Ultragenyx Pharmaceutical Inc.
Form 10-K
February 21, 2018
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UNITED STATES SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

Form 10-K

ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934
For the fiscal year ended December 31, 2017

OR

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

Commission File No. 001-36276

Ultragenyx Pharmaceutical Inc.

(Exact name of registrant as specified in its charter)

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

(415) 483-8800

(Registrant’s telephone number, including area code)

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

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

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

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

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

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. YES NO

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate Website, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T (§232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files). YES NO

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K (§229.405 of this chapter) is not contained herein, and will not be contained, to the best of registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K.

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, a smaller reporting company, or emerging growth company. See the definitions of "large accelerated filer," "accelerated filer," "smaller reporting company," and "emerging growth company" in Rule 12b-2 of the Exchange Act. (Check one):

Large accelerated filer Accelerated filer

Non- accelerated filer (Do not check if a smaller reporting company) Smaller reporting company

Emerging growth company

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act.

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Exchange Act). YES NO

The aggregate market value of the voting and non-voting common equity held by non-affiliates of the Company as of June 30, 2017 was approximately $2.6 billion, based upon the closing price on The Nasdaq Global Select Market reported for such date. Shares of common stock held by each executive officer and director and by each person who is known to own 10% or more of the outstanding common stock have been excluded in that such persons may be deemed to be affiliates of the Company. This determination of affiliate status is not necessarily a conclusive determination for other purposes.

As of February 15, 2018, the Company had 49,605,852 shares of common stock issued and outstanding.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant's definitive proxy statement relating to its 2018 Annual Meeting of Stockholders, to be held on or about June 19, 2018, are incorporated by reference into Part III of this Annual Report on Form 10-K where

indicated. Such proxy statement will be filed with the U.S. Securities and Exchange Commission within 120 days after the end of the fiscal year to which this report relates.

Table of Contents

CAUTIONARY NOTE REGARDING FORWARD-LOOKING STATEMENTS

This Annual Report on Form 10-K, or Annual Report, 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 Annual Report 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,” “potential,” “predict,” “project,” “seek,” “should,” “target,” “will,” “would,” or the negative of these w comparable terminology. These forward-looking statements include, but are not limited to, statements about:

- our commercialization, marketing, and manufacturing capabilities and strategy;
- our expectations regarding the timing of clinical study commencements and reporting results from same;
- the timing and likelihood of regulatory approvals for our product candidates;
- the anticipated indications for our product candidates, if approved;
- the potential market opportunities for commercializing our product and product candidates;
- our expectations regarding the potential market size and the size of the patient populations for our product and product candidates, if approved for commercial use;
- estimates of our expenses, future revenue, capital requirements, and our needs for additional financing;
- 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, product and product candidates and the integration and performance of any acquired businesses;
    - the initiation, timing, progress, and results of ongoing and future preclinical 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 and product candidates;
- our ability to maintain and establish collaborations or strategic relationships or obtain additional funding;
- our ability to maintain and establish relationships with third parties, such as contract research organizations, suppliers, and distributors;
- our financial performance and the expansion of our organization;
- our ability to obtain supply of our product and product candidates;
- the scalability and commercial viability of our manufacturing methods and processes;
- developments and projections relating to our competitors and our industry; and
- other risks and uncertainties, including those listed under Part I, Item 1A. Risk Factors.

Any forward-looking statements in this Annual Report reflect our current views with respect to future events or to 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 discussed under Part I, Item 1A. Risk Factors and discussed elsewhere in this Annual Report. Given these uncertainties, you should 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 Annual Report 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.

As used in this Annual Report, “Ultragenyx,” “we,” “our,” and similar terms include Ultragenyx Pharmaceutical Inc. and its subsidiaries, unless the context indicates otherwise.

PART I

Item 1. Business

Overview

We are a biopharmaceutical company focused on the identification, acquisition, development, and commercialization of novel products for the treatment of serious 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 approved product and current product candidate pipeline have 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. We have built our own commercial organization, which is highly targeted 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 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 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 genetic diseases.

On November 7, 2017, we completed our acquisition of Dimension Therapeutics, Inc., a Delaware corporation, which became our wholly-owned subsidiary. Upon the closing of the acquisition, we paid aggregate consideration of approximately $152.3 million, not including related transaction fees and expenses, using available cash and investments. For additional information regarding the acquisition, see Note 3 to our consolidated financial statements.

