Ultragenyx Pharmaceutical Inc.
Form 10-K
February 20, 2019
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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, 2018

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 every Interactive Data File required to be submitted 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 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.

Large accelerated filer Accelerated filer

Non- accelerated filer 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, 2018 was approximately $3.2 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 14, 2019, the Company had 51,278,958 shares of common stock issued and outstanding.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant's definitive proxy statement relating to its 2019 Annual Meeting of Stockholders, to be held on or about June 11, 2019, are incorporated by reference into Part III of this Annual Report on Form 10-K where indicated. Such proxy statement will be filed with the U.S. Securities and Exchange Commission within 120 days after the end of the fiscal year to which this report relates.

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PART III

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,” “forecast,” “intend,” “may,” “plan,” “potential,” “predict,” “project,” “seek,” “should,” “target,” “will,” “would,” or the negativ or other 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 products and product candidates;
- our expectations regarding the potential market size and the size of the patient populations for our products and product candidates, if approved for commercial use;
- estimates of our expenses, 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, products and product candidates and the integration and performance of any businesses we have acquired or may acquire;
    - 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 products 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, contract manufacturing organizations, suppliers, and distributors;
- our financial performance and the expansion of our organization;
- our ability to obtain supply of our products 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 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.

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., and we have since assembled an experienced team with extensive rare disease drug development and commercialization capabilities.

Our Strategy

The critical components of our business strategy include the following:

- Focus on rare and ultra-rare genetic diseases with significant unmet medical need and clear biology. There are numerous rare and ultra-rare genetic diseases that currently have no drug therapy approved or in development. Patients suffering from these diseases often have a significant morbidity and/or mortality. We focus 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. 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, gene therapy and mRNA 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.
- In-license promising product candidates; retain global commercialization rights to product candidates. Our current product candidates are generally 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 expertise in rare disease drug development and commercialization. We generally intend to retain global commercialization rights to our products and product candidates whenever possible to maximize the potential value of our product portfolio. We do not currently 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. Because rare disease programs involve fewer patients and may have accelerated paths to market, 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, with some economies of scale.
- Commercialize through patient-focused global organization. We seek to commercialize our products in North America, the European Union, or EU, Latin America, and select international markets, We have established our own commercial organization in these markets and a network of third-party distributors in smaller markets. We believe our commercial organization is highly specialized and focused, due to the nature of rare disease treatment. In the

United States, we have a team of patient diagnosis liaisons who are responsible for finding new doctors with patients with the disease, a separate team of UltraCare Liaisons who assist physicians in placing patients on therapy, and UltraCare Guides who support patients and their families with treatment or reimbursement needs. In addition, we offer a free drug program for patients who are actively navigating the reimbursement process.

Approved Products and Clinical Product Candidates

Our current approved products and clinical-stage pipeline consist of three product categories: biologics, small molecules, and gene therapy product candidates.

We have two commercially approved products, Crysvita® (burosumab) for the treatment of X-linked hypophosphatemia, or XLH, and Mepsevii™ for the treatment of mucopolysaccharidosis VII, or MPSVII or Sly Syndrome, and three additional product candidates in the clinical pipeline. The following table summarizes our approved products and clinical product candidate pipeline:

Approved Products

Crysvita for the treatment of XLH

Crysvita is a fully human monoclonal antibody administered via subcutaneous injection that binds to and inhibits 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, and osteomalacia which can lead to fractures. Crysvita is the only approved treatment that addresses the underlying cause of XLH. There are approximately 48,000 patients with XLH in the developed world, including approximately 36,000 adults and 12,000 children.

In February 2018, we and Kyowa Hakko Kirin Co. Ltd, or KHK, announced that Crysvita received a positive European Commission decision granting a conditional marketing authorization to KHK for the treatment of XLH with radiographic evidence of bone disease in children 1 year of age and older and adolescents with growing skeletons. We also reported 64-week data from our Phase 2 study in children less than five years old (mean age 2.9 years), showing continued improvement in rickets and bowing. These longer term data from this study demonstrated that outcomes with Crysvita treatment were 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 Crysvita studies.

In February 2018, we reported that bone biopsy data from adult patients in our 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, and a meaningful improvement in mineralization lag time. These results, including safety, are consistent with the data provided to the U.S. Food and Drug Administration, or FDA.

In April 2018, we and KHK announced the FDA approval and commercial launch of Crysvita for the treatment of XLH in adult and pediatric patients one year of age and older. With the approval of Crysvita, 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 June 2018 for $80.6 million. We shared the net proceeds from the sale of the PRV equally with KHK.

In May 2018, we reported that the Phase 3 study of Crysvita met its primary endpoint demonstrating that Crysvita was superior to oral phosphate and active vitamin D (conventional therapy) in improving rickets as assessed by the RGI-C global score in children with XLH after 40 weeks of treatment (LS Mean treatment difference of +1.14, $p<0.0001$). The study also showed improvement in important metabolic and functional measures with Crysvita treatment, and a safety profile similar to that observed in other Crysvita pediatric XLH studies. In February 2019, we and KHK announced longer-term 64-week data from this study, demonstrating that Crysvita continued to demonstrate superiority to conventional therapy for all key efficacy endpoints, showing a meaningful improvement in rickets severity, lower limb deformity, growth, and physical functioning as demonstrated by increases in distance walked. The 64-week safety profile was similar to that observed at 40 weeks and in other Crysvita pediatric XLH studies.

In December 2018, we and KHK announced that Crysvita was approved by Health Canada for the treatment of XLH in adult and pediatric patients one year of age and older. Crysvita became available to Canadian patients by prescription in January 2019.

In addition to regulatory submissions and approvals of Crysvita in the U.S., EU, and Canada, we have submitted regulatory filings in various Latin American countries, and anticipate regulatory decisions in these markets by the end of 2019.

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

We are also developing Crysvita 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 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. There are approximately 2,000 to 4,000 patients with TIO in the developed world.

In October 2018, we presented positive 48-week and 72-week data from an ongoing Phase 2 study of Crysvita in adults with TIO syndrome at the American Society for Bone and Mineral Research 2018 Annual Meeting in Montreal. In adults with TIO, Crysvita was associated with increases in serum phosphorous and 1,25(OH)2D; improvement in osteomalacia; improvement in mobility and vitality; and reductions in fatigue. Regulatory discussions regarding a potential filing are ongoing with the FDA and we expect to have a final plan in mid-2019.

Please see "—License and Collaboration Agreements—Approved Products—Kyowa Hakko Kirin" for a description of our collaboration and license agreement with KHK.

Mepsevii for the treatment of MPS VII

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 patients with MPS VII. MPS VII can lead to an abnormally

coarsened face, pulmonary disease, cardiovascular complications, enlargement of the liver and spleen, joint stiffness, short stature, cognitive impairment and the skeletal disease known as dysostosis multiplex. MPS VII is one of the rarest MPS disorders, affecting an estimated 200 patients in the developed world.

Mepsevii was approved by the FDA in November 2017 and is the only-approved drug therapy for MPS VII. With this approval, the FDA issued a PRV, and we completed the sale of the PRV in January 2018 for $130.0 million.

In August 2018, the European Commission approved under exceptional circumstances the Marketing Authorization Application, or MAA, for Mepsevii for the treatment of non-neurological manifestations of MPS VII. Mepsevii is now approved for use in all 28 EU member states as well as in Iceland, Liechtenstein and Norway, and recently launched in Germany.

In October 2018, Brazil's National Health Surveillance Agency, or ANVISA, approved Mepsevii for the treatment of MPS VII for patients of all ages. Additional regulatory decisions for patients in Columbia and Chile are anticipated by the end of 2019.

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

Clinical Product Candidates

UX007 for the treatment of Long Chain Fatty-Acid Oxidation Disorders, or LC-FAOD

We are developing UX007 for oral administration intended as a substrate replacement therapy for patients with LC-FAOD. UX007 is a highly purified, pharmaceutical-grade, synthetic, seven-carbon fatty acid triglyceride created via a multi-step chemical process. It is 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 long-chain fatty acids, 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 management with the current standard of care, many patients continue to suffer significant morbidities and mortality.

In November 2016, we reported positive 78-week data from the Phase 2 study in patients with LC-FAOD. The study was single-arm open-label and evaluated 29 pediatric and adult patients across three main symptom groups (musculoskeletal, liver/hypoglycemia, and cardiac). In order to enroll, patients had to have incompletely controlled LC-FAOD characterized by serious disease manifestations, or a frequent medical events history despite standard of care. The study began with a four-week run-in period to assess baseline data while on the standard of care therapy including MCT oil, if applicable. Patients on MCT oil then discontinued it and UX007 was titrated to a target dose of 25-35% of total daily caloric intake. Patients were followed to evaluate the acute effects of UX007 treatment over 24 weeks on several endpoints, including cycle ergometry performance, 12-minute walk test, liver disease/hypoglycemia, cardiac disease, and quality of life. Patients who opted to continue were treated for a total of 78 weeks, and rates of major clinical events, or MCEs, such as rhabdomyolysis, hypoglycemia and cardiac events, were monitored and compared to rates for the two years prior to treatment with UX007. The majority of patients enrolled presented with musculoskeletal manifestations compared to a limited number who presented with liver and cardiac symptoms. Patients spanned a wide age range from ten months to 58 years old. Prior to initiating treatment with UX007, 27 of the 29 patients were on the standard of care MCT oil management. Following discontinuation of MCT oil management, the average dose of UX007 was 30% of total daily caloric intake.

The frequency and duration of MCEs were reduced significantly during treatment with UX007. The MCE rate aggregates events related to hypoglycemia, cardiomyopathy and rhabdomyolysis. For this study, events that qualified included those that led to a hospitalization, emergency room visit, or an emergency intervention at home. There was a 48.1 percent reduction (p=0.0208) in the mean annualized rate of MCEs and a 50.3 percent reduction (p=0.0284) in the mean annualized duration of all MCEs after 78 weeks of treatment, compared to the mean annualized number and duration of events in the 18 to 24 months prior to treatment with UX007. Among the event subtypes, rhabdomyolysis was the predominant MCE and there were fewer hypoglycemia events and only a few cardiomyopathy events. There was a reduction in the mean annualized rates and total duration of all events for rhabdomyolysis, cardiomyopathy, and hypoglycemia events after initiation of treatment with UX007. These findings were generally comparable to those observed in the retrospective compassionate use study previously conducted by Ultragenyx with partial reduction in rhabdomyolysis and near complete reduction of hypoglycemia events.

In November 2018, we announced that the FDA accepted our proposal to submit a new drug application, or NDA, for UX007 for the treatment of LC-FAOD; we intend to submit this NDA to the FDA in mid-2019. The submission will include data from the Phase 2 study of UX007, data from the long-term efficacy and safety extension study, a retrospective medical record review, data from patients treated through expanded access, and data from a randomized controlled investigator-sponsored study showing an effect of UX007 on cardiac function. We are also continuing discussions with EU regulatory authorities regarding our registrational pathway.

In January 2019, we announced positive topline data from the ongoing long-term extension study of UX007 in patients with LC-FAOD, demonstrating sustained reductions in the duration and frequency of MCEs and a long-term safety profile similar to what has previously been seen with UX007. A total of 75 patients are enrolled in the study including 24 patients who were previously enrolled in the company-sponsored Phase 2 study, 20 naïve patients who had not previously been treated with UX007 and 31 patients from expanded access or investigator-sponsored studies. Patients who previously completed the Phase 2 company-sponsored study and rolled over to the extension study received treatment for an additional 78 weeks (minimum of 3 years of total UX007 treatment). The median annualized MCE and duration rates during the extension treatment period were zero. Over the entire treatment period, patients had a 67 percent reduction in median annualized event rate and a 66 percent reduction in the median annualized duration rate. Patients who were naïve to UX007 at study entry have received up to 78 weeks of treatment. These patients have demonstrated a 70 percent reduction in the median annualized event rate (2.3 events/year pre-UX007 to 0.7 events/year during extension study treatment period) and an 80 percent reduction in the median annualized duration rate (10.0 days/year pre-UX007 treatment to 2.0 days/year during extension study treatment period). Overall, the safety profile observed in the long-term extension study was consistent with what has been previously observed with UX007. The most common treatment-related adverse events were diarrhea, vomiting, and abdominal pain. One patient discontinued due to a treatment-related adverse event. There were two deaths during the extension study, both deemed to be related to disease progression and not due to treatment with UX007. One of these patients was naïve to UX007 and one was previously in an investigator-sponsored study. Both patients had Trifunctional Protein (TFP) Deficiency type LC-FAOD, a type known to have a high mortality rate, and both had experienced severe disease manifestations when initiating UX007 treatment in the extension study.

Please see "—License and Collaboration Agreements—Clinical Product Candidates—Baylor Research Institute" for a description of our license agreement with Baylor Research Institute.

DTX301 for the treatment of ornithine transcarbamylase, or OTC, deficiency

We are developing DTX301 as an adeno-associated virus 8, or AAV8, gene therapy product candidate designed for patients with OTC deficiency. OTC is part of the urea cycle, an enzymatic pathway in the liver that converts excess nitrogen, in the form of ammonia, to urea for excretion. OTC deficiency is the most common urea cycle disorder and leads to increased levels of ammonia. Patients with OTC deficiency suffer from acute hyperammonemic episodes that can lead to hospitalization, adverse cognitive and neurological effects, and death. We estimate that there are approximately 10,000 patients in the developed world with OTC deficiency, of which we estimate approximately 80% are classified as late-onset, our target population. DTX301 has received Orphan Drug Designation in both the United States and Europe and Fast Track Designation in the United States.

In March 2018, we announced positive 12-week safety and efficacy data from the first dose cohort of the Phase 1/2 study of DTX301 in OTC deficiency. All three patients in the first, lowest-dose cohort received a single DTX301 dose (2.0×10^{12} GC/kg), and the pre-defined endpoint for efficacy evaluation occurred 12 weeks after dosing. The first patient's rate of ureagenesis was normalized, maintained and then substantially increased over 24 weeks. The rate of ureagenesis at baseline was 67% of normal (200 umol/kg/hr), with the normal rate of ureagenesis defined as 300 umol/kg/hr. The patient had an initial peak effect at Week 6 to 112% of normal (67% increase from baseline to 335 umol/kg/hr), and then declined at Week 12 to 87% of normal (30% increase from baseline to 261 umol/kg/hr,) during the steroid regimen that was used to treat the patient's mild alanine aminotransferase, or ALT, elevations. After steroids were weaned, ureagenesis began to rebound to 91% of normal at Week 20 (36% increase from baseline to 273 umol/kg/hr) and then substantially increased to 134% of normal at Week 24 (100.8% increase from baseline to 402 umol/kg/hr). The protocol allows for the tapering or discontinuation of alternate urea-cycle pathway medications. At Week 24, all alternate urea-cycle pathway medications were discontinued based on Patient 1 choice and with investigator concurrence. The second and third patients did not show a clinically meaningful change in rate of ureagenesis over the post dosing periods of 20 weeks and 12 weeks, respectively. The Data Monitoring Committee (DMC) completed its review of the Cohort 1 data, and we proceeded to the second, higher-dose cohort of the study.

In September 2018, we announced data from the second dose cohort of the Phase 1/2 study of DTX301 showing that a second patient in the study (Cohort 2, Patient 4) demonstrated normalization of ureagenesis to 104 percent at Week 24. The other two patients in Cohort 2 (study patients 5 and 6) did not show clinically meaningful changes in rate of ureagenesis at Week 12. In addition, we announced that the first patient in the study (Cohort 1, Patient 1) completed the initial 52-week study period, and demonstrated a further increased level of ureagenesis at Week 52 as well as ongoing clinical stability seven months after discontinuing all alternate pathway medication and recent liberalization of a protein-restricted diet. As of the cutoff date of September 12, 2018 there were no infusion-related adverse events and no serious adverse events reported in the study. All adverse events have been Grade 1 or 2. The only treatment-related adverse events were mild, clinically asymptomatic elevations in ALT in two patients in Cohort 1 and one patient in Cohort 2, which have all been controlled with standard tapering courses of steroids. These alanine aminotransferase, or ALT, levels elevations were mild and similar to what has been observed in other programs using AAV gene therapy. All patients have remained clinically and metabolically stable. The Data Monitoring Committee completed its review of Week 12 data from Cohort 2 and recommended that we proceed to the third dose (1.0×10^{13} GC/kg) cohort of the study. Cohort 3 is currently enrolling patients and data from the cohort are expected in mid-2019.

Please see "—License and Collaboration Agreements—Clinical Product Candidates—REGENXBIO Inc." for a description of our license agreement with REGENXBIO Inc.

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DTX401 for the treatment of glycogen storage disease type Ia, or GSDIa

DTX401 is our AAV8 gene therapy program for the treatment of patients with GSDIa. GSDIa is the most common genetically inherited glycogen storage disease. It is caused by a defective gene for the enzyme G6Pase- , resulting in the inability to regulate blood sugar (glucose). Hypoglycemia in patients with GSDIa can be life-threatening, and the accumulation of the complex sugar glycogen in certain organs and tissues can impair the ability of these tissues to function normally. If chronically untreated, patients can develop severe lactic acidosis, progress to renal failure, and potentially die in infancy or childhood. There are no approved pharmacologic therapies. An estimated 6,000 patients worldwide are affected by GSDIa. DTX401 is an investigational AAV8 gene therapy designed to deliver stable expression and activity of G6Pase- under control of the native promoter. DTX401 is administered as a single intravenous infusion and has been shown in preclinical studies to improve G6Pase- activity and reduce hepatic glycogen levels, a well-described biomarker of disease progression. DTX401 has been granted Orphan Drug Designation in the United States and Europe.

In January 2019, we announced positive topline data from the first dose cohort of the Phase 1/2 study of DTX401 in GSDIa. All three patients in the first, lowest-dose cohort received a single dose of 2.0 x 10^12 GC/kg. The first patient in Cohort 1 had a clinically meaningful improvement in time to hypoglycemia from 3.8 hours at baseline to 7.7 hours at Week 12 (103 percent increase). This patient received a tapering course of steroids, beginning on day 59, to manage a mild asymptomatic elevation in ALT levels, which returned to normal levels following the start of the steroid taper. Patient 2 had a clinically meaningful improvement in time to hypoglycemia from 4.1 hours at baseline to 9.0 hours at Week 12 (120 percent increase). In this instance, the fasting challenge was terminated based on possible hypoglycemia symptoms, and at the time the test was terminated, the patient's glucose level remained well above 60 mg/dL. This patient received a tapering course of steroids beginning at Week 12 to address a slightly elevated ALT. Patient 3 showed a biologic response, reflected by an improvement in time to hypoglycemia from 5.4 hours at baseline to 6.5 hours at Week 12 (20 percent increase). Additional data from future fasting test assessments are needed to determine whether the results from all three patients are sustained or improved over time. As of the primary cutoff date of November 28, 2018, there have been no infusion-related adverse events and no treatment-related serious adverse events reported. All adverse events have been Grade 1 or 2. Patients 1 and 2 had mild elevations in ALT, similar to what has been observed in other programs using AAV-based gene therapy. These two patients successfully completed their tapering steroid regimens. The initial highest dose of steroids in the steroid taper regimen was prospectively reduced to 40 mg/kg to help reduce any risk for hypoglycemia in this particular null genotype population based on the advice of GSDIa experts. Enrollment in the next dose cohort has begun and we expect data from this cohort around mid-2019.

Please see "—License and Collaboration Agreements—Clinical Product Candidates—REGENXBIO Inc." for a description of our license agreement with REGENXBIO Inc.

DTX201 for the treatment of Hemophilia A

DTX201 is our Factor VIII gene therapy program for the treatment of hemophilia A that we are developing in collaboration with Bayer Healthcare LLC, or Bayer. Hemophilia A is the most common form of hemophilia with approximately 144,000 patients in the developed world. The first patient has been enrolled in a Phase 1/2 study of DTX201 in hemophilia A.

Please see "—License and Collaboration Agreements—Clinical Product Candidates—Bayer" for a description of our license agreement with Bayer.

Other Development

In October 2018, we announced that a Phase 3 study evaluating UX007 in patients with glucose transporter type-1 deficiency syndrome, or Glut1 DS, experiencing disabling paroxysmal movement disorders did not achieve its primary endpoint of demonstrating a statistically significant reduction in the frequency of paroxysmal movement events with UX007 treatment compared to placebo, and did not demonstrate a meaningful difference between treatment groups. The study also did not meet its key secondary endpoints. The safety profile observed in this study was consistent with what has been previously reported with UX007. We are discontinuing further clinical development of UX007 for the treatment of Glut1 DS.

Preclinical Pipeline

DTX701 for the treatment of Wilson Disease

DTX701 is in preclinical development for Wilson disease, a rare inherited disorder caused by mutations in the ATP7B gene, which results in deficient production of ATP7B, a protein that transports copper. Loss of function of this copper-binding protein results in the accumulation of copper in the liver and other tissues, most notably the central nervous system. Patients with Wilson disease experience hepatic, neurologic and/or psychiatric problems. Those with liver disease can experience such symptoms as fatigue, lack of appetite, abdominal pain and jaundice, and can progress to fibrosis, cirrhosis, life-threatening liver failure and death. Wilson disease can be treated by reducing copper absorption or removing excess copper from the body using life-long chelation therapy, but unmet needs exist because some treated patients experience clinical deterioration and severe side effects. Wilson disease affects more than 50,000 individuals in the developed world.

UX068 for the treatment of creatine transporter deficiency, or CTD

UX068 is in preclinical development for the treatment of CTD, an X-linked recessive disorder due to mutations in the SLC6A8 gene. Patients with CTD can suffer from CNS deficits, seizures, progressive intellectual disability, autism, speech/language/gross motor delays, and muscle hypotonia and hypotrophy. CTD affects approximately 10,000 to 50,000 patients in the developed world.

UX053 for the treatment of glycogen storage disease type III, or GSDIII

We signed a research collaboration and license agreement with Arcturus Therapeutics, Inc. to develop mRNA therapeutics for select rare disease targets in October 2015. The Arcturus collaboration may help us address a wider range of rare diseases than possible with current approaches. As part of the collaboration, Arcturus will utilize its LUNA® Lipid Mediated Delivery platform to deliver mRNA for two targets selected by us; we also have the option to additional targets during the collaborative research period.

The collaboration includes preclinical candidate UX053 for the treatment of GSDIII, a disease caused by a glycogen debranching enzyme (AGL) deficiency that results in glycogen accumulation in the liver and muscle. GSDIII can cause hepatomegaly, hypoglycemia, hyperlipidemia, some progressive liver cirrhosis, and muscle disease later in life, and affects more than 10,000 patients in the developed world.

Other preclinical programs

We continue to work on other compounds in various preclinical stages of development.

Competition

In the case of indications that we are targeting, it is possible that other companies may produce, develop, and commercialize compounds that might treat these diseases.

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

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

With respect to UX007/triheptanoin, there are currently no approved drugs or treatments for patients with LC-FAOD. LC-FAOD is commonly treated with diet therapy and MCT oil. UX007 may compete with this approach. Although we believe that UX007 should be considered a drug and will be regulated that way, it is possible that other companies or individuals may attempt to produce triheptanoin for use in LC-FAOD. Investigators are testing triheptanoin in clinical studies across multiple indications, including LC-FAOD. It is also possible that other companies may produce,

develop, and commercialize other medium odd-chain fatty acids, or completely different compounds, to treat LC-FAOD. Other companies may also utilize other approaches, such as gene therapy, to treat LC-FAOD.

With respect to DTX301, the current treatments for patients with OTC deficiency are nitrogen scavenging drugs and severe limitations in dietary protein. Drug therapy includes sodium phenylbutyrate (Buphenyl) and glycerol phenylbutyrate (Ravicti), both nitrogen scavengers that help eliminate excess nitrogen, in the form of ammonia, by facilitating its excretion. During a metabolic crisis, patients routinely receive carbohydrate and lipid rich nutrition, including overnight feeding through a nasogastric tube, to limit bodily protein breakdown and ammonia production. In acute cases, ammonia must be removed by dialysis or hemofiltration. Liver transplant may also be a solution for OTC deficiency. In addition, Synlogic, Inc. has an ongoing Phase 1 study of SYNB1020 for the potential treatment of hyperammonemia.

With respect to DTX401, there are currently no pharmacologic treatments for patients with GSDIa and we are not aware of any programs in development.

License and Collaboration Agreements

Our products and current product candidate pipeline have been either in-licensed from academic institutions or derived from partnerships with other pharmaceutical companies. Following is a description of our significant license and collaboration agreements.

Approved Products

Kyowa Hakko Kirin

In August 2013, we entered into a collaboration and license agreement with KHK. Under the terms of this collaboration and license agreement, as amended, we and KHK will collaborate on the development and commercialization of Crysvita in the field of orphan diseases in the United States and Canada, or the "profit-share territory", and in the EU and Switzerland, or the European territory, and we will have the right to develop and commercialize such products in the field of orphan diseases in Mexico and Central and South America, or Latin America. In the field of orphan diseases, and except for ongoing studies being conducted by KHK, we will be the lead party for development activities in the profit-share territory and in the European territory until the applicable transition date; we will also be the lead party for core development activities conducted in Japan and Korea for which the core development plan is limited to clinical trials mutually agreed to by us and KHK. We will share the costs for development activities in the profit share territory and European territory conducted pursuant to the development plan before the applicable transition date equally with KHK and KHK shall be responsible for 100% of the costs for development activities in Japan and Korea. On the applicable transition date in the profit-share territory and the European territory, KHK will become the lead party and be responsible for the costs of the development activities. However, we will continue to share the costs of the studies commenced prior to the applicable transition date equally with KHK. We have the primary responsibility for conducting certain research and development activities. We are obligated to provide assistance in accordance with the agreed upon development plan as well as participate on various committees. Crysvita was approved in the EU in February 2018 and was approved by the FDA in April 2018. We and KHK share commercial responsibilities and profits in the profit share territory until the applicable transition date, KHK has the commercial responsibility in the European territory, and we are responsible for commercializing burosumab in Latin America.

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

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

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

In May 2017, we signed an agreement with a wholly-owned subsidiary of KHK pursuant to which we were granted the right to commercialize Crysvita in Turkey. KHK's subsidiary has the option to assume responsibility for commercialization efforts from us, after a certain minimum period.

The collaboration and license agreement will continue for as long as products in the field of orphan diseases are sold in the profit-share territory, European territory, Turkey, or Latin America, unless the agreement is terminated in accordance with its terms.

KHK may terminate the agreement in certain countries or territories based upon our failure to meet certain milestones. Specifically, if we do not make a first commercial sale, on a country-by-country basis, in Latin America by certain deadlines, KHK may terminate the agreement only with respect to the applicable territory or country in which the milestone was not timely met. In certain circumstances, we have the right to obtain an extension of the applicable deadline by making a payment to KHK in the low single-digit to low double-digit millions of dollars, depending on the milestone. Also, in the event of the occurrence of certain excusable delays, the deadline for meeting the applicable milestone above is extended to account for the period of the delay. Furthermore, either party may terminate the agreement for the material breach or bankruptcy of the other party. In any event of termination by KHK, unless such termination is the result of KHK's termination for certain types of breach of the agreement by us, we may receive low single-digit to low double-digit royalties on net post-termination sales by KHK in one or more countries or territories, the amount of which varies depending on the timing of, and reason for, such termination. In any event of termination, our rights to Crysvita under the agreement and our obligations to share development costs will cease, and the program will revert to KHK, worldwide if the agreement is terminated as a whole or solely in the terminated countries if the agreement is terminated solely with respect to certain countries.

Saint Louis University

In November 2010, we entered into a license agreement with Saint Louis University, or SLU, wherein SLU granted us certain exclusive rights to intellectual property related to Mepsevii. Under the terms of the license agreement, SLU granted us an exclusive worldwide license to make, have made, use, import, offer for sale, and sell therapeutics related to SLU's beta-glucuronidase product for use in the treatment of human diseases. Under this agreement, we agreed to use best efforts to develop and commercialize a licensed product as soon as practicable consistent with sound and reasonable business practices and judgment.

Under the license agreement, upon reaching a certain level of worldwide sales of the product, we will pay to SLU a low single-digit royalty on net sales of the licensed products in any country or region, subject to certain potential deductions. Our obligation to pay royalties to SLU continues on a country-by-country basis until the expiration of the last-to-expire licensed patent covering the product in such country or, in the United States, Japan, and the EU, until the later expiration of any orphan drug exclusivity. We may terminate the agreement for convenience at any time and SLU may terminate the agreement for our material breach, bankruptcy, or challenge of the licensed patents or technology, and SLU may terminate the agreement or render our license non-exclusive if we fail to meet our diligence obligations. Unless terminated as set forth above, this license agreement continues in full force and effect until the latest of expiration of the last patent based on technology licensed under the agreement, at which point our license becomes fully paid.

Clinical Product Candidates

Baylor Research Institute

In September 2012, we entered into a license agreement with Baylor Research Institute, or BRI, under which we exclusively licensed certain intellectual property related to triheptanoin. The license includes patents, patent applications, know-how, and intellectual property related to the composition and formulation of triheptanoin as well as its use in treating a number of orphan diseases, including LC-FAOD. The license grant includes the sole right to develop, manufacture, and commercialize licensed products for all human and animal uses. Under the license agreement, we are obligated to use commercially reasonable efforts to develop and commercialize licensed products in select orphan indications. If we fail to meet our diligence obligations with respect to a specified orphan indication or set of orphan indications, BRI may convert our license to a non-exclusive license with respect to such orphan indication or set of orphan indications until we receive regulatory approval for licensed products in the applicable orphan indication or set of orphan indications. We are also obligated to pay a mid-single digit royalty on net sales to BRI, subject to certain reductions and offsets. Our obligation to pay royalties to BRI continues on a licensed product-by-licensed product and country-by-country basis until the later of the expiration of the first regulatory exclusivity granted with respect to such product in such country or the expiration of the last-to-expire licensed patent claiming such product in such country, in each case in connection with approval in such country for LC-FAOD or an orphan disease covered by our license from BRI. We may make future payments of up to $5.3 million contingent upon attainment of certain development milestones and $7.5 million if certain sales milestones are achieved. We may terminate the agreement for convenience at any time and either we or BRI may terminate the agreement for the material breach or bankruptcy of the other party. If we terminate for BRI's breach or bankruptcy, our license from BRI will remain in effect, subject to our continued payment of reduced milestones and royalties. Unless terminated by its terms, this license agreement continues in full force and effect, on a product-by-product and country-by-country basis, until our royalty obligations expire, at which point our license from BRI with respect to such product in such country becomes irrevocable, perpetual, fully paid and royalty-free.

REGENXBIO Inc.

In October 2013, we entered into an exclusive license agreement with REGENXBIO Inc., or REGENX, under which we are developing products to treat hemophilia A, OTC deficiency and GSD1a. Under the 2013 license agreement, REGENX granted us an exclusive worldwide license to make, have made, use, import, sell, and offer for sale licensed products with respect to such disease indications, subject to certain exclusions. We do not have the right to control prosecution of the in-licensed patent applications, and our rights to enforce the in-licensed patents are subject to certain limitations. Under the 2013 license agreement, we pay or will pay REGENX an annual maintenance fee and certain milestone fees per disease indication, low to mid single-digit royalty percentages on net sales of licensed products, and milestone and sublicense fees, if any, owed by REGENX to its licensors as a result of our activities under the 2013 license agreement. We are required to develop licensed products in accordance with certain milestones. In the event that we fail to meet a particular milestone within established deadlines, we can extend the relevant deadline by providing a separate payment to REGENX. The 2013 license agreement will expire upon the expiration, lapse, abandonment, or invalidation of the last claim of the licensed intellectual property to expire, lapse, or become abandoned or unenforceable in all the countries of the world. Upon expiration, our know-how license will become non-exclusive, perpetual, irrevocable and royalty-free with respect to licensed know-how that REGENX owns in the field and will continue with respect to all of REGENX’s other know-how in the field under certain of its licenses for so long as its rights from those licensors continue. Subject to certain obligations to Bayer, we may terminate the 2013 license agreement upon prior written notice or for a material breach. REGENX may terminate the license agreement if we or our controlling affiliate become insolvent, are late in paying money due, commence certain actions relating to the licensed patents or materially breach the agreement. If the 2013 license agreement is terminated with respect to an indication, we grant certain rights to REGENX, including transferring ownership of any applicable regulatory approvals and granting an exclusive license under certain of our intellectual property for use with respect to products covered by the intellectual property we had licensed from REGENX in that indication.

In March 2015, we entered into an option and license agreement with REGENX under which we are developing product candidates to treat PKU, citrullinemia type 1 and Wilson disease and had an option for another disease indication. The 2015 option and license agreement grants us an exclusive worldwide license to make, have made, use, import, sell, and offer for sale licensed products with respect to such disease indications, subject to certain exclusions. In October 2018, we exercised our remaining option for another disease indication and paid $1.0 million for the option fee. We do not have the right to control prosecution of the in-licensed patent applications, and our rights to enforce the in-licensed patents are subject to certain limitations. Under the 2015 option and license agreement, we pay or will pay REGENX an annual maintenance fee and certain milestone fees per disease indication, mid to high single-digit royalty percentages on net sales of licensed products, and mid-single to low double-digit percentages of any sublicense fees we receive from sublicenses for the licensed intellectual property rights. We are required to develop licensed products in accordance with certain milestones. In the event that we fail to meet a particular milestone within established deadlines, we can extend the relevant deadline by providing a separate payment to REGENX. The 2015 option and license agreement will expire upon the expiration of the royalty obligations with respect to all licensed products for all licensed indications under all licenses granted under all exercised commercial options. Upon expiration, our know-how license will become non-exclusive, perpetual, irrevocable and royalty-free with respect to licensed know-how that REGENX owns in the field and will continue with respect to all of REGENX's other know-how in the field under certain of its licenses for so long as its rights from those licensors continue. We may terminate the 2015 option and license agreement upon prior written notice or for a material breach. REGENX may terminate the 2015 option and license agreement if we or our controlling affiliate become insolvent, are late in paying money due, commence certain actions relating to the licensed patents or materially breach the agreement. If the 2015 option and license agreement is terminated with respect to an indication, we grant certain rights to REGENX, including transferring ownership of any applicable regulatory approvals and granting an exclusive license under certain of our intellectual property for use with respect to products covered by the intellectual property we had licensed from REGENX in that indication.

