, or understandings with respect to any material in-licensing or acquisition transactions. Finally, we may use any remaining net proceeds to invest in early-stage translational research, additional clinical activities, supportive general and administrative activities, hiring of additional personnel, and expansion of our facilities, as well as for additional working capital and other general corporate purposes.
Risk factors	You should read the Risk Factors section of this prospectus and our most recent Annual Report on Form 10-K and our subsequent Quarterly Report on Form 10-Q, incorporated by reference herein, for a discussion of factors to consider carefully before deciding to invest in shares of our common stock.
NASDAQ Global Select Market symbol	RARE

The number of shares of common stock to be outstanding after this offering is based on 35,612,019 shares of common stock outstanding as of March 31, 2015.

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

2,722,451 shares of common stock issuable upon the exercise of outstanding stock options as of March 31, 2015 having a weighted-average exercise price of $20.80 per share;

39,000 shares of common stock issuable upon the vesting of restricted stock units outstanding as of March 31, 2015;

324,351 shares of common stock issuable upon the exercise of outstanding warrants as of March 31, 2015 having a weighted-average exercise price of $3.01 per share;

2,595,430 shares of common stock reserved for issuance pursuant to future equity awards under our 2014 Incentive Plan as of March 31, 2015, as well as any future increases in the number of shares of our common stock reserved for future issuance under this plan; and

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950,295 shares of common stock reserved for future issuance under our 2014 Employee Stock Purchase Plan, or 2014 ESPP, as of March 31, 2015, as well as any future increases in the number of shares of our common stock reserved for future issuance under the 2014 ESPP.

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

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

assumes no exercise of outstanding options or warrants after March 31, 2015.

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SUMMARY FINANCIAL DATA

The following table summarizes our statements of operations and balance sheet data. We have derived the following statements of operations data for the years ended December 31, 2012, 2013, and 2014 from our audited financial statements incorporated by reference in this prospectus from our Annual Report on Form 10-K for the fiscal year ended December 31, 2014, or our 2014 Annual Report, and we have derived the following statements of operations data for the three months ended March 31, 2014 and March 31, 2015 and the balance sheet data as of March 31, 2015 from our unaudited interim financial statements incorporated by reference in this prospectus from our Quarterly Report on Form 10-Q for the quarter ended March 31, 2015, or our March 2015 Quarterly Report. You should read this data together with our financial statements and related notes, as well as the information under the captions Selected Financial Data and Management s Discussion and Analysis of Financial Condition and Results of Operations appearing in our 2014 Annual Report and our March 2015 Quarterly Report, which are incorporated by reference herein. Our historical results are not necessarily indicative of our future results, and results of interim periods are not necessarily indicative of results for the entire year.

	Year Ended December 31,			Three Months Ended March 31,	
	2012	2013	2014	2014	2015
	(in thousands, except share and per share amounts)			(unaudited)	
Statements of Operations Data:					
Operating expenses:					
Research and development	$ 12,641	$ 27,829	$ 45,967	$ 8,353	$ 17,364
General and administrative	3,344	4,451	10,811	1,986	4,138
Total operating expenses	15,985	32,280	56,778	10,339	21,502
Loss from operations	(15,985)	(32,280)			