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

- Focus on rare and ultra-rare diseases with significant unmet medical need and clear biology. There are numerous rare and ultra-rare genetic diseases that currently have no approved drug therapy and for which no therapies are currently in development. Patients suffering from these diseases often have a high unmet medical need with significant morbidity and/or mortality. We are focused on developing and commercializing therapies for multiple such indications with the utmost urgency. We also focus on diseases that have biology that is well understood. For example, Mepsevii™ is a replacement therapy for a single deficient enzyme and several of our product candidates

are replacement therapies for a single deficient substrate in the body. We believe that developing drugs that directly impact known disease pathways will increase the probability of success of our development programs. Our four modalities of small molecules, biologics, mRNA and AAV gene therapy provide us with what we believe is an optimal set of options to treat metabolic genetic diseases by selecting the best treatment strategy available for each disease.

- Leverage our experience and relationships to in-license promising product candidates; retain global commercialization rights to product candidates. Our management team seeks to develop and maintain strong relationships with key opinion leaders in the genetic field and leverage our success in the development and commercialization of therapies for rare and ultra-rare genetic diseases. All of our current clinical product candidates are in-licensed from academic institutions or derived from partnerships with other pharmaceutical companies. We believe parties agree to license product candidates to us because they are confident in our team's drug development capabilities and our plans and execution thus far in bringing rare disease therapies to market. We intend to seek and retain global commercialization rights to our product and product candidates whenever possible to maximize the potential value of our product portfolio. Because we typically in-license product candidates that require translational or clinical research, at this time we do not intend to invest significant capital in basic research, which can be expensive and time-consuming.

- Focus on excellent, rapid, and efficient clinical and regulatory execution on multiple programs in parallel. We believe that building a successful and sustainable rare disease-focused company requires very specific expertise in the areas of patient identification, clinical study design and conduct, and regulatory strategy. We have assembled a team capable of managing global clinical development activities in an efficient manner and with multinational experience in obtaining regulatory approvals for rare disease products. Clinical development programs for rare and ultra-rare diseases can often be smaller in size than those for larger market indications. Development of multiple programs in rare diseases also generates organizational efficiencies and economies of scale. We also seek to manage our fixed cost structure by outsourcing most manufacturing of our product and product candidates. As a result of these efficiencies, we are able to feasibly develop multiple clinical-stage product candidates in parallel, resulting in a more diversified portfolio that provides multiple opportunities to create value.
- Establish global commercial organization. We have established our own unique commercial organization in major pharmaceutical markets and developed a network of third-party distributors in smaller markets and expect to expand these efforts. We believe our commercial organization is highly targeted, in part as a result of the relatively small number of specialists who typically treat patients with the diseases to be addressed by our product and product candidates.

Product - Mepsevii™

On November 15, 2017, the U.S. Food and Drug Administration, or FDA, approved our first product, Mepsevii (vestronidase alfa), the first medicine approved for the treatment of children and adults with MPS VII, also known as Sly syndrome. Mepsevii is available to patients in the U.S. In order to support patients, we launched UltraCare™, a comprehensive support service that provides ongoing support to patients and caregivers. UltraCare will help patients obtain coverage and assist with financial support for both medication and administration of medication. With this approval, the FDA issued a Rare Pediatric Disease Priority Review Voucher, or PRV, which confers priority review to a subsequent drug application that would not otherwise qualify for priority review. We completed the sale of the PRV in January 2018 for $130.0 million.

Mepsevii is an intravenous, or IV, enzyme replacement therapy for the treatment of MPS VII. MPS VII 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. Mepsevii is designed to replace the deficient lysosomal enzyme beta-glucuronidase in MPS VII patients. Patients with MPS VII suffer from severe cellular and organ dysfunction that typically leads to death in the teens or early adulthood and 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. Mepsevii is the only FDA-approved drug therapy for MPS VII.

In Europe, the European Medicines Agency, or EMA, is currently reviewing the Marketing Authorization Application, or MAA, for vestronidase alfa, and an opinion from the Committee for Medicinal Products for Human Use, or CHMP, is expected in the first half of 2018. 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 and some evidence or trend in improvement in clinical endpoints was observed to support the primary endpoint. The EMA recognized that a statistically significant result on clinical endpoints was unlikely given the small number of patients expected to be enrolled in the study.

We are also supplying vestronidase alfa to investigators who are treating patients under emergency investigational new drug, or eIND, applications and other expanded access programs.

Please see "—License and Collaboration Agreements—Approved Product—Saint Louis University" for a description of our license agreement with Saint Louis University.

Clinical Product Candidates

Our current clinical-stage pipeline consists of three product categories: biologics, small-molecule substrate replacement therapies, and gene therapy. 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. Gene therapy is a therapeutic approach in which an isolated gene sequence or segment of DNA is administered to a patient, most commonly for the purpose of treating a genetic disease that is caused by mutations. Gene therapy aims to address the disease-causing effects of absent or dysfunctional genes by delivering functional copies of the gene to the patient's cells, offering the potential for durable therapeutic benefit.

The following table summarizes our advanced product candidate pipeline:

Burosumab for the treatment of XLH

Burosumab is a fully human monoclonal antibody administered via subcutaneous injection that is designed to bind and reduce the biological activity of fibroblast growth factor 23, or FGF23, to increase abnormally low phosphate levels in patients with 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 April 2017, we announced positive 64-week data from a 52-patient pediatric Phase 2 randomized, multicenter, open-label, dose-finding study of burosumab for the treatment of XLH in children aged five to 12 years of age. Patients demonstrated increases in mean serum phosphorus, renal phosphate reabsorption (TmP/GFR) and serum 1,25 dihydroxy vitamin D levels through 64 weeks of treatment. Rickets severity was assessed using the RSS scoring system. There was a statistically significant improvement in rickets scores in all groups at 64 weeks, with the greatest improvements in patients with higher baseline rickets scores (RSS ≥1.5) who received bi-weekly dosing of burosumab. Overall, patients (n=52) had a 51% reduction in RSS score ($p < 0.0001$). Patients with higher baseline rickets scores (n=34) had a 59% reduction in RSS score ($p < 0.0001$). Patients who were dosed bi-weekly (n=26) had a 58% reduction in RSS score ($p < 0.0001$). Patients with higher baseline rickets scores who were dosed bi-weekly (n=17) had a 62% reduction in RSS score ($p < 0.0001$). The change in the severity of rickets was assessed by the RGI-C score. Data show significant improvement in rickets in all groups at 64 weeks. Overall, all patients (n=52) experienced a mean improvement in RGI-C score of

+1.57 (p< 0. 0001) and those patients with higher baseline rickets scores (n=34) experienced a mean improvement of +1.98 (p< 0.0001). Within the higher severity subset, 77% (26/34) experienced substantial healing (score > 2). Overall, all patients who were dosed bi-weekly (n=26) experienced a mean improvement in RGI-C score of +1.62 (p< 0.0001). Patients with higher baseline rickets scores who were dosed bi-weekly (n=17) showed a mean improvement of +2.08 (p< 0.0001) (substantial healing), and 82% experienced substantial healing (score > 2). Patients with higher baseline rickets scores showed more growth impairment (baseline height percentile= 5.84), and these patients demonstrated greater improvement in growth. Among all patients (n=52), growth velocity improved by a mean of +0.55 cm/year (p=0.0376), and there was 0.15 change in height z-score (p<0.0001). Patients with higher baseline rickets scores had a +0.86 cm/year improvement in growth velocity (p=0.0175) and a 0.17 change in height z-score (p=0.0016). Patients who were dosed bi-weekly (n=26) experienced a +0.73 cm/year change in growth velocity (p=0.0160) and a 0.18 change in height z-score (p=0.0002). Patients with higher baseline rickets scores who were dosed bi-weekly (n=17) had a +1.11 cm/year change in growth velocity (p=0.0076) and a 0.18 change in height z-score (p=0.0063). Approximately 65% of patients had injection site reactions, all of which were considered mild. There was one previously reported serious adverse event considered possibly treatment-related. This was a patient with fever and muscle pain who improved without complication and is still in the study. There have been no deaths or discontinuations from the study. No clinically meaningful changes were observed in mean serum calcium, urinary calcium and in serum intact parathyroid hormone. None of the patients had serum phosphorus levels above the upper limit of normal at any time point. No clinically significant changes were observed in renal ultrasounds pre- and post-treatment.

In September 2017 we announced 40-week data from the 64-week Phase 2 study in children less than five years old (mean age 2.9 years). Burosumab increased mean serum phosphorus levels by 1.2 mg/dL into the low normal range after one week of treatment and these levels were maintained through week 40 with 77% of children achieving normal serum phosphorus levels at week 40. Serum 1,25 dihydroxy vitamin D levels were also increased from baseline to week 40. Rickets severity was assessed using the RSS scoring system. The mean total RSS score improved significantly (59% reduction) at week 40 (p<0.0001). The change in rickets severity was also assessed at week 40 by the RGI-C score which showed substantial healing (RGIC score > 2) in all patients (p<0.0001). Burosumab treatment also resulted in significantly improved bowing as determined by RGI-C lower limb deformity (p<0.0001). Additionally, mean levels of alkaline phosphatase were significantly reduced (-39%, p<0.0001) in these patients at week 40. All patients experienced one or more adverse events. There was one serious adverse event of a tooth abscess that was considered unrelated to burosumab treatment. All other events were assessed as mild or moderate in severity except for a Grade 3 food allergy that was considered unrelated to burosumab treatment. Three patients had injection site reactions and four patients experienced hypersensitivity events that were all mild and considered unrelated to burosumab treatment. No clinically meaningful changes were observed in mean serum calcium, urinary calcium and in serum intact parathyroid hormone. There have been no events of hyperphosphatemia and there have been no deaths or discontinuations from the study.

In February 2018, we reported continued improvement in rickets and bowing in 64 week data from this Phase 2 study. This longer term data from this study demonstrated that treatment with burosumab was consistent with and further improved from what was seen at 40 weeks. These included sustained improvements in serum phosphorus levels, and a progressive reduction into the normal range of alkaline phosphatase. There were continued improvements in bowing and rickets scores at 64 weeks. The safety profile observed in this study was consistent with other burosumab studies.

In December 2017, we and our partners Kyowa Kirin International PLC, a wholly owned subsidiary of KHK, announced that the Committee for Medicinal Products for Human Use (CHMP), the European Medicines Agency's (EMA) scientific committee, adopted a Positive Opinion recommending the conditional marketing authorization of burosumab for the treatment of XLH with radiographic evidence of bone disease in children one year of age and older and adolescents with growing skeletons. The CHMP's recommendation has been referred to the European Commission (EC), which is expected to render its final decision in February of 2018.

We have an ongoing Phase 3 randomized open-label clinical study comparing the efficacy and safety of burosumab to oral phosphate and active vitamin D therapy in approximately 60 pediatric patients with XLH. The study is evaluating changes in rickets, growth velocity and height, pharmacodynamic assessments, walking ability, patient reported outcomes assessing pain, fatigue and physical function, and safety. We expect data from this study in the second half of 2018. This study will not be required to support a US approval and will serve as a confirmatory study in Europe.

We are also continuing to develop burosumab in adults with XLH. In April 2017, we announced positive 24-week data from the randomized, double-blind, placebo-controlled Phase 3 study of burosumab in adults with X-linked hypophosphatemia (XLH). The study enrolled 134 patients, randomized 1:1 to burosumab at a dose of 1 mg/kg or placebo every four weeks for 24 weeks. The study met the primary endpoint of increasing serum phosphorus levels as 94% of patients treated with burosumab (n=68) achieved serum phosphorus levels above the lower limit of normal and maintained levels in the low normal range through 24 weeks, compared to 8% in the placebo arm (n=66; $p<0.0001$). There were three pre-specified key secondary endpoints, including stiffness and physical function, both measured by the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC®), and pain measured by the Brief Pain Inventory Question 3 (BPI Q3; pain at its worst in the last 24 hours). At week 24, stiffness improved by a mean score of 7.87 points for patients treated with burosumab compared to a 0.25 point worsening among patients in the placebo group (mean difference of 8.12; $p=0.0122$). Physical function improved by 3.11 points for patients treated with burosumab compared to a 1.79 point worsening among patients in the placebo group (mean difference of 4.90 points; $p=0.0478$). Pain score improved by 0.79 for patients treated with burosumab compared to a 0.32 improvement among patients in the placebo group (mean score difference of 0.46 points;

p=0.0919). Results were directionally consistent towards improvement across all three key secondary endpoints. After pre-planned multiplicity adjustment, the improvement in stiffness among patients treated with burosumab remained statistically significant at the less than the 0.0167 threshold, while physical function and pain scores demonstrated strong trends.

In December 2017, we announced additional positive 48-week data from the study. From 24 to 48 weeks of treatment, 84% of patients who had received burosumab since the beginning of the study (n=68) achieved and maintained serum phosphorus levels above the lower limit of normal (2.5 mg/dL). 89% of patients who crossed over from placebo to burosumab after 24 weeks (n=66) achieved and maintained serum phosphorus levels above the lower limit of normal. Patients treated with burosumab showed continued improvement in stiffness and physical function as measured by WOMAC. For patients treated with burosumab, stiffness further improved from a mean change of 7.42 points at 24 weeks to 16.03 points at 48 weeks. Patients who crossed over from placebo to burosumab treatment had a mean change of 15.82 points from 24 to 48 weeks. Physical function also further improved from a mean change of 2.78 points at 24 weeks to 7.76 points at 48 weeks. For patients in the crossover group, physical function improved by a mean change of 8.18 points from 24 to 48 weeks. Burosumab was associated with a reduction in pain measured by BPI Q3, as well as a reduction in the use of pain medication. For patients treated with burosumab, pain scores further improved from a mean change of 0.81 points at 24 weeks to 1.09 points at 48 weeks. Patients who crossed over from placebo to burosumab treatment had a mean change of 1.18 points from 24 to 48 weeks. The patient frequency of reported opioid use decreased by 76% from 17 patients (25%) at baseline to four patients (6%) at week 48 in the burosumab group, and by 70% from 13 patients (20%) to four patients (6%) in the crossover group. The patient frequency of reported nonsteroidal anti-inflammatory drugs (NSAIDs) use decreased by 72% from 47 patients (69%) at baseline to 13 patients (19%) at week 48 in the burosumab group, and by 74% from 43 patients (65%) to 11 patients (17%) in the crossover group. Burosumab treatment resulted in increased healing of fractures (active fractures and pseudofractures) compared to placebo at week 24, and this improvement continued through 48 weeks. When evaluating follow-up X-rays in the 52% of patients with identified fractures or pseudofractures at baseline, the 43% rate of fracture healing observed at 24 weeks on burosumab increased to 63% at 48 weeks. In the crossover group which had an 8% rate of fracture healing at 24 weeks, the rate increased to 35% at week 48. The crossover patient group fracture healing result was consistent with the effect observed in the first 24 weeks of the burosumab group treatment.

There was no difference in the overall frequency of treatment emergent serious and non-serious adverse events, treatment related adverse events and serious adverse events between the group who received burosumab for the 48-week period compared to the group who received placebo for the 24-week double-blind period and then crossed over to burosumab. The safety profile at 48 weeks was generally similar to that observed at 24 weeks. The most common adverse events in patients during treatment with burosumab (>10%) were arthralgia (24%), nasopharyngitis (22%), headache (20%), back pain (16%), tooth abscess (13%), fatigue (13%), restless leg syndrome (11%), pain in extremity (11%), pain (11%), toothache (11%), vitamin D deficiency (10%), and musculoskeletal pain (10%). Eleven percent of patients who received burosumab experienced clinical symptoms compatible with hypersensitivity. There were 15 patients who experienced serious adverse events (SAEs) during treatment with burosumab, but none of these SAEs were considered treatment-related. No meaningful changes were observed in serum intact parathyroid hormone levels or ectopic mineralization as assessed by renal ultrasounds or echocardiograms. Of the 134 patients enrolled in the study, one patient in the burosumab arm discontinued treatment during the 24-week double-blind treatment period, as previously reported. During the open-label period, seven patients discontinued treatment. No discontinuations were related to adverse events or tolerability. There has been one non-treatment related death due to a car accident that was reported after the Week 48 data cutoff date.

In February 2018, we reported that bone biopsy data from adult patients in the bone quality study demonstrated continued improvement in osteomalacia. At 48 weeks, all ten patients with evaluable paired bone biopsies demonstrated meaningful improvements from baseline in mean osteoid volume/bone volume. The mean decrease

from 26.1% to 11.2% among these patients represents a 57% improvement from baseline in mean osteoid volume/bone volume which is the gold standard for the evaluation of osteomalacia. The patients also demonstrated mean improvements of 32% and 26% in osteoid thickness and osteoid surface/bone surface parameters respectively. These patients also experienced a meaningful improvement in mineralization lag time. These results, including safety, are consistent with the data provided to the FDA in the first 6 of these 10 patients showing a substantial reduction in osteomalacia.

In October 2017, we announced that the FDA accepted the biologics license application, or BLA, for burosumab to treat pediatric and adult patients with XLH and has granted Priority Review status. The Prescription Drug User Fee Act, or PDUFA, action date for the BLA is April 17, 2018. The Agency has indicated that it is not currently planning to hold an advisory committee meeting to discuss the BLA. The FDA previously granted Fast Track Designation to the burosumab program for the treatment of XLH, and Breakthrough Therapy Designation for pediatric patients one year of age or older. The FDA also designated burosumab as a drug for a "rare pediatric disease," enabling issuance of a priority review voucher if burosumab is approved.

Burosumab for the treatment of tumor-induced osteomalacia, or TIO