Ultragenyx Pharmaceutical Inc.
Form 424B5
July 14, 2015
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Registration No. 333-201838

The information in this preliminary prospectus supplement is not complete and may be changed. This preliminary prospectus supplement and the accompanying prospectus are not an offer to sell these securities, and it is not soliciting an offer to buy these securities in any jurisdiction where the offer or sale is not permitted.

Subject to completion, dated July 14, 2015

Prospectus Supplement

(To Prospectus dated February 3, 2015)

$250,000,000

Common Stock

We are offering $250,000,000 of 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 13, 2015 was $118.97 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	$	$
Underwriting discounts and commissions[(1)]	$	$
Proceeds to Ultragenyx Pharmaceutical Inc., before expenses	$	$

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

We anticipate granting the underwriters an option for a period of 30 days to purchase up to $37,500,000 of 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 , 2015.

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

JMP Securities **Wedbush PacGrow**

July , 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	shares
Underwriters option to purchase additional shares	We have granted the underwriters a 30-day option to purchase up to an additional shares of our common stock.
Common stock to be outstanding after this offering	shares (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 $235.9 million, or approximately $271.4 million if the underwriters exercise their option to purchase additional shares in full, after deducting the estimated underwriting discounts and commissions and estimated offering expenses payable by us at the assumed public offering price of $118.97 per share, which is the last reported sale price of our common stock on The NASDAQ Global Select Market on July 13, 2015. 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;

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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

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)	(56,778)	(10,339)	(21,502)
Interest income	1	216	608	93	273
Other expense, net	(350)	(3,006)	(3,632)	(3,384)	(150)
Net loss	$ (16,334)	$ (35,070)	$ (59,802)	$ (13,630)	$ (21,379)
Net loss attributable to common stockholders[1]	$ (19,561)	$ (50,289)	$ (64,610)	$ (18,438)	$ (21,379)
Net loss per share attributable to common stockholders, basic and diluted[1]	$ (14.20)	$ (14.87)	$ (2.25)	$ (0.85)	$ (0.63)
Shares used in computing net loss per share attributable to common stockholders, basic and diluted[1]	1,377,207	3,382,489	28,755,758	21,582,435	34,008,830

	As of March 31, 2015	
	Actual	As-Adjusted[2][3]
	(in thousands)	
	(unaudited)	
Balance Sheet Data:		
Cash, cash equivalents and short-term investments	$ 342,566	$ 578,496
Working capital	336,271	572,201
Total assets	355,840	591,770
Accumulated deficit	(160,420)	(160,420)
Total stockholders equity	341,119	577,049

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(1) See (a) Notes 2 and 13 to our audited financial statements included in our 2014 Annual Report incorporated by reference herein and (b) Notes 2 and 10 to our interim financial statements included in our March 2015 Quarterly Report incorporated herein by reference for an explanation of the calculations of our basic and diluted net loss per share attributable to common stockholders.

(2) The as-adjusted balance sheet data reflects the sale of an assumed 2,101,370 shares of common stock offered by us in this offering at an assumed public offering price of $118.97 per share, which is the last reported sale price of our common stock on The NASDAQ Global Select Market on July 13, 2015, after deducting estimated underwriting discounts and commissions and estimated offering expenses payable by us.

(3) A $1.00 increase (decrease) in the assumed public offering price of $118.97 per share, which is the last reported sale price of our common stock on The NASDAQ Global Select Market on July 13, 2015, would increase (decrease) the as-adjusted amount of each of cash, cash equivalents and short-term investments, working capital, total assets and total stockholders equity by approximately $2.0 million, assuming that the number of shares offered by us remains the same and after deducting estimated underwriting discounts and commissions and estimated offering expenses payable by us. A 100,000 share increase (decrease) in the number of shares offered by us at the assumed public offering price of $118.97 per share would increase (decrease) the as-adjusted amount of each of cash, cash equivalents and short-term investments, working capital, total assets and total stockholders equity by approximately $11.2 million after deducting estimated underwriting discounts and commissions and estimated offering expenses payable by us.

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RISK FACTORS

Investing in our common stock involves a high degree of risk. Before investing in our common stock, you should consider carefully the risks described below, together with the other information contained in this prospectus supplement and incorporated by reference in this prospectus supplement, including the risks and uncertainties discussed under Risk Factors herein and in our most recent Annual Report on Form 10-K and our subsequent Quarterly Report on Form 10-Q, which are incorporated by reference herein in their entirety. If any of the risks incorporated by reference herein or set forth below occur, our business, financial condition, results of operations and future growth prospects could be materially and adversely affected. In these circumstances, the market price of our common stock could decline, and you may lose all or part of your investment.

Risks Related to this Offering

If you purchase our common stock in this offering, you will incur immediate and substantial dilution in the book value of your shares.

Investors purchasing shares of common stock in this offering will pay a price per share that substantially exceeds the as-adjusted book value per share of our tangible assets after subtracting our liabilities. As a result, investors purchasing shares of common stock in this offering will incur immediate dilution of $103.67 per share, based on an assumed public offering price of $118.97 per share, which is the last reported sale price of our common stock on The NASDAQ Global Select Market on July 13, 2015, and our as-adjusted net tangible book value as of March 31, 2015 after giving effect to this offering. For information on how the foregoing amounts were calculated, see Dilution.

This dilution is due to the substantially lower price paid by our investors who purchased shares prior to this offering as compared to the price offered to the public in this offering, and the exercise of stock options granted to our employees. In addition, as of March 31, 2015, we had outstanding 2,761,451 restricted stock units and options and warrants to purchase 324,351 shares of our common stock; the vesting of the restricted stock units and the exercise of any of these options or warrants would result in additional dilution. As a result of the dilution to investors purchasing shares in this offering, investors may receive significantly less than the purchase price paid in this offering, if anything, in the event of our liquidation.