Bayer

In June 2014, we entered into an agreement with Bayer to research, develop and commercialize AAV gene therapy products for treatment of hemophilia A. Under this agreement, we granted Bayer an exclusive license to develop and commercialize one or more novel gene therapies for hemophilia A. We are responsible for the development of DTX201 through a proof-of-concept clinical trial, with reimbursement from Bayer for project costs. Bayer is responsible operationally, including for conducting the proof-of-concept clinical trial, and will incur the costs of the conduct of the trial. Upon the successful demonstration of clinical proof of concept, Bayer agreed to use commercially reasonable efforts to manage and fund any subsequent clinical trials and commercialization of gene therapy products for treatment of hemophilia A. Bayer will have worldwide rights to commercialize the potential future product.

Under the agreement, Bayer paid us an upfront cash payment and will pay us development and commercialization milestone payments, and tiered royalties based on product sales. The agreement expires on a licensed treatment-by-licensed treatment and country-by-country basis until the later of ten years from the date of first commercial sale or when patent claims have expired, lapsed, been abandoned, or been invalidated in such country. Either party may terminate the agreement for an uncured material breach by the other party. Bayer may terminate the agreement upon prior notice to us, either in its entirety or with respect to certain territories subject to the agreement. Bayer may also terminate the agreement upon notice of a product's failure to meet certain criteria or after the successful completion of certain Phase 1 trials in the event Bayer makes a good faith determination that there is a material safety issue with respect to such product. Either party may terminate the agreement upon bankruptcy or insolvency of the other party, and we may terminate the agreement if Bayer institutes certain actions. Under certain termination circumstances, we would have worldwide rights to the terminated program(s).

University of Pennsylvania

In January 2015, we entered into an agreement with the University of Pennsylvania to sponsor certain research of Dr. Wilson at University of Pennsylvania School of Medicine related to liver gene therapy and hemophilia. Under the agreement, the University of Pennsylvania granted us an option to obtain a worldwide, non-exclusive or exclusive, royalty-bearing license, with the right to sublicense, under certain patent rights conceived, created or reduced to practice in the conduct of the research. We are required to reimburse the University of Pennsylvania for filing, prosecuting and maintaining such patent rights unless and until we decline to exercise our option. The University is required to provide us with task-based, scientific reports of progress and results of the research, and granted us a royalty-free, nontransferable, non-exclusive right to copy and distribute any research reports furnished to us for any reasonable purpose, provided the results are not made publicly available until certain conditions are met, and the right to use, disclose and otherwise exploit the research results for any reasonable purpose, subject to similar restrictions on our public disclosure of the research results.

This agreement expires on the earlier of the completion of certain tasks and activities or December 31, 2021. The agreement may be extended further, or renewed, by mutual agreement. If extended or renewed, then either party may terminate the agreement if Dr. Wilson becomes unavailable and an acceptable substitute is not found within a certain period of time, or if we fail to mutually agree on an acceptable work plan and budget for the sponsored research. We may also terminate the sponsored research agreement upon written notice, as long as we have met all of our payment and performance obligations. Either party may terminate this agreement for an uncured material breach. In the event of termination, we shall pay University of Pennsylvania the amount needed to cover costs through the effective termination date as well as allowable commitments extending beyond the termination date (up to one-fourth of the total budget).

In May 2016, we entered into a research, collaboration and license agreement with the University of Pennsylvania under which we are collaborating on the pre-clinical development of gene therapy products for the treatment of citrullinemia type I, phenylketonuria, and Wilson disease, each, a Subfield. Under the agreement, we were granted an exclusive, worldwide, royalty-bearing right and license to certain patent rights arising out of the research program, and a non-exclusive, worldwide, royalty-bearing right and license to certain University of Pennsylvania intellectual property, in each case to research, develop, make, have made, use, sell, offer for sale, commercialize and import licensed products in each Subfield for the term of the agreement. We will fund the cost of the research program and will be responsible for clinical development, manufacturing and commercialization of each Subfield. In addition, we will be required to make milestone payments (up to a maximum of $5 million per Subfield) if certain development milestones are achieved over time, and to pay low to mid single-digit royalties on net sales of each Subfield’s licensed products. We will also make milestone payments of up to $25.0 million per approved product if certain commercial milestones are achieved.

Takeda Pharmaceutical Company Limited

In June 2016, we entered into a collaboration and license agreement with Takeda. Under the terms of the license agreement, we obtained, among other things, an exclusive license for a pre-clinical compound from Takeda in a pre-determined field of use, which includes an option to an additional field of use for this product. We are responsible for the development costs for the pre-clinical compound pursuant to an initial development plan.

As part of the agreement, we established a five-year research collaboration with Takeda whereby the parties may mutually agree to add additional option product candidates to the collaboration, in which case we will bear the cost of the development activities, with certain exceptions, and terms to be negotiated

We also granted Takeda an exclusive option for Asian rights, for a limited period, to any licensed products and any additional products resulting from the collaboration, as well as an option to exclusively license one of our products for development and commercialization in Japan. If Takeda exercises any of its option rights to license a product pursuant to the agreement, Takeda will pay for the development costs within the licensed territory, will share in a portion of the global development costs, and will make a milestone payment upon regulatory approval. Takeda will also owe royalties on net sales in the licensed territory for any licensed product, depending on the development stage when the product is licensed as well as sales levels. The royalties related to the option to license our product, as well as the additional product are subject to future good faith negotiations at the time that the option is exercised.

We discontinued the development efforts on the pre-clinical compound in the pre-determined field of use. We continue to evaluate additional product candidates for potential addition to the collaboration.

Patents and Proprietary Rights

The proprietary nature of, and protection for, our products, product candidates, processes, and know-how are important to our business. Our success depends in part on our ability to protect the proprietary nature of our products, product candidates, technology, and know-how, to operate without infringing on the proprietary rights of others, and to prevent others from infringing our proprietary rights. We seek patent protection in the United States and internationally for our products, product candidates, and other technology. Our policy is to patent or in-license the technology, inventions and improvements that we consider important to the development of our business. In addition to patent protection, we use other means to protect our proprietary rights, including the pursuit of marketing or data exclusivity periods, orphan drug status, and similar rights that are available under regulatory provisions in certain countries, including the United States, Europe, Japan, and China. See "Government Regulation—U.S. Government Regulation — Orphan Designation and Exclusivity," "Government Regulation—U.S. Government Regulation — Pediatric Studies and Exclusivity," "Government Regulation—U.S. Government Regulation — Patent Term Restoration," "Government Regulation—U.S. Government Regulation — Biosimilars and Exclusivity," "Government Regulation—U.S. Government Regulation — Abbreviated New Drug Applications for Generic Drugs and New Chemical Entity Exclusivity," and "Government Regulation—EU Regulation — Orphan Designation and Exclusivity" below for additional information.

We also rely on trade secrets, know-how, and continuing innovation to develop and maintain our competitive position. We cannot be certain that patents will be granted with respect to any of our pending patent applications or with respect to any patent applications filed by us in the future, nor can we be sure that any of our existing patents or any patents granted to us in the future will be commercially useful in protecting our technology.

We seek regulatory approval for our product candidates in disease areas with high unmet medical need, significant market potential, and where we expect to have a proprietary position through patents covering various aspects of our product candidates, such as composition, dosage, formulation, use, and manufacturing process, among others. Our success depends in part on an intellectual property portfolio that supports our future revenue streams and erects barriers to our competitors. We are maintaining and building our patent portfolio by filing new patent applications, prosecuting existing applications, and licensing and acquiring new patents and patent applications.

Despite these measures, any of our intellectual property and proprietary rights could be challenged, invalidated, circumvented, infringed or misappropriated, or such intellectual property and proprietary rights may not be sufficient to achieve or maintain market exclusivity or otherwise to provide competitive advantages. For more information, please see “Risks Related to Our Intellectual Property.”

We own or in-license a number of patents in the U.S. and foreign countries that cover our products, product candidates, and methods of their use. With respect to our owned or in-licensed issued patents in the U.S. and Europe, we may be entitled to obtain an extension of patent term to extend the patent expiration date. For example, in the U.S., this extended coverage period is known as patent term extension (PTE) and can only be obtained provided we apply for and receive a marketing authorization for a product. The period of extension may be up to five years beyond the expiration of the patent, but cannot extend the remaining term of a patent beyond a total of 14 years from the date of product approval. Only one patent among those eligible for an extension may be extended. In Europe, Supplementary Protection Certificates (SPC) may also be available to patents, which would be available by applying to the member states. However, there is no guarantee that the applicable authorities, including the FDA, will agree with our assessment of whether such extensions should be granted, and even if granted, the length of such extensions. The exact duration of the extension depends on the time we spend in clinical studies as well as getting marketing approval from the FDA. The exclusivity positions for our commercial products, Mepsevii and Crysvita, and our clinical-stage product candidates as of December 31, 2018 are summarized below.

Crysvita (Burosumab) Exclusivity

We have in-licensed rights from Kyowa Hakko Kirin Co., Ltd., or KHK, to patents and patent applications relating to Crysvita and its use for the treatment of XLH and various other hypophosphatemic conditions. Pursuant to this license, we have rights to a number of issued patents and pending applications, including four issued U.S. patents, as well as patents and applications in other jurisdictions covering generic and specific antibodies against FGF23 as well as their use for the treatment of XLH and related conditions. The patent terms for the issued patents in the U.S. are from 2022 to 2029 (without patent term extension), while the issued patents outside the U.S. expire between 2021 and 2028 (without patent extension). KHK has applied for an extension of patent term in the U.S. and Europe for Crysvita to 2032 and 2033, respectively. We also jointly own with KHK a pending application in the U.S. and corresponding foreign patent applications relating to dosing regimens for administration of anti-FGF23 antibodies, including Crysvita. Any patents issuing from these jointly-owned applications would be expected to expire in 2035. In addition to the foregoing patent protections, Crysvita is protected in the U.S. by regulatory data exclusivity until 2030 and by orphan drug exclusivity for treating XLH until 2025.

Mepsevii (Vestronidase Alfa) Exclusivity

We own four issued U.S. patents covering Mepsevii and its use in the treatment of lysosomal storage disorders such as MPS VII. The patents in the U.S. expire in 2035. Mepsevii is also protected in the U.S. by regulatory data exclusivity until 2029 and by orphan drug exclusivity for treating MPS VII until 2024. In Europe, we have an issued patent expiring in 2035 that covers Mepsevii and its use in the treatment of MPS VII. Mepsevii is also protected in Europe by orphan drug exclusivity and regulatory data exclusivity until 2028. Outside the U.S. and Europe, we own corresponding pending patent applications covering Mepsevii and methods of its use. Any patents issuing from these

pending patent applications would be expected to expire in 2035.

UX007 Exclusivity

We have an exclusive license from the Baylor Research Institute, or BRI, to patents and patent applications relating to the UX007 composition and its use for the treatment of FAOD. In the U.S., the in-licensed BRI patent portfolio includes issued patents with claims covering the UX007 composition that expire between 2020 and 2025 (without patent term extension). The BRI portfolio additionally includes issued U.S. and foreign patents with claims covering the use of UX007 for the treatment of FAOD that expire in 2020 (without patent term extension). We also own a pending U.S. patent application and corresponding foreign patent applications relating to our pharmaceutical-grade UX007 composition. Any patents issuing from these owned applications would be expected to expire in 2034. We intend to pursue marketing and orphan drug exclusivity periods that are available under regulatory provisions in certain countries. UX007 has received orphan designation in the U.S. for FAOD and in Europe for various subtypes of FAOD.

DTX301 Exclusivity

We have in-licensed patents and patent applications owned by the University of Pennsylvania, or UPENN, relating to various adeno-associated viruses and vectors utilizing the capsids of those viruses. These patents and patent applications are licensed or sublicensed to REGENXBIO and sublicensed to us. Our product candidate DTX301 utilizes an AAV8 capsid and a codon-optimized version of the OTC gene. The in-licensed patents relevant to the AAV8 capsid expire between 2022 and 2024 in the U.S., and in 2022 in foreign countries. Our in-license also includes a pending application in the U.S. and corresponding pending foreign patent applications directed to the codon-optimized version of the OTC gene used in DTX301. Any patents issuing from these applications relating to the codon-optimized OTC gene would be expected to expire in 2035 (without patent term extension). We intend to pursue marketing and orphan drug exclusivity periods that are available under regulatory provisions in certain countries. DTX301 for the treatment of OTC deficiency has received orphan drug designation in the U.S. and Europe.

DTX401 Exclusivity

We have two in-licenses to patents and patent applications covering elements of our DTX401 product candidate. First, we have in-licensed patents owned by UPENN and sublicensed to us by REGENXBIO relating to the AAV8 capsid used in DTX401 that expire between 2022 and 2024 in the U.S., and in 2022 in foreign countries. Second, we have a non-exclusive license from the National Institutes of Health (NIH) to an issued U.S. patent expiring in 2034 (without patent term extension) and corresponding foreign patent applications covering a recombinant nucleic acid construct used in DTX401 that includes a codon-optimized version of the G6Pase gene. We intend to pursue marketing and orphan drug exclusivity periods that are available under regulatory provisions in certain countries. DTX401 for the treatment of GSD1a has received orphan drug designation in the U.S. and Europe.

Trademarks

We have registered trademarks covering the Ultragenyx word mark in the U.S. and multiple other jurisdictions. In addition, we have a registered trademark in the U.S. covering a stylized design of our Ultragenyx Pharmaceutical logo. We also have a pending trademark application in the U.S. and registered trademarks in multiple other jurisdictions relating to our Mepsevii brand name for vestronidase alfa. We additionally have a license from KHK to registered trademarks and trademark applications covering the Crysvita brand name for burosumab in the U.S., Canada, Turkey, and various Latin American territories.

Other

We rely upon unpatented trade secrets, know-how, and continuing technological innovation to develop and maintain our competitive position. We seek to protect our ownership of know-how and trade secrets through an active program of legal mechanisms including assignments, confidentiality agreements, material transfer agreements, research collaborations, and licenses.

Manufacturing

We currently contract with third parties for the manufacturing and testing of our products and product candidates for use in preclinical, clinical, and commercial applications and intend to do so in the future. We do not own or operate manufacturing facilities for the cGMP production of clinical or commercial quantities of our product candidates. We do, however, have process and analytical development capabilities focused on the gene therapy technologies. The use of contracted manufacturing and reliance on collaboration partners is relatively cost-efficient and has minimized the need for our direct investment in manufacturing facilities and additional staff early in development. Although we rely on contract manufacturers, we have personnel with extensive manufacturing experience to oversee our contract

manufacturers. All of our third-party manufacturers are subject to periodic audits to confirm compliance with applicable regulations and must pass inspection before we can manufacture our drugs for commercial sales.

To date, our third-party manufacturers have met our manufacturing requirements. To meet our projected needs for commercial manufacturing, third parties with whom we currently work might need to increase their scale of production or we will need to secure alternate suppliers. We believe that there are alternate sources of supply that can satisfy our clinical and commercial requirements, although we cannot be certain that identifying and establishing relationships with such sources, if necessary, would not result in significant delay or material additional costs.

Products

Mepsevii

The Mepsevii drug substance and drug product are manufactured by Rentschler Biopharma SE, or Rentschler, under non-exclusive commercial supply and services agreements effective December 2017 and January 2018, respectively. The drug substance agreement has an initial term of five years, which will be automatically extended for another five years following the initial term, and will continue in full force and effect for its term unless earlier terminated. Following the initial term, we and Rentschler can withdraw from the agreement without cause upon prior notice for specified periods. In addition, either party may terminate the agreement if the other party breaches a material provision of the agreement and such breach remains uncured for a specified period following receipt by the breaching party of written notice of such breach. The drug product agreement expires on December 31, 2025 and will continue in full force and effect for its term unless earlier terminated. Either party may terminate the agreements with immediate effect if the other party violates or breaches certain obligations set forth in the agreement, undergoes a material change in control, or infringes its intellectual property rights. We can also terminate the agreements if Rentschler loses the right to operate under the agreement. Either party can also terminate the agreements if Rentschler is unable to deliver its agreed upon services for a certain period in the case of a force majeure event. The cell line to produce Mepsevii is specific for this product and is in our control and stored in multiple secure locations. All other raw materials are commercially available. Under the drug product agreement, the last product will be produced no later than June 30, 2019, unless this date is extended in accordance with the agreement. We intend to transfer the drug product manufacturing to a new site as the Rentschler drug product manufacturing in Laupheim, Germany is being discontinued.

Crysvita

The drug substance and drug product for burosumab are made by KHK in Japan under the collaboration and license agreement with KHK. The cell line to produce burosumab is specific for this product and is in KHK’s control. All other raw materials are commercially available.

Product Candidates

UX007

The pharmaceutical-grade drug substance for UX007 is manufactured by IOI Oleo GmbH, or IOI Oleo, in Germany under an exclusive worldwide supply agreement, subject to certain limitations, executed in 2012 with an initial term of three years. The agreement automatically renews for two-year periods at the end of each then current term unless either party notifies the other party of its intention not to renew in writing at least three calendar months before the expiration of the then current term. Additionally, if a party materially breaches an obligation under the agreement and does not cure such breach within 60 days of receiving notice of the breach from the non-breaching party, the non-breaching party may terminate the agreement immediately upon written notice to the breaching party. Multiple parties have manufactured the UX007 drug product for us, which is not considered a very specialized task.

DTX301

The drug substance and drug product for DTX301, our AAV product candidate, are manufactured on a non-exclusive basis by a contract manufacturing organization, or CMO, pursuant to cGMP requirements.

DTX301 is currently manufactured using HEK293 adherent mammalian cells. Adherent and suspension HEK293 cells are straightforward to grow and transfect readily, and as a result, are widely used in the biotechnology industry to

produce therapeutic proteins and viral vectors for gene therapy on a small scale. Vectors produced using HEK293 cells have been, or are being, used safely in multiple clinical trials, including trials conducted in the United States and EU by other biopharmaceutical companies and academic government institutions. A key advantage of the HEK293 cell manufacturing system is flexibility and the relative speed with which AAV vectors can be manufactured for early Phase 1/2 clinical trials, allowing the establishment of early indications of therapeutic benefit in patients. As we advance and scale up our processes for Phase 3 clinical and commercial scale manufacturing, we intend to transition from the HEK293 cell manufacturing scale used for our DTX301 Phase 1/2 programs to a cell-based suspension bioreactor format.

DTX401

Similar to DTX301, the drug substance and drug product for DTX401 are manufactured on a non-exclusive basis by a CMO pursuant to cGMP requirements.

DTX401 is currently manufactured using HEK293 suspension mammalian cells. Similar to DTX301, HEK293 cells are widely used in the biotechnology industry and the regulatory agencies in the United States and EU are familiar with the technology. As the clinical program advances we may consider alternate cell manufacturing systems such as HeLa cell systems.

Commercialization and Product Support

We have built our own commercial organizations in North America, Europe and Latin America to effectively support the commercialization of our products and product candidates, if approved, and we expect to expand on these efforts. We may elect to utilize strategic partners, distributors, or contract management organizations to assist in the commercialization of our products. The commercial infrastructure for rare disease products typically consists of a targeted, specialty field organization that educates a limited and focused group of physicians supported by field management and internal support teams, which includes our patient support services hub and distribution team. One challenge, unique to commercializing therapies for rare diseases, is the difficulty in identifying eligible patients due to the very small and sometimes heterogeneous disease populations. Our management team focuses on maximizing patient identification for both clinical development and commercialization purposes in rare diseases.

Additional capabilities important to the rare disease marketplace include the management of key accounts such as managed care organizations, group-purchasing organizations, specialty pharmacies, and government accounts. To develop the appropriate commercial infrastructure, we will have to invest a significant amount of financial and management resources, some of which will be committed prior to regulatory approval of the products that they are intended to support.

We continue to build a medical affairs organization and multiple capabilities across North America, Europe, Turkey, and Latin America to meet the scientific educational needs of the healthcare providers and patients in the rare disease community, focusing on providing accurate disease state and balanced product information across our portfolio for appropriate management of patients with rare disorders.

Medical affairs is comprised of the following capabilities in support of our mission: medical information, patient advocacy, patient diagnosis, medical science liaisons, research and educational grants. Medical affairs will engage as early as Phase 1 and will continue work throughout the lifecycle of each product and product candidate as dictated by the specific scientific needs in each therapeutic area.

Government Regulation

Government authorities in the United States (including federal, state, and local authorities) and in other countries, extensively regulate, among other things, the manufacturing, research and clinical development, marketing, labeling and packaging, storage, distribution, post-approval monitoring and reporting, advertising and promotion, pricing, and export and import of pharmaceutical products, such as those we are developing. We must obtain the requisite approvals from regulatory authorities in the United States and foreign countries prior to the commencement of clinical studies or marketing of the product in those countries. Accordingly, our operations are and will be subject to a variety of regulations and other requirements, which vary from country to country. The process of obtaining regulatory approvals and the subsequent compliance with appropriate federal, state, local, and foreign statutes and regulations require the expenditure of substantial time and financial resources.

Global Regulation of Clinical Studies

Clinical studies involve the administration of an investigational medicinal product to human subjects under the supervision of qualified investigators in accordance with protocols, Good Clinical Practices, or GCP, the ethical principles that have their origin in the Declaration of Helsinki and applicable regulatory requirements. A protocol for each clinical study and any subsequent protocol amendments are typically submitted to the FDA or other applicable regulatory authorities as part of an IND or clinical trial application, or CTA. Additionally, approval must also be obtained from each clinical study site’s institutional review board, or IRB, or Ethics Committee, or EC, before the studies may be initiated, and the IRB or EC must monitor the study until completed. There are also requirements

governing the reporting of ongoing clinical studies and clinical study results to public registries.

The clinical investigation of a drug is generally divided into three or four phases. Although the phases are usually conducted sequentially, they may overlap or be combined.

- Phase 1. The drug is initially introduced into healthy human subjects or patients with the target disease or condition. These studies are designed to evaluate the safety, dosage tolerance, pharmacokinetics and pharmacologic actions of the investigational new drug in humans, and if possible, to gain early evidence on effectiveness.
- Phase 2. The drug is administered to a limited patient population to evaluate dosage tolerance and optimal dosage, identify possible adverse side effects and safety risks, and preliminarily evaluate efficacy.
- Phase 3. The drug is administered to an expanded patient population, generally at geographically dispersed clinical study sites to generate enough data to statistically evaluate dosage, clinical effectiveness and safety, to establish the overall benefit-risk relationship of the investigational new drug product, and to provide an adequate basis for product approval.
- Phase 4. In some cases, additional studies and patient follow-up are conducted to gain experience from the treatment of patients in the intended therapeutic indication. Regulatory authorities may condition approval of a marketing application for a product candidate on the sponsor's agreement to conduct additional clinical studies after approval. In other cases, a sponsor may voluntarily conduct additional clinical studies after approval to gain more information about the drug. Such post-approval studies are typically referred to as Phase 4 clinical studies.

A pivotal study is a clinical study that adequately meets regulatory authority requirements for the evaluation of a drug candidate's efficacy and safety such that it can be used to justify the approval of the product. Generally, pivotal studies are Phase 3 studies, but regulatory authorities may accept results from Phase 2 studies if the study design provides a well-controlled and reliable assessment of clinical benefit, particularly in situations where there is an unmet medical need and the results are sufficiently robust.

U.S. Government Regulation

In the United States, the FDA regulates drugs under the Federal Food, Drug, and Cosmetic Act, or FDCA, and its implementing regulations, and biologics under the FDCA and the Public Health Service Act, or PHSA, and its implementing regulations. FDA approval is required before any new drug or dosage form, including a new use of a previously approved drug, can be marketed in the United States. Drugs and biologics are also subject to other federal, state, and local statutes and regulations.

The process required by the FDA before product candidates may be marketed or sold in the United States generally involves the following:

- completion of extensive preclinical laboratory tests and preclinical animal studies performed in accordance with the Good Laboratory Practices, or GLP, regulations;
- submission to the FDA of an IND, which must become effective before human clinical studies may begin and must be updated annually;
- conducting adequate and well-controlled human clinical studies to establish the safety and efficacy of the product candidate for each proposed indication under an active IND and approved by an independent IRB representing each clinical site;
- preparation of and submission to the FDA of a new drug application, or NDA, or biologics license application, or BLA, after completion of all pivotal clinical studies;
- potential review of the product application by an FDA advisory committee, where appropriate and if applicable;
- satisfactory completion of an FDA pre-approval inspection of the manufacturing facilities where the proposed drug substance and drug product are produced to assess compliance with Good Manufacturing Practices, or GMP;
- FDA inspection of one or more clinical sites to assure compliance with GCP; and
- FDA review and approval of an NDA or BLA.

Submission of an NDA or BLA to the FDA

Assuming successful completion of all required testing in accordance with all applicable regulatory requirements, detailed investigational new drug product information is submitted to the FDA in the form of an NDA or BLA requesting approval to market the product for one or more indications. Under federal law, the submission of most NDAs and BLAs is subject to a significant application user fee, unless waived.

Once an NDA or BLA has been submitted, the FDA's goal is to review the application within ten months after it accepts the application for filing, or, if the application relates to an unmet medical need in the treatment of a serious or life-threatening condition, six months after the FDA accepts the application for filing. The review process can be significantly extended by FDA requests for additional information or clarification.

The FDA's Decision on an NDA or BLA

The FDA may issue an approval letter or a Complete Response Letter. An approval letter authorizes commercial marketing of the drug with specific prescribing information for specific indications. As a condition of NDA or BLA approval, the FDA may impose additional requirements, such as post-marketing studies and/or a risk evaluation and mitigation strategy (REMS) to help ensure that the benefits of the drug outweigh the potential risks. A REMS can

include medication guides, communication plans for healthcare professionals, and elements to assure safe use. A Complete Response Letter indicates that the review cycle of the application is complete and the application is not ready for approval. A Complete Response Letter may require additional clinical data and/or an additional pivotal Phase 3 clinical study(ies), and/or other significant, expensive and time-consuming requirements related to clinical studies, preclinical studies or manufacturing.

Expedited Review and Accelerated Approval Programs

A sponsor may seek approval of its product candidate under programs designed to accelerate FDA's review and approval of NDAs and BLAs. For example, Fast Track Designation may be granted to a drug intended for treatment of a serious or life-threatening disease or condition and data demonstrate its potential to address unmet medical needs for the disease or condition. The key benefits of fast track designation are the eligibility for priority review, rolling review (submission of portions of an application before the complete marketing application is submitted), and accelerated approval, if relevant criteria are met. The FDA may grant the NDA or BLA a priority review designation, which sets the target date for FDA action on the application at six months after the FDA accepts the application for filing. Priority review is granted where there is evidence that the proposed product would be a significant improvement in the safety or effectiveness of the treatment, diagnosis, or prevention of a serious condition. Priority review designation does not change the scientific/medical standard for approval or the quality of evidence necessary to support approval.

The FDA may approve an NDA or BLA under the accelerated approval program if the drug treats a serious condition, provides a meaningful advantage over available therapies, and demonstrates an effect on either (1) a surrogate endpoint that is reasonably likely to predict clinical benefit, or (2) on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments. Post-marketing studies or completion of ongoing studies after marketing approval are generally required to verify the drug's clinical benefit in relationship to the surrogate endpoint or ultimate outcome in relationship to the clinical benefit.

In addition, the Food and Drug Administration Safety and Innovation Act, or FDASIA, established the new Breakthrough Therapy designation. A sponsor may seek FDA designation of its product candidate as a breakthrough therapy if the drug is intended, alone or in combination with one or more other drugs, to treat a serious or life-threatening disease or condition and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. If a drug is designated as breakthrough therapy, FDA will provide more intensive guidance on the drug development program and expedite its review.

Orphan Designation and Exclusivity

The FDA may grant orphan drug designation to drugs intended to treat a rare disease or condition that affects fewer than 200,000 individuals in the United States, or if it affects more than 200,000 individuals in the United States and there is no reasonable expectation that the cost of developing and making the drug for this type of disease or condition will be recovered from sales in the United States.

Orphan drug designation entitles a party to financial incentives such as opportunities for grant funding towards clinical study costs, tax advantages, and user-fee waivers. Orphan drug designation does not convey any advantage in, or shorten the duration of, the regulatory review and approval process. In addition, the first NDA or BLA applicant to receive orphan drug designation for a particular drug is entitled to orphan drug exclusivity, which means the FDA may not approve any other application to market the same drug for the same indication for a period of seven years in the United States, except in limited circumstances. Orphan drug exclusivity does not prevent the FDA from approving a different drug for the same disease or condition, or the same drug for a different disease or condition.

Pediatric Studies and Exclusivity

NDAs and BLAs must contain data to assess the safety and effectiveness of an investigational new drug product for the claimed indications in all relevant pediatric populations in order to support dosing and administration for each

pediatric subpopulation for which the drug is safe and effective. The FDA may, on its own initiative or at the request of the applicant, grant deferrals for submission of some or all pediatric data until after approval of the product for use in adults or full or partial waivers if certain criteria are met. Discussions about pediatric development plans can be discussed with the FDA at any time, but usually occur any time between the end-of-Phase 2 meeting and submission of the NDA or BLA. Unless otherwise required by regulation, the requirements for pediatric data do not apply to any drug for an indication for which orphan designation has been granted.

Pediatric exclusivity is another type of non-patent exclusivity in the United States that may be granted if certain FDA requirements are met, such as FDA's determination that information relating to the use of a new drug in the pediatric population may produce health benefits, and the applicant agrees to perform and report on FDA-requested studies within a certain time frame. Pediatric exclusivity adds a period of six months of exclusivity to the end of all existing marketing exclusivity and patents held by the sponsor for that active moiety. This is not a patent term extension, but it effectively extends the regulatory period during which the FDA cannot accept or approve another application relying on the NDA or BLA sponsor's data.

Biosimilars and Exclusivity

The Patient Protection and Affordable Care Act of 2010, or Affordable Care Act, includes a subtitle called the Biologics Price Competition and Innovation Act of 2009, or BPCI Act, which created an abbreviated approval pathway for biological products shown to be similar to, or interchangeable with, an FDA-licensed reference biological product.

A reference biologic is granted twelve years of exclusivity from the time of first licensure of the reference product. The first biologic product submitted under the abbreviated approval pathway that is determined to be interchangeable with the reference product has exclusivity against other biologics submitting under the abbreviated approval pathway for the lesser of (i) one year after the first commercial marketing, (ii) eighteen months after approval if there is no legal challenge, (iii) eighteen months after the resolution in the applicant's favor of a lawsuit challenging the biologics' patents if an application has been submitted, or (iv) 42 months after the application has been approved if a lawsuit is ongoing within the 42-month period.

Abbreviated New Drug Applications for Generic Drugs and New Chemical Entity Exclusivity

The Drug Price Competition and Patent Term Restoration Act of 1984, or the Hatch-Waxman Amendments, authorized the FDA to approve generic drugs that are bioequivalent (i.e. identical) to previously approved branded drugs. To obtain approval of a generic drug, an applicant must submit an abbreviated new drug application, or ANDA, to the FDA. In support of such applications, a generic manufacturer may rely on the preclinical and clinical testing conducted for a drug product previously approved under an NDA, known as the reference listed drug, or RLD.

Specifically, in order for an ANDA to be approved, the FDA must find that the generic version is bioequivalent to the RLD with respect to the active ingredients, the route of administration, the dosage form, quality and performance characteristics, the strength of the drug, and intended use.

The FDCA provides a period of five years of non-patent exclusivity for a new drug containing a new chemical entity. In cases where such exclusivity has been granted, an ANDA may not be filed with the FDA until the expiration of five years unless the submission is accompanied by a Paragraph IV certification, in which case the applicant may submit its application four years following the original product approval. The FDCA also provides for a period of three years of exclusivity if an NDA or supplement includes reports of one or more new clinical investigations, other than bioavailability or bioequivalence studies, that were conducted by or for the applicant and are essential to the approval of the application. This three-year exclusivity period often protects changes to a previously approved drug product, such as a new dosage form, route of administration, combination or indication.

When an ANDA applicant files its application with the FDA, it must certify, among other things, that the new product will not infringe the already approved product's listed patents or that such patents are invalid or unenforceable, which is called a Paragraph IV certification. If the applicant does not challenge the listed patents or indicates that it is not seeking approval of a patented method of use, the ANDA application will not be approved until all the listed patents claiming the referenced product have expired. If the ANDA applicant has provided a Paragraph IV certification to the FDA, the applicant must also send notice of the Paragraph IV certification to the NDA and patent holders once the ANDA has been accepted for filing by the FDA. The NDA and patent holders may then initiate a patent infringement lawsuit in response to the notice of the Paragraph IV certification. The filing of a patent infringement lawsuit within 45 days after the receipt of a Paragraph IV certification automatically prevents the FDA from approving the ANDA until the earlier of 30 months after the receipt of the Paragraph IV notice, expiration of the patent, or a decision in the infringement case that is favorable to the ANDA applicant.

Patent Term Restoration

Some of our U.S. patents may be eligible for limited patent term extension under the Hatch-Waxman Amendments. The Hatch-Waxman Amendments permit a patent restoration term of up to five years as compensation for patent term lost during product development and the FDA regulatory review process. However, patent term restoration cannot extend the remaining term of a patent beyond a total of 14 years from the product's approval date. The patent term restoration period is generally one-half the time between the effective date of an IND and the submission date of an NDA or BLA, plus the time between the submission date and the approval of that application. Only one patent

applicable to an approved product is eligible for the extension and the application for the extension must be submitted prior to the expiration of the patent. The U.S. Patent and Trademark Office, or USPTO, in consultation with the FDA, reviews and approves the application for any patent term extension or restoration. Thus, for each approved product, we may apply for restoration of patent term for one of our related owned or licensed patents to add patent life beyond the original expiration date, depending on the expected length of the clinical studies and other factors involved in the filing of the relevant NDA or BLA.

EU Regulation

In the EU, to obtain regulatory approval of an investigational medicinal product, we must submit a marketing authorization application, or MAA. The content of the MAA is similar to that of an NDA or BLA filed in the United States, with the exception of, among other things, country-specific document requirements.

Authorization Procedures

Medicines can be authorized by using the centralized authorization procedure or national authorization procedures. The centralized authorization procedure results in a single marketing authorization issued by the European Medicines Agency, or EMA, that is valid across the European Economic Area, or EEA, which is comprised of the 28 member states of the EU plus Norway, Iceland, and Lichtenstein. The centralized procedure is compulsory for human medicines that are derived from biotechnology processes, such as genetic engineering; contain a new active substance indicated for the treatment of certain diseases, such as HIV/AIDS, cancer, diabetes, neurodegenerative disorders or autoimmune diseases and other immune dysfunctions; and officially designated orphan medicines. Medicines that fall outside the mandatory scope of the centralized procedure have three routes to authorization: (i) they can be authorized under the centralized procedure if they concern a significant therapeutic, scientific or technical innovation, or if their authorization would be in the interest of public health; (ii) they can be authorized under a decentralized procedure where an applicant applies for simultaneous authorization in more than one EU country; or (iii) they can be authorized in a EU member state in accordance with that state's national procedures and then be authorized in other EU countries by a procedure whereby the countries concerned agree to recognize the validity of the original, national marketing authorization (mutual recognition procedure).

A Pediatric Investigation Plan, or PIP, and/or a request for waiver or deferral, is required for submission prior to submitting an MAA. A PIP describes, among other things, proposed pediatric studies and their timing relative to clinical studies in adults and an MAA must comply with the PIP to be validated.

MAA Review and Approval Timeframe and Accelerated Assessment

Under the centralized procedure in the EU, the maximum timeframe for the evaluation of an MAA that has been validated is 210 days, excluding time taken by an applicant to respond to questions. A favorable opinion on the application by the Committee for Medicinal Products for Human Use, or CHMP, will typically result in the granting of the marketing authorization within 67 days of receipt of the opinion. Generally, the entire review process takes approximately one year. Accelerated evaluation might be granted by the CHMP in exceptional cases, when a medicinal product is expected to be of a major public health interest, particularly from the point of view of therapeutic innovation. In this circumstance, EMA ensures that the opinion of the CHMP is given within 150 days, excluding time taken by an applicant to respond to questions.

Exceptional Circumstances/Conditional Approval

Orphan drugs or drugs with unmet medical needs may be eligible for EU approval under exceptional circumstances or with conditional approval. Approval under exceptional circumstances is applicable to orphan products and is used when an applicant is unable to provide comprehensive data on the efficacy and safety under normal conditions of use because the indication for which the product is intended is encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence, when the present state of scientific knowledge does not allow comprehensive information to be provided, or when it is medically unethical to collect such information. Conditional marketing authorization is applicable to orphan medicinal products, medicinal products for seriously debilitating or life-threatening diseases, or medicinal products to be used in emergency situations in response to recognized public threats. Conditional marketing authorization can be granted on the basis of less complete data than is normally required in order to meet unmet medical needs and in the interest of public health, provided the risk-benefit balance is positive, it is likely that the applicant will be able to provide the comprehensive clinical data, and unmet medical needs will be fulfilled. Conditional marketing authorization is subject to certain specific obligations to be reviewed annually.

PRIME Program

PRIME is a program launched by the EMA to enhance support for the development of medicines that target an unmet medical need. The program focuses on medicines that may offer a major therapeutic advantage over existing treatments, or benefit patients without treatment options. These medicines are considered priority medicines by EMA. To be accepted for PRIME, a medicine has to show its potential to benefit patients with unmet medical needs based on early clinical data. Through PRIME, the EMA offers early and proactive support to medicine developers to optimize development plans and the generation of robust data on a medicine’s benefits and risks and enables accelerated assessment of medicines applications.

Orphan Designation and Exclusivity

As in the United States, we may apply for designation of a product as an orphan drug for the treatment of a specific indication in the EU before the application for marketing authorization is made. The EMA's Committee for Orphan Medicinal Products, or COMP, grants orphan drug designation to promote the development of products that are intended for the diagnosis, prevention or treatment of life-threatening or chronically debilitating conditions affecting not more than 5 in 10,000 persons in the EU Community and for which no satisfactory method of diagnosis, prevention, or treatment has been authorized (or the product would be a significant benefit to those affected). Additionally, designation is granted for products intended for the diagnosis, prevention, or treatment of a life-threatening, seriously debilitating or serious and chronic condition when, without incentives, it is unlikely that sales of the drug in the EU would be sufficient to justify the necessary investment in developing the medicinal product. Orphan drug designation entitles a party to financial incentives such as reduction of fees or fee waivers and 10 years of market exclusivity is granted following medicinal product approval. This period may be reduced to six years if the orphan drug designation criteria are no longer met, including where it is shown that the product is sufficiently profitable not to justify maintenance of market exclusivity. Orphan drug designation does not convey any advantage in, or shorten the duration of, the regulatory review and approval process.

New Chemical Entity Exclusivity

In the EU, new chemical entities, sometimes referred to as new active substances, qualify for eight years of data exclusivity upon marketing authorization and an additional two years of market exclusivity. This data exclusivity, if granted, prevents regulatory authorities in the EU from referencing the innovator's data to assess a generic (abbreviated) application for eight years, after which generic marketing authorization can be submitted, and the innovator's data may be referenced, but not approved for two years. The overall ten-year period will be extended to a maximum of eleven years if, during the first eight of those ten years, the marketing authorization holder obtains an authorization for one or more new therapeutic indications which, during the scientific evaluation prior to their authorization, are held to bring a significant clinical benefit in comparison with existing therapies.

Post-Approval Requirements

Drugs manufactured or distributed pursuant to regulatory approvals are subject to pervasive and continuing regulation by the regulatory authorities, including, among other things, requirements relating to formal commitments for post approval clinical trials and studies, manufacturing, recordkeeping, periodic reporting, product sampling and distribution, marketing, labeling, advertising and promotion and reporting of adverse experiences with the product. After approval, most changes to the approved product, such as adding new indications or other labeling claims are subject to prior regulatory authority review and approval.

Drug manufacturers are subject to periodic unannounced inspections by regulatory authorities and country or state agencies for compliance with GMP and other requirements. Changes to the manufacturing process are strictly regulated, and, depending on the significance of the change, may require prior regulatory approval before being implemented. Regulations also require investigation and correction of any deviations from GMP and impose reporting and documentation requirements upon us and any third-party manufacturers that we may decide to use. Accordingly, manufacturers must continue to expend time, money and effort in the area of production and quality control to maintain compliance with GMP and other aspects of regulatory compliance.

Pharmaceutical Coverage, Pricing and Reimbursement

In the United States and markets in other countries, sales of any products for which we receive regulatory approval for commercial sale will depend in part on the availability of coverage and reimbursement from third-party payors.

Third-party payors include government authorities, managed care providers, private health insurers and other organizations. The process for determining whether a payor will provide coverage for a drug product may be separate from the process for setting the reimbursement rate that the payor will pay for the drug product. Third-party payors may limit coverage to specific drug products on an approved list, or formulary, which might not include all of the approved drugs for a particular indication. Moreover, a payor's decision to provide coverage for a drug product does not imply that an adequate reimbursement rate will be approved. Adequate third-party reimbursement may not be available to enable us to maintain price levels sufficient to realize an appropriate return on our investment in product development.

In the EU, governments influence the price of pharmaceutical products through their pricing and reimbursement rules and control of national health care systems that fund a large part of the cost of those products to patients. Some jurisdictions operate positive and negative list systems under which products may only be marketed once a reimbursement price has been agreed to by the government. Other member states allow companies to fix their own prices for medicines, but monitor and control company profits. In addition, in some countries, cross-border imports from low-priced markets exert a commercial pressure on pricing within a country.

Other Healthcare Laws and Compliance Requirements

If we obtain regulatory approval for any of our product candidates, we may be subject to various laws targeting, among other things, fraud and abuse in the healthcare industry. These laws may impact, among other things, our proposed sales, marketing, and education programs. The laws that may affect our ability to operate include:

- the federal Anti-Kickback Statute, which prohibits, among other things, persons from knowingly and willfully soliciting, receiving, offering or paying remuneration, directly or indirectly, to induce, or in return for, the purchase or recommendation of an item or service reimbursable under a federal healthcare program, such as the Medicare and Medicaid programs;
- federal civil and criminal false claims laws and civil monetary penalty laws, which prohibit, among other things, individuals or entities from knowingly presenting, or causing to be presented, claims for payment from Medicare, Medicaid, or other third-party payers that are false or fraudulent;
- the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, as amended, which prohibits executing a scheme to defraud any healthcare benefit program and making false statements relating to healthcare matters and imposes certain requirements relating to the privacy, security and transmission of individually identifiable health information;
- the EU General Data Protection Regulation (GDPR), which seeks to harmonize data privacy laws across Europe to ensure data subjects' fundamental right to privacy in the EU in the digital age by imposing requirements and limitations relating to the processing, storage, purpose of collection, accuracy, security and transmission of personal data and the notification of regulation authorities about data breaches, accompanied by a strong sanctioning mechanism;
- the 21st Century Cures Act, or the Cures Act, which introduced a wide range of reforms, such as broadening the types of data required to support drug approval, extending protections for generic competition, accelerating approval of breakthrough therapies, expanding the orphan drug product program, requiring disclosures about compassionate care programs, and clarifying how manufacturers communicate about their products;
- the federal transparency laws, including the federal Physician Payment Sunshine Act, that requires drug manufacturers to disclose payments and other transfers of value provided to physicians and teaching hospitals; and
- state and foreign law equivalents of each of the above federal laws, such as transparency laws, anti-kickback and false claims laws which may apply to items or services reimbursed by any third-party payer, including commercial insurers, and privacy and security of health information laws.

Additional Regulation

The U.S. Foreign Corrupt Practices Act or FCPA, to which we are subject, prohibits corporations and individuals from engaging in certain activities to obtain or retain business or to influence a person working in an official capacity. It is illegal to pay, offer to pay or authorize the payment of anything of value to any foreign government official, government staff member, political party or political candidate in an attempt to obtain or retain business or to otherwise influence a person working in an official capacity. Similar laws exist in other countries, such as the United Kingdom, that restrict improper payments to public and private parties. Many countries have laws prohibiting these types of payments within the respective country. In addition to these anti-corruption laws, we are subject to import and export control laws, tariffs, trade barriers, economic sanctions and regulatory limitations on our ability to operate in certain foreign markets.

In addition, federal, state and foreign government bodies and agencies have adopted, are considering adopting, or may adopt laws and regulations regarding the collection, use, storage and disclosure of personally identifiable information or other information treated as confidential obtained from consumers and individuals.

We are also subject to regulation under the Occupational Safety and Health Act, the Environmental Protection Act, the Toxic Substances Control Act, the Resource Conservation and Recovery Act and other present and potential federal,

state or local regulations. These and other laws govern our use, handling and disposal of various biological and chemical substances used in, and waste generated by, our operations.

Customers

Our customers include collaboration partners, drug wholesalers, and retail pharmacy distributors. For the year ended December 31, 2018, 35% and 46% of our total revenues were generated by KHK and Bayer, respectively.

Employees

As of December 31, 2018, we had 610 full-time employees. None of our employees is represented by labor unions or covered by collective bargaining agreements. We consider our relationship with our employees to be good.

General Information

We were incorporated in California in April 2010 and reincorporated in Delaware in June 2011. Our principal executive offices are located at 60 Leveroni Court, Novato, California 94949. Our telephone number is (415) 483-8800 and our e-mail address is info@ultragenyx.com. Our Internet website address is www.ultragenyx.com. No portion of our website is incorporated by reference into this Annual Report.

You are advised to read this Annual Report in conjunction with other reports and documents that we file from time to time with the Securities and Exchange Commission, or SEC. In particular, please read our definitive proxy statements, our Quarterly Reports on Form 10-Q and any Current Reports on Form 8-K that we may file from time to time. The SEC maintains information for electronic filers (including Ultragenyx) at its website at www.sec.gov. We make our periodic and current reports available on our internet website, free of charge, as soon as reasonably practicable after such material is electronically filed with, or furnished to, the SEC.

Item 1A. Risk Factors

Investing in our common stock involves a high degree of risk. You should carefully consider the following risks, together with all the other information in this Annual Report, including our financial statements and notes thereto, before deciding to invest in our common stock. If any of the following risks actually materialize, our operating results, financial condition, and liquidity could be materially adversely affected. As a result, the trading price of our common stock could decline and you could lose part or all of your investment.

Risks Related to Our Financial Condition and Capital Requirements

We have a history of operating losses and anticipate that we will continue to incur losses for the foreseeable future.

We are a biopharmaceutical company with a history of operating losses, and anticipate continuing to incur operating losses for the foreseeable future. Biopharmaceutical product development is a highly speculative undertaking and involves a substantial degree of risk. We have devoted substantially all of our financial resources to identifying, acquiring, and developing our products and product candidates, including conducting clinical studies, developing manufacturing processes, manufacturing product candidates for clinical studies, and providing selling, general and administrative support for these operations. The amount of our future net losses will depend, in part, on non-recurring events, the success of our commercialization efforts, and the rate of our future expenditures. We anticipate that our expenses will increase substantially if and as we:

- continue our research and nonclinical and clinical development of our product candidates;
- expand the scope of our current clinical studies for our product candidates;
- advance our programs into more expensive clinical studies;
- initiate additional nonclinical, clinical, or other studies for our product candidates;
- pursue preclinical and clinical development for additional indications for existing products and product candidates;
- change or add additional manufacturers or suppliers;
- seek to expand upon or build our own manufacturing-related facilities and capabilities;
- seek regulatory and marketing approvals for our product candidates that successfully complete clinical studies;
- continue to establish Medical Affairs field teams to initiate relevant disease education;
- continue to establish a marketing and distribution infrastructure and field force to commercialize our products and any product candidates for which we may obtain marketing approval;
- continue to manage our international subsidiaries and establish new ones;
- continue to operate as a public company and comply with legal, accounting and other regulatory requirements;
- seek to identify, assess, license, acquire, and/or develop other product candidates, technologies, and/or businesses;
- make milestone or other payments under any license or other agreements;
- seek to maintain, protect, and expand our intellectual property portfolio;
- seek to attract and retain skilled personnel;
- create additional infrastructure, including facilities and systems, to support the growth of our operations, our product development, and our commercialization efforts; and
- experience any delays or encounter issues with any of the above, including, but not limited to, failed studies, complex results, safety issues, inspection outcomes, or other regulatory challenges that require longer follow-up of existing studies, additional major studies, or additional supportive studies in order to pursue marketing approval.

The net losses we incur may fluctuate significantly from quarter to quarter and year to year, such that a period-to-period comparison of our results of operations may not be a good indication of our future performance.

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We are just starting to generate revenue from product sales.

Our ability to generate significant revenue from product sales depends on our ability, alone or with strategic collaboration partners, to successfully commercialize our products and to complete the development of, and obtain the regulatory and marketing approvals necessary to commercialize, one or more of our product candidates. Our ability to generate substantial future revenue from product sales, including named patient sales, depends heavily on our success in many areas, including, but not limited to:

- obtaining regulatory and marketing approvals with broad indications for product candidates for which we complete clinical studies;
- developing a sustainable and scalable manufacturing process for our products and any approved product candidates and establishing and maintaining supply and manufacturing relationships with third parties that can conduct the processes and provide adequate (in amount and quality) product supply to support market demand for our products and product candidates, if approved;
- launching and commercializing our products and product candidates for which we obtain regulatory and marketing approval, either directly or with a collaborator or distributor;
- obtaining market acceptance of our products and product candidates as viable treatment options;
- obtaining adequate market share, reimbursement and pricing for our products and product candidates;
- our ability to sell our products and product candidates on a named patient basis or through an equivalent mechanism and the amount of revenue generated from such sales;
- our ability to find patients so they can be diagnosed and begin receiving treatment;
- addressing any competing technological and market developments;
- negotiating favorable terms, including commercial rights, in any collaboration, licensing, or other arrangements into which we may enter, any amendments thereto or extensions thereof;
- maintaining, protecting, and expanding our portfolio of intellectual property rights, including patents, trade secrets, and know-how; and
- attracting, hiring, and retaining qualified personnel.

If the number of our addressable rare disease patients is not as significant as we estimate, the indication approved by regulatory authorities is narrower than we expect, or the reasonably accepted population for treatment is narrowed by competition, physician choice, or treatment guidelines, we may not generate significant revenue from sales of our products, even if approved.

We expect we will need to raise additional capital to fund our activities. This additional financing may not be available on acceptable terms, if at all. Failure to obtain this necessary capital when needed may force us to delay, limit, or terminate our product development efforts or other activities.

As of December 31, 2018, our available cash, cash equivalents, and investments were $459.7 million. We expect we will need additional capital to continue to commercialize our products, and to develop and obtain regulatory approval for, and to commercialize, all of our product candidates. In addition, our operating plans may change as a result of many factors that may currently be unknown to us, and we may need to seek additional funds sooner than planned. Our future funding requirements will depend on many factors, including but not limited to:

- the scope, rate of progress, results, and cost of our clinical studies, nonclinical testing, and other related activities;
- the cost of manufacturing clinical and commercial supplies of our products and product candidates;
- the cost of creating additional infrastructure, including facilities and systems;
- the number and characteristics of the product candidates that we pursue;
- the cost, timing, and outcomes of regulatory approvals;
- the cost and timing of establishing and operating our international subsidiaries;
- the cost and timing of establishing and operating field forces, marketing, and distribution capabilities;

- the cost and timing of other activities needed to commercialize our products; and
- the terms and timing of any collaborative, licensing, acquisition, and other arrangements that we may establish, including any required milestone, royalty, and reimbursements or other payments thereunder.

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Any additional fundraising efforts may divert our management's attention from their day-to-day activities, which may adversely affect our ability to develop our product candidates and commercialize our products. In addition, we cannot guarantee that future financing will be available in sufficient amounts or on terms acceptable to us, if at all. The terms of any financing may adversely affect the holdings or the rights of our stockholders and the issuance of additional securities, whether equity or debt, by us, or the possibility of such issuance, may cause the market price of our shares to decline. The sale of additional equity or convertible securities would dilute all of our stockholders. If we incur debt, it could result in increased fixed payment obligations and we may be required to agree to certain restrictive covenants, such as limitations on our ability to incur additional debt, limitations on our ability to acquire, sell, or license intellectual property rights, and other operating restrictions that could adversely impact our ability to conduct our business. If we are granted priority review vouchers in connection with regulatory approvals for our product candidates, we may be unable to sell the vouchers or, if we do sell the vouchers, we may have to sell them on unfavorable terms and at prices that are lower than expected. There is no guarantee that we will be granted priority review vouchers in connection with product approvals, and regulatory authorities may cease granting such vouchers in the future. We could also be required to seek funds through collaborative partnerships, strategic alliances, and licensing or other arrangements and we may be required to relinquish rights to some of our technologies or product candidates, future revenue streams, research programs, and other product candidates or otherwise agree to terms unfavorable to us, any of which may have a material adverse effect on our business, operating results, and prospects. Even if we believe we have sufficient funds for our current or future operating plans, we may seek additional capital if market conditions are favorable or if we have specific strategic considerations.

If we are unable to obtain funding on a timely basis or at all, we may be required to significantly curtail, delay, or discontinue one or more of our research or development programs or the commercialization of our products and any approved product candidates or be unable to expand our operations or otherwise capitalize on our business opportunities, as desired, which could materially affect our business, financial condition, and results of operations.

Risks Related to the Discovery and Development of Our Product Candidates

Clinical drug development involves a lengthy and expensive process with uncertain outcomes and the potential for substantial delays, and the results of earlier studies may not be predictive of future study results.

Before obtaining marketing approval from regulatory authorities for the sale of our product candidates, we must conduct extensive clinical studies to demonstrate the safety and efficacy of the product candidates in humans. Clinical testing is expensive, time consuming, and uncertain as to outcome. We cannot guarantee that any clinical studies will be conducted as planned or completed on schedule, if at all. A failure of one or more clinical studies can occur at any stage of testing, and our future clinical studies may not be successful. Product candidates that have shown promising results in early-stage clinical studies may still suffer significant setbacks in subsequent clinical studies. The safety or efficacy results generated to date in clinical studies do not ensure that later clinical studies will demonstrate similar results. For example, our Phase 3 studies that evaluated Ace-ER in patients with GNE myopathy and UX007 in patients with Glut1 DS experiencing disabling paroxysmal movement disorders did not achieve their primary or secondary endpoints. Results from investigator-sponsored studies or compassionate-use studies may not be confirmed in company-sponsored studies or may negatively impact the prospects for our programs. Additionally, given the nature of the rare diseases we are seeking to treat, we often have to devise newly-defined endpoints to be tested in our studies, which can lead to some subjectivity in interpreting study results and could result in regulatory agencies not agreeing with the validity of our endpoints, or our interpretation of the clinical data, and therefore denying approval. Given the illness of the patients in our studies and the nature of their rare diseases, we may also be required or choose to conduct certain studies on an open-label basis. We have in the past, and may in the future elect to review interim clinical data at multiple time points during the studies, which could introduce bias into the study results and potentially result in denial of approval.

In the biopharmaceutical industry, there is a high failure rate for drugs and biologics proceeding through clinical studies, and product candidates in later stages of clinical studies may fail to show the desired safety and efficacy despite having progressed through nonclinical studies and initial clinical studies. A number of companies in the biopharmaceutical industry have suffered significant setbacks in advanced clinical studies due to lack of efficacy or adverse safety profiles, notwithstanding promising results in earlier studies.

Scenarios that may prevent successful or timely completion of clinical development include but are not limited to:

- delays or failures in generating sufficient preclinical, toxicology, or other in vivo or in vitro data to support the initiation or continuation of human clinical studies or filings for regulatory approval;
- failure to demonstrate a starting dose for our product candidates in the clinic that might be reasonably expected to result in a clinical benefit;
- delays or failures in developing gene therapy, mRNA or other novel and complex product candidates, which are expensive and difficult to develop and manufacture;
- delays resulting from a shutdown, or uncertainty surrounding the potential for future shutdowns of the U.S. government, including the FDA;
- delays or failures in reaching a consensus with regulatory agencies on study design;

- delays in reaching agreement on acceptable terms with contract research organizations, or CROs, clinical study sites, and other clinical trial-related vendors;
- failure or delays in obtaining required regulatory agency approval and/or IRB or EC approval at each clinical study site or in certain countries;
- failure to correctly design clinical studies which may result in those studies failing to meet their endpoints or the expectations of regulatory agencies;
- changes in clinical study design or development strategy resulting