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

If our existing stockholders sell, or indicate an intention to sell, substantial amounts of our common stock in the public market after the lock-up and other legal restrictions on resale discussed in this prospectus lapse, the market price of our common stock could decline. Based upon the number of shares of common stock outstanding as of March 31, 2015, and an assumed offering price per share of $118.97 as of July 13, 2015, upon the closing of this offering we will have outstanding a total of approximately 37,713,389 shares of common stock. Of these shares, the shares of our common stock sold in our public offerings in 2014 and 2015 (other than any shares purchased by our then-existing investors and directors and officers) are currently freely tradable, and the shares to be sold in this offering, plus any shares sold upon exercise of the underwriters option to purchase additional shares, will be freely tradable, without restriction, in the public market immediately following this offering. Morgan Stanley & Co. LLC, J.P. Morgan Securities LLC and Cowen and Company, LLC may, however, in their sole discretion, permit our officers, directors and stockholders who are subject to these lock-up agreements to sell shares prior to the expiration of the lock-up agreements.

Certain holders of shares of our common stock are entitled to rights with respect to the registration of their shares under the Securities Act. See Description of Capital Stock Registration Rights. Registration of these shares under the Securities Act would result in the shares becoming freely tradable without restriction under the Securities Act, except for shares purchased by affiliates. Any sales of securities by these stockholders could have a material adverse effect on the trading price of our common stock.

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We will have broad discretion in the use of the net proceeds to us from this offering; we may not use the offering proceeds that we receive effectively.

Our management will have broad discretion in the application of the net proceeds to us from this offering, including for any of the purposes described in the section entitled Use of Proceeds, and you will not have the opportunity as part of your investment decision to assess whether the net proceeds are being used appropriately. Because of the number and variability of factors that will determine our use of the net proceeds to us from this offering, their ultimate use may vary from their currently intended use. The failure by our management to apply these funds effectively could harm our business. Pending their use, we may invest the net proceeds to us from this offering in investment-grade, interest-bearing securities. These investments may not yield a favorable return to our stockholders.

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CAUTIONARY NOTE REGARDING FORWARD-LOOKING STATEMENTS

This prospectus contains forward-looking statements that involve risks and uncertainties. We make such forward-looking statements pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995 and other federal securities laws. All statements other than statements of historical facts contained in this prospectus are forward-looking statements. In some cases, you can identify forward-looking statements by words such as anticipate, believe, contemplate, continue, could, estimate, expect, intend, may, plan, potentia seek, should, target, will, would, or the negative of these words or other comparable terminology. These forward-looking statements include, but are not limited to, statements about:

- our expectations regarding the timing of commencing our clinical studies and reporting results from same;
- the timing of planned regulatory approval filings and the likelihood of regulatory approvals for our product candidates;
- the potential market opportunities for commercializing our product candidates;
- our expectations regarding the potential market size and the size of the patient populations for our product candidates, if approved for commercial use;
- estimates of our expense, future revenue, capital requirements, and our needs for additional financing;
- estimates of our operating expenses and the timing of our use of cash;
- our ability to develop, acquire, and advance product candidates into, and successfully complete, clinical studies;
- the implementation of our business model and strategic plans for our business and product candidates;
- the initiation, timing, progress, and results of future preclinical studies and clinical studies, and our research and development programs;
- the scope of protection we are able to establish and maintain for intellectual property rights covering our product candidates;
- our ability to maintain and establish collaborations or obtain additional funding;

our ability to maintain and establish relationships with third parties, such as contact research organizations, suppliers and distributors;

our financial performance and expansion of our organization;

our ability to obtain supply of our product candidates;

developments and projections relating to our competitors and our industry;

our use of proceeds from this offering;

our expectations regarding the time during which we will be an emerging growth company under the JOBS Act; and

other risks and uncertainties, including those listed in Risk Factors.

Any forward-looking statements in this prospectus reflect our current views with respect to future events or our future financial performance and involve known and unknown risks, uncertainties, and other factors that may cause our actual results, performance, or achievements to be materially different from any future results, performance, or achievements expressed or implied by these forward-looking statements. Factors that may cause actual results to differ materially from current expectations include, among other things, those listed under Risk Factors and elsewhere and incorporated by reference in this prospectus. Given these uncertainties, you should

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not place undue reliance on these forward-looking statements. Except as required by law, we assume no obligation to update or revise these forward-looking statements for any reason, even if new information becomes available in the future.

This prospectus 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.

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USE OF PROCEEDS

We estimate that the net proceeds to us from the assumed sale of 2,101,370 shares of common stock offered by us in this offering will be approximately $235.9 million, based on an assumed public offering price of $118.97 per share, which is the last reported sale price of our common stock on The NASDAQ Global Select Market on July 13, 2015, after deducting the estimated underwriting discounts and commissions and estimated offering expenses payable by us. If the underwriters exercise their option to purchase additional shares in full, we estimate that our net proceeds will be approximately $271.4 million, after deducting the estimated underwriting discounts and commissions and estimated offering expenses payable by us. Each $1.00 increase (decrease) in the assumed public offering price of $118.97 per share, which is the last reported sale price of our common stock on The NASDAQ Global Select Market on July 13, 2015, would increase (decrease) the net proceeds to us by approximately $2.0 million, assuming that the number of shares offered by us, remains the same and after deducting estimated underwriting discounts and commissions and estimated offering expenses payable by us. We may also increase or decrease the number of shares we are offering. Each increase (decrease) of 100,000 shares in the number of shares offered by us would increase (decrease) the net proceeds to us from this offering by approximately $11.2 million, assuming that the assumed public offering price remains the same and after deducting the estimated underwriting discounts and commissions and estimated offering expenses payable by us.

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.

Our expected use of net proceeds to us from this offering represents our current intentions based upon our present plans and business condition. As of the date of this prospectus, we cannot predict all of the particular uses for the net proceeds to be received upon the completion of this offering or the actual amounts that we will spend on the uses set forth above. Due to the many variables inherent to the development of our product candidates, we cannot currently predict the stage of development we expect the net proceeds to us of this offering to achieve for our clinical studies and product candidates.

The amount and timing of our actual expenditures will depend upon numerous factors, including the results of our research and development efforts, the timing and success of preclinical studies, our ongoing clinical studies or clinical studies we may commence in the future and the timing of regulatory submissions. As a result, our management will have broad discretion over the use of the net proceeds to us from this offering.

Pending the use of the proceeds to us from this offering, we intend to invest these proceeds in interest-bearing, investment-grade securities, certificates of deposit, or government securities.

Our operating expenses for the three month period ended March 31, 2015 were $21.5 million. Operating expenses for the three months ended June 30, 2015 are expected to have been moderately higher than operating expenses in the first quarter of 2015. In addition, we expect that our quarterly and annual operating expenses will increase and accelerate for the remainder of 2015, as well as further increase and accelerate in 2016, as we continue to advance the development of our current product candidates and expand our product pipeline. We estimate that, with our current operating plan, without giving effect to the proceeds from this offering, our existing cash, cash equivalents and short-term investments, will fund our activities into 2018.

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PRICE RANGE OF COMMON STOCK

Our common stock has been publicly traded on The NASDAQ Global Select Market under the symbol RARE since January 31, 2014. Prior to that time, there was no public market for our common stock. The following table sets forth the high and low sale prices per share for our common stock on The NASDAQ Global Select Market for the periods indicated:

	High	Low
2014		
First Quarter (beginning January 31, 2014)	$ 69.77	$ 35.15
Second Quarter	$ 60.00	$ 32.02
Third Quarter	$ 60.04	$ 37.77
Fourth Quarter	$ 58.33	$ 38.01
2015		
First Quarter	$ 65.35	$ 44.27
Second Quarter	$ 105.97	$ 56.11
Third Quarter (through July 13, 2015)	$ 119.85	$ 98.68

On July 13, 2015, the last reported sale price of our common stock on The NASDAQ Global Select Market was $118.97 per share. As of July 6, 2015, we had approximately 10 holders of record of our common stock. This number does not include beneficial owners whose shares are held by nominees in street name.

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DIVIDEND POLICY

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

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CAPITALIZATION

The following table sets forth our cash, cash equivalents and short-term investments and capitalization as of March 31, 2015:

on an actual basis; and

on an as-adjusted basis to reflect the issuance and sale by us of an assumed 2,101,370 shares of our common stock in this offering at an assumed public offering price of $118.97 per share, which was the last reported sale price of our common stock on The NASDAQ Global Select Market on July 13, 2015, after deducting estimated underwriting discounts and commissions and estimated offering expenses payable by us.

You should read this information together with our financial statements and related notes and 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 March 2015 Quarterly Report, incorporated by reference in this prospectus. For more details on how you can obtain our Commission reports and other information, you should read the section of the prospectus entitled Where You Can Find More Information.

	As of March 31, 2015	
	Actual	As Adjusted[1]
	(in thousands, except share and per share data)	
	(unaudited)	
Cash, cash equivalents and short-term investments	$ 342,566	$ 578,496
Stockholders equity:		
Preferred stock, par value $0.001 per share 25,000,000 shares authorized; no shares issued or outstanding, actual and as-adjusted		
Common stock, par value $0.001 per share 250,000,000 shares authorized; 35,612,019 shares issued and outstanding, actual; 250,000,000 shares authorized, 37,713,389 shares issued and outstanding, as-adjusted	36	38
Additional paid-in capital	501,597	737,525
Accumulated other comprehensive loss	(94)	(94)
Accumulated deficit	(160,420)	(160,420)
Total stockholders equity	341,119	577,049
Total capitalization	$ 341,119	$ 577,049

(1)

A $1.00 increase (decrease) in the assumed public offering price of $118.97 per share, which is the last reported sale price of our common stock on The NASDAQ Global Select Market on July 13, 2015, would increase (decrease) the as-adjusted amount of each of cash, cash equivalents and short-term investments, additional paid-in capital, total stockholders equity and total capitalization by approximately $2.0 million, assuming that the number of shares offered by us, remains the same and after deducting estimated underwriting discounts and commissions and estimated offering expenses payable by us. A 100,000 share increase (decrease) in the number of shares offered by us at the assumed public offering price of $118.97 per share would increase (decrease) the as-adjusted amount of each of cash, cash equivalents and short-term investments, additional paid-in capital, total stockholders equity and total capitalization by approximately $11.2 million after deducting estimated underwriting discounts and commissions and estimated offering expenses payable by us. The as-adjusted information discussed above is illustrative only and will adjust based on the actual public offering price and other terms of this offering determined at pricing.

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The number of shares of common stock issued and outstanding in the table above excludes the following shares as of March 31, 2015:

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

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.

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DILUTION

If you invest in our common stock in this offering, your ownership interest will be diluted to the extent of the difference between the public offering price per share of our common stock and the as-adjusted net tangible book value per share of our common stock immediately after this offering.

Net tangible book value per share is determined by dividing our total tangible assets less our total liabilities by the number of shares of common stock outstanding. Our historical net tangible book value as of March 31, 2015 was approximately $341.1 million, or $9.58 per share.

Dilution per share to new investors represents the difference between the amount per share paid by purchasers of shares of common stock in this offering and the as-adjusted net tangible book value per share of common stock immediately after completion of this offering. After giving effect to the sale of an assumed 2,101,370 shares of common stock in this offering by us at an assumed public offering price of $118.97 per share, which is the last reported sale price of our common stock on The NASDAQ Global Select Market on July 13, 2015, and after deducting the estimated underwriting discounts and commissions and estimated offering expenses payable by us, our as-adjusted net tangible book value as of March 31, 2015 would have been $577.0 million, or $15.30 per share. This represents an immediate increase in net tangible book value of $5.72 per share to existing stockholders and an immediate dilution of $103.67 per share to investors participating in this offering, as illustrated in the following table:

Assumed public offering price per share		$ 118.97
Historical net tangible book value per share as of March 31, 2015	$ 9.58	
Increase in as-adjusted net tangible book value per share attributable to new investors	5.72	
As-adjusted net tangible book value per share after this offering		15.30
Dilution per share to investors participating in this offering		$ 103.67

Each $1.00 increase (decrease) in the assumed public offering price of $118.97 per share, which is the last reported sale price of our common stock on The NASDAQ Global Select Market on July 13, 2015, would increase (decrease) the as-adjusted net tangible book value by approximately $2.0 million, or approximately $0.05 per share, and increase (decrease) the dilution per share to new investors by approximately $0.95 per share, assuming that the number of shares offered by us, remains the same and after deducting estimated underwriting discounts and commissions and estimated offering expenses payable by us. An increase of 100,000 shares in the number of shares offered by us would increase the as-adjusted net tangible book value by approximately $11.2 million, or $0.26 per share, and the dilution per share to new investors would decrease by approximately $0.26 per share, assuming that the assumed public offering price remains the same and after deducting the estimated underwriting discounts and commissions and estimated offering expenses payable by us. Similarly, a decrease of 100,000 shares in the number of shares offered by us would decrease the as-adjusted net tangible book value by approximately $11.2 million, or approximately $0.26 per share, and the dilution per share to new investors would increase by approximately $0.26 per share, assuming that the assumed public offering price remains the same and after deducting the estimated underwriting discounts and commissions and estimated offering expenses payable by us. The as-adjusted information discussed above is illustrative only and will adjust based on the actual public offering price and other terms of this offering determined at pricing.

The foregoing calculations exclude the following shares as of March 31, 2015:

2,722,451 shares of common stock issuable upon the exercise of outstanding stock options 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;

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324,351 shares of common stock issuable upon the exercise of outstanding warrants 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 well as any future increases in the number of shares of our common stock reserved for future issuance under this plan; and

950,295 shares of common stock reserved for future issuance under our 2014 ESPP, as well as any future increases in the number of shares of our common stock reserved for future issuance under the 2014 ESPP.

Furthermore, we may choose to raise additional capital through the sale of equity or convertible debt securities due to market conditions or strategic considerations even if we believe we have sufficient funds for our current or future operating plans. New investors will experience further dilution if any of our outstanding options or warrants are exercised, new options are issued and exercised under our equity incentive plans or we issue additional shares of common stock, other equity securities or convertible debt securities in the future.

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DESCRIPTION OF CAPITAL STOCK

General

Our authorized capital stock consists of 250,000,000 shares of common stock, par value $0.001 per share, and 25,000,000 shares of preferred stock, par value $0.001 per share. The following description of our capital stock is intended as a summary only and is qualified in its entirety by reference to our amended and restated certificate of incorporation, and amended and restated by-laws, copies of which are incorporated by reference as exhibits to the registration statement, of which this prospectus forms a part, and to the applicable provisions of the Delaware General Corporation Law.

Common Stock

As of June 30, 2015, there were 36,071,596 shares of our common stock outstanding, held of record by approximately 10 stockholders. Based on shares outstanding as of June 30, 2015, and assuming the sale of 2,101,370 shares of our common stock in this offering at an assumed public offering price of $118.97 per share, which was the last reported sale price of our common stock on The NASDAQ Global Select Market on July 13, 2015, upon completion of this offering, there will be 38,172,966 shares of our common stock outstanding.

Holders of our common stock are entitled to one vote for each share of common stock held of record for the election of directors and on all matters submitted to a vote of stockholders. Holders of our common stock are entitled to receive dividends ratably, if any, as may be declared by our board of directors out of legally available funds, subject to any preferential dividend rights of any preferred stock then outstanding. Upon our dissolution, liquidation or winding up, holders of our common stock are entitled to share ratably in our net assets legally available after the payment of all our debts and other liabilities, subject to the preferential rights of any preferred stock then outstanding. Holders of our common stock have no preemptive, subscription, redemption or conversion rights. The rights, preferences and privileges of holders of common stock are subject to, and may be adversely affected by, the rights of the holders of shares of any series of preferred stock that we may designate and issue in the future. Except as described below in Anti-Takeover Effects of Delaware Law, Our Certificate of Incorporation and Our By-laws, the affirmative vote of a majority of our outstanding shares of capital stock is generally required to take action under our amended and restated certificate of incorporation and amended and restated by-laws.

Preferred Stock

Our board of directors is authorized, without action by the stockholders, to designate and issue up to an aggregate of 25,000,000 shares of preferred stock in one or more series. The board of directors can fix the rights, preferences and privileges of the shares of each series and any of its qualifications, limitations or restrictions. Our board of directors may authorize the issuance of preferred stock with voting or conversion rights that could adversely affect the voting power or other rights of the holders of common stock. The issuance of preferred stock, while providing flexibility in connection with possible future financings and acquisitions and other corporate purposes could, under certain circumstances, have the effect of delaying or preventing a change in control of our company and might harm the market price of our common stock.

Our board of directors will make any determination to issue such shares based on its judgment as to our best interests and the best interests of our stockholders. As of June 30, 2015, no shares of preferred stock were outstanding and we have no current plans to issue any shares of preferred stock.

Warrants

As of June 30, 2015, warrants to purchase a total of 149,700 shares of our common stock were outstanding with an exercise price of $3.01 per share. These warrants are exercisable immediately and each expire on the first to occur of (i) the closing date of any reorganization, consolidation or merger of the Company, transfer of all or substantially all of the assets of the Company or any simultaneous sale of more than a majority of the then

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outstanding securities of the Company other than a mere reincorporation transaction, or (ii) the 10 year anniversary of the date of such warrant which in the case of the outstanding warrants of the Company is June 2020 and June 2021, respectively.

Registration Rights

We are party to an amended and restated investors rights agreement, dated as of December 18, 2012, with certain holders of our common stock. Under the amended and restated investors rights agreement, holders of registrable shares have certain demand registration rights and piggyback registration rights, as described more fully below. These registration rights will terminate (i) on February 5, 2019, which is the fifth anniversary of the closing of our initial public offering, or (ii) after this offering, as to any holder of registrable securities, when such holder holds 1% or less of our common stock and all registrable securities held by such holder can be sold in any 90-day period without registration in compliance with Rule 144.

Demand Registration Rights

Under the amended and restated investors rights agreement, beginning July 29, 2014, which is the date that is 180 days after the effective date of the registration statement for our initial public offering, or 45 days following the effective date of any other Company-initiated registration statement, the holders of at least 50% of the registrable shares (or a lesser percentage if the anticipated aggregate offering price is not less than $10 million) then outstanding can, on not more than two occasions, demand that we file a registration statement or request that their shares be included on a registration statement that we are otherwise filing, in either case, registering the resale of their shares of common stock. We are required to use our best efforts to effect the registration and will pay all registration expenses, other than underwriting discounts and commissions, related to any demand registration. These registration rights are subject to conditions and limitations, including the right, in certain circumstances, of the underwriters of an offering to limit the number of shares included in such registration and our right, in certain circumstances, not to effect a requested registration.

Piggyback Registration Rights

If we propose to register any of our securities under the Securities Act for our own account or the account of any other holder, the significant holders (as defined in the amended and restated investors rights agreement) are entitled to notice of such registration and to request that we include registrable shares for resale on such registration statement, subject to the right of any underwriter to limit the number of shares included in such registration.

We will pay all registration expenses, other than underwriting discounts and commissions, related to any piggyback registration. The amended and restated investors rights agreement contains customary cross-indemnification provisions, pursuant to which we are obligated to indemnify the selling stockholders, in the event of misstatements or omissions in the registration statement attributable to us and they are obligated to indemnify us for misstatements or omissions attributable to them.

Anti-Takeover Effects of Delaware Law, our Certificate of Incorporation and our By-laws

Our certificate of incorporation and by-laws include a number of provisions that may have the effect of encouraging persons considering unsolicited tender offers or other unilateral takeover proposals to negotiate with our board of directors rather than pursue non-negotiated takeover attempts. These provisions include the items described below.

Board Composition and Filling Vacancies

In accordance with our certificate of incorporation, our board is divided into three classes serving three-year terms, with one class being elected each year. Our certificate of incorporation also provides that directors may be removed only for cause. Furthermore, any vacancy on our board of directors, however occurring, including a vacancy resulting from an increase in the size of our board, may only be filled by a resolution of the board.

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No Written Consent of Stockholders

Our certificate of incorporation provides that all stockholder actions are required to be taken by a vote of the stockholders at an annual or special meeting, and that stockholders may not take any action by written consent in lieu of a meeting.

Meetings of Stockholders

Our certificate of incorporation and by-laws provide that, subject to any rights of holders of any series of preferred stock, only the board or the chairman of the board may call special meetings of stockholders and only those matters set forth in the notice of the special meeting may be considered or acted upon at a special meeting of stockholders. Our by-laws limit the business that may be conducted at an annual meeting of stockholders to those matters properly brought before the meeting.

Advance Notice Requirements

Our by-laws establish advance notice procedures with regard to stockholder proposals relating to the nomination of candidates for election as directors or new business to be brought before meetings of our stockholders. These procedures provide that notice of stockholder proposals must be timely given in writing to our corporate secretary prior to the meeting at which the action is to be taken. Generally, to be timely, notice must be received at our principal executive offices not less than 90 days or more than 120 days prior to the first anniversary date of the annual meeting for the preceding year. The notice must contain certain information specified in the by-laws. These provisions may have the effect of precluding the conduct of certain business at a meeting if the proper procedures are not followed. These provisions may also discourage or deter a potential acquirer from conducting a solicitation of proxies to elect the acquirer s own slate of directors or otherwise attempting to obtain control of our company.

Amendment to By-laws and Certificate of Incorporation

As required by the Delaware General Corporation Law, any amendment of our certificate of incorporation must first be approved by a majority of our board of directors and, if required by law or our certificate of incorporation, thereafter be approved by a majority of the outstanding shares entitled to vote on the amendment, and a majority of the outstanding shares of each class entitled to vote thereon as a class, except that the amendment of the provisions relating to directors, stockholders, the amendment of our by-laws and certificate of incorporation and exclusive jurisdiction of Delaware Courts must be approved by not less than 75% of the outstanding shares entitled to vote on the amendment, and not less than 75% of the outstanding shares of each class entitled to vote thereon as a class. Our by-laws may be amended by the affirmative vote of a majority of the directors then in office, subject to any limitations set forth in the by-laws, and may also be amended by the affirmative vote of at least 75% of the outstanding shares entitled to vote on the amendment.

Blank Check Preferred Stock

Our certificate of incorporation provides for 25,000,000 authorized shares of preferred stock. The existence of authorized but unissued shares of preferred stock may enable our board of directors to render more difficult or to discourage an attempt to obtain control of us by means of a merger, tender offer, proxy contest or otherwise. For example, if in the due exercise of its fiduciary obligations, our board of directors were to determine that a takeover proposal is not in the best interests of us or our stockholders, our board of directors could cause shares of preferred stock to be issued without stockholder approval in one or more private offerings or other transactions that might dilute the voting or other rights of the proposed acquirer or insurgent stockholder or stockholder group. In this regard, our

certificate of incorporation grants our board of directors broad power to establish the rights and preferences of authorized and unissued shares of preferred stock. The issuance of shares of preferred stock could decrease the amount of earnings and assets available for distribution to holders of shares of common stock. The issuance may also adversely affect the rights and powers, including voting rights, of these holders and may have the effect of delaying, deterring or preventing a change in control of us.

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Section 203 of the Delaware General Corporation Law

We are subject to the provisions of Section 203 of the Delaware General Corporation Law. In general, Section 203 prohibits a publicly-held Delaware corporation from engaging in a business combination with an interested stockholder for a three-year period following the time that this stockholder becomes an interested stockholder, unless the business combination is approved in a prescribed manner. A business combination includes, among other things, a merger, asset or stock sale or other transaction resulting in a financial benefit to the interested stockholder. An interested stockholder is a person who, together with affiliates and associates, owns, or did own within three years prior to the determination of interested stockholder status, 15% or more of the corporation s voting stock.

Under Section 203, a business combination between a corporation and an interested stockholder is prohibited unless it satisfies one of the following conditions:

- before the stockholder became interested, the board of directors approved either the business combination or the transaction which resulted in the stockholder becoming an interested stockholder;
- upon consummation of the transaction which resulted in the stockholder becoming an interested stockholder, the interested stockholder owned at least 85% of the voting stock of the corporation outstanding at the time the transaction commenced, excluding for purposes of determining the voting stock outstanding, shares owned by persons who are directors and also officers, and employee stock plans, in some instances; or
- at or after the time the stockholder became interested, the business combination was approved by the board of directors of the corporation and authorized at an annual or special meeting of the stockholders by the affirmative vote of at least two-thirds of the outstanding voting stock which is not owned by the interested stockholder.

A Delaware corporation may opt out of these provisions with an express provision in its original certificate of incorporation or an express provision in its certificate of incorporation or by-laws resulting from a stockholders amendment approved by at least a majority of the outstanding voting shares. We have not opted out of these provisions. As a result, mergers or other takeover or change in control attempts of us may be discouraged or prevented.

Exclusive Jurisdiction of Certain Actions

Our certificate of incorporation requires, to the fullest extent permitted by law, that derivative actions brought in our name, actions against our directors, officers and employees for breach of fiduciary duty and other similar actions may be brought only in the Court of Chancery in the State of Delaware, unless we otherwise consent. Although we believe this provision benefits us by providing increased consistency in the application of Delaware law in the types of lawsuits to which it applies, the provision may have the effect of discouraging lawsuits against our directors and officers. Although our certificate of incorporation contains the choice of forum provision described above, it is possible that a court could rule that such a provision is inapplicable for a particular claim or action or that such provision is unenforceable.

NASDAQ Global Select Market listing

Our common stock is listed on The NASDAQ Global Select Market under the symbol RARE .

Transfer Agent and Registrar

The transfer agent and registrar for our common stock is American Stock Transfer & Trust Company, LLC. The transfer agent and registrar s address is 620 15th Avenue, Brooklyn, New York 11219.

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MATERIAL U.S. FEDERAL INCOME TAX CONSEQUENCES TO NON-U.S. HOLDERS

The following discussion is a summary of the material U.S. federal income tax consequences to non-U.S. holders (as defined below) of the purchase, ownership and disposition of our common stock issued pursuant to this offering, but does not purport to be a complete analysis of all potential tax effects. The effects of other U.S. federal tax laws, such as estate and gift tax laws, and any applicable state, local or foreign tax laws are not discussed. This discussion is based on the Internal Revenue Code of 1986, as amended, or the Code, Treasury Regulations promulgated under the Code, judicial decisions, and published rulings and administrative pronouncements of the U.S. Internal Revenue Service, or IRS, in effect as of the date of this offering. These authorities may change or be subject to differing interpretations. Any such change may be applied retroactively in a manner that could adversely affect a non-U.S. holder of our common stock. We have not sought and will not seek any rulings from the IRS regarding the matters discussed below. There can be no assurance the IRS or a court will not take a contrary position regarding the tax consequences of the purchase, ownership and disposition of our common stock.

This discussion is limited to non-U.S. holders that hold our common stock as a capital asset within the meaning of Section 1221 of the Code (property held for investment). This discussion does not address all U.S. federal income tax consequences relevant to a non-U.S. holder s particular circumstances, including the impact of the Medicare contribution tax on net investment income. In addition, it does not address consequences relevant to non-U.S. holders subject to particular rules, including, without limitation:

- U.S. expatriates and certain former citizens or long-term residents of the United States;
- persons subject to the alternative minimum tax;
- persons holding our common stock as part of a hedge, straddle or other risk reduction strategy or as part of a conversion transaction or other integrated investment;
- banks, insurance companies and other financial institutions;
- brokers, dealers or traders in securities;
- controlled foreign corporations, passive foreign investment companies and corporations that accumulate earnings to avoid U.S. federal income tax;
- partnerships or other entities or arrangements treated as partnerships for U.S. federal income tax purposes;
- tax-exempt organizations or governmental organizations;

persons deemed to sell our common stock under the constructive sale provisions of the Code;

persons who hold or receive our common stock pursuant to the exercise of any employee stock option or otherwise as compensation; and

tax-qualified retirement plans.

If a partnership (or other entity treated as a partnership for U.S. federal income tax purposes) holds our common stock, the tax treatment of a partner in the partnership will depend on the status of the partner, the activities of the partnership and certain determinations made at the partner level. Accordingly, partnerships holding our common stock and the partners in such partnerships should consult their tax advisors regarding the U.S. federal income tax consequences to them.

THIS DISCUSSION IS FOR INFORMATION PURPOSES ONLY AND IS NOT INTENDED AS TAX ADVICE. INVESTORS SHOULD CONSULT THEIR TAX ADVISORS WITH RESPECT TO THE APPLICATION OF THE U.S. FEDERAL INCOME TAX LAWS TO THEIR PARTICULAR SITUATIONS AS WELL AS ANY TAX CONSEQUENCES OF THE PURCHASE, OWNERSHIP AND

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DISPOSITION OF OUR COMMON STOCK ARISING UNDER THE U.S. FEDERAL ESTATE OR GIFT TAX LAWS OR UNDER THE LAWS OF ANY STATE, LOCAL OR NON-U.S. TAXING JURISDICTION OR UNDER ANY APPLICABLE INCOME TAX TREATY.

Definition of a Non-U.S. Holder

For purposes of this discussion, a non-U.S. holder is any beneficial owner of our common stock that is neither a U.S. person nor a partnership for United States federal income tax purposes. A U.S. person is any of the following:

- an individual who is a citizen or resident of the United States;
- a corporation (or other entity taxable as a corporation for U.S. federal income tax purposes) created or organized under the laws of the United States, any state thereof, or the District of Columbia;
- an estate, the income of which is subject to U.S. federal income tax regardless of its source; or
- a trust that (1) is subject to the primary supervision of a U.S. court and the control of one or more United States persons (within the meaning of Section 7701(a)(30) of the Code), or (2) has a valid election in effect to be treated as a United States person for U.S. federal income tax purposes.

Distributions

As described in the section entitled Dividend Policy, we do not anticipate paying any cash dividends on our common stock in the foreseeable future. However, if we do make distributions on our common stock, such distributions of cash or property on our common stock will constitute dividends for U.S. federal income tax purposes to the extent paid from our current or accumulated earnings and profits, as determined under U.S. federal income tax principles. Amounts not treated as dividends for U.S. federal income tax purposes will constitute a return of capital and first be applied against and reduce a non-U.S. holder s adjusted tax basis in its common stock, but not below zero. Any excess will be treated as capital gain and will be treated as described below in the section titled Sale or Other Taxable Disposition.

Subject to the discussions below regarding backup withholding and foreign accounts, dividends paid to a non-U.S. holder of our common stock generally will be subject to U.S. federal withholding tax at a rate of 30% of the gross amount of the dividends (or such lower rate specified by an applicable income tax treaty). Even if a non-U.S. holder is eligible for a lower treaty rate, dividend payments will generally be subject to withholding at a 30% rate (rather than the lower treaty rate) unless the non-U.S. holder provides a valid IRS Form W-8BEN or W-8BEN-E (or applicable successor form) certifying such holder s qualification for the reduced rate.

Subject to the discussions below regarding backup withholding and foreign accounts, if dividends paid to a non-U.S. holder are effectively connected with the non-U.S. holder s conduct of a trade or business within the United States (and, if required by an applicable income tax treaty, the non-U.S. holder maintains a permanent establishment in the United States to which such dividends are attributable), the non-U.S. holder will be exempt from U.S. federal withholding tax. To claim the exemption, the non-U.S. holder must furnish to us or our paying agent a valid IRS Form W-8ECI (or applicable successor form), certifying that the dividends are effectively connected with the non-U.S.

holder s conduct of a trade or business within the United States.

Any dividends paid on our common stock that are effectively connected with a non-U.S. holder s U.S. trade or business (and, if required by an applicable tax treaty, attributable to a permanent establishment maintained by the non-U.S. holder in the United States) generally will be subject to U.S. federal income tax on a net income basis in the same manner as if such holder were a U.S. person. A non-U.S. holder that is a corporation also may, under certain circumstances, be subject to a branch profits tax at a rate of 30% (or such lower rate specified by an applicable tax treaty) on any effectively connected dividends that it receives. Non-U.S. holders should consult their tax advisors regarding any applicable tax treaties that may provide for different rules.

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Non-U.S. holders should consult their tax advisors regarding their entitlement to benefits under a tax treaty. You may obtain a refund of any excess amounts withheld by timely filing an appropriate claim for refund with the IRS.

Sale or Other Taxable Disposition

Subject to the discussions below regarding backup withholding and foreign accounts, a non-U.S. holder will not be subject to U.S. federal income tax on any gain realized upon the sale or other disposition of our common stock unless:

- the gain is effectively connected with the non-U.S. holder s conduct of a trade or business within the United States (and, if required by an applicable income tax treaty, the non-U.S. holder maintains a permanent establishment in the United States to which such gain is attributable);
- the non-U.S. holder is a nonresident alien individual present in the United States for 183 days or more during the taxable year of the disposition and certain other requirements are met; or
- our common stock constitutes a U.S. real property interest, or USRPI, by reason of our status as a U.S. real property holding corporation, or a USRPHC, for U.S. federal income tax purposes.

Gain described in the first bullet point above will generally be subject to U.S. federal income tax on a net income basis at the regular graduated U.S. federal income tax rates. If a non-U.S. holder is eligible for the benefits of a tax treaty between the United States and its country of residence, any such gain will be subject to U.S. federal income tax in the manner specified by the treaty. To claim the benefit of a treaty, a non-U.S. holder must properly submit an IRS Form W-8BEN (or suitable successor or substitute form). A non-U.S. holder that is a foreign corporation also may be subject to a branch profits tax at a rate of 30% (or such lower rate specified by an applicable income tax treaty) on such effectively connected gain, as adjusted for certain items.

A non-U.S. holder described in the second bullet point above will be subject to U.S. federal income tax at a rate of 30% (or such lower rate specified by an applicable income tax treaty) on any gain derived from the disposition, which may be offset by certain U.S. source capital losses of the non-U.S. holder (even though the individual is not considered a resident of the United States) provided the non-U.S. holder has timely filed U.S. federal income tax returns with respect to such losses.

With respect to the third bullet point above, we believe we are not currently and do not anticipate becoming a USRPHC. However, because the determination of whether we are a USRPHC depends on the fair market value of our USRPIs relative to the fair market value of our other business assets and our non-U.S. real property interests, there can be no assurance we are not a USRPHC or will not become one in the future. Even if we are or were to become a USRPHC, gain arising from the sale or other taxable disposition by a non-U.S. holder of our common stock will not be subject to U.S. federal income tax if our common stock is regularly traded, as defined by applicable Treasury Regulations, on an established securities market, and such non-U.S. holder owned, actually or constructively, 5% or less of our common stock throughout the shorter of the five-year period ending on the date of the sale or other disposition or the non-U.S. holder s holding period.

Non-U.S. holders should consult their tax advisors regarding potentially applicable income tax treaties that may provide for different rules.

Information Reporting and Backup Withholding

A non-U.S. holder will not be subject to backup withholding with respect to payments of dividends on our common stock we make to the non-U.S. holder, provided the holder certifies its non-U.S. status, such as by providing a valid IRS Form W-8BEN, W-8ECI, or other applicable IRS Form, or otherwise establishes an exemption. However, information returns will be filed with the IRS in connection with any dividends on our

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common stock paid to the non-U.S. holder, regardless of whether any tax was actually withheld. Copies of these information returns may also be made available under the provisions of a specific treaty or agreement to the tax authorities of the country in which the non-U.S. holder resides or is established.

Information reporting and, depending on the circumstances, backup withholding will apply to the proceeds of a sale of our common stock within the United States or conducted through certain U.S.-related financial intermediaries, unless the beneficial owner certifies under penalty of perjury that it is a non-U.S. holder on Form W-8BEN or other applicable form or such owner otherwise establishes an exemption.

Backup withholding is not an additional tax. Any amounts withheld under the backup withholding rules may be allowed as a refund or a credit against a non-U.S. holder s U.S. federal income tax liability, provided the required information is timely furnished to the IRS.

Additional Withholding Tax on Payments Made to Foreign Accounts

Sections 1471 through 1474 of the Code (FATCA) generally impose a 30% withholding tax on dividends paid on, and the gross proceeds from the sale or other disposition of, our common stock paid to a foreign financial institution (as defined in the Code) or to a non-financial foreign entity (as defined in the Code) (whether such foreign financial institution or non-financial foreign entity is the beneficial owner or an intermediary), unless (1) in the case of a foreign financial institution, the entity undertakes certain diligence and reporting obligations, (2) in the case of a non-financial foreign entity, the entity either certifies that it does not have any substantial United States owners (as defined in the Code) or furnishes identifying information regarding each substantial United States owner, or (3) the foreign financial institution or non-financial foreign entity otherwise qualifies for an exemption from these rules. If the payee is a foreign financial institution and is subject to the diligence and reporting requirements in (1) above, it must enter into an agreement with the U.S. Department of the Treasury requiring, among other things, that it undertake to identify accounts held by certain U.S. persons or U.S.-owned foreign entities (as defined in applicable Treasury Regulations), annually report certain information about such accounts, and withhold 30% on payments to non-compliant foreign financial institutions and certain other account holders. Foreign governments may enter into an agreement with the IRS to implement FATCA in a different manner. Under current IRS guidance, these withholding and reporting requirements will apply currently with respect to dividends on the common stock, but will not apply to withholding on gross proceeds on the sale or other taxable disposition of the common stock until January 1, 2017. If you are located in a jurisdiction that has an intergovernmental agreement with the United States governing FATCA, you may be subject to different rules. Prospective investors should consult their tax advisors regarding these withholding provisions.

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UNDERWRITERS

Under the terms and subject to the conditions in an underwriting agreement dated the date of this prospectus supplement, the underwriters named below, for whom Morgan Stanley & Co. LLC, J.P. Morgan Securities LLC and Cowen and Company, LLC are acting as representatives, have severally agreed to purchase, and we have agreed to sell to them, severally, the number of shares indicated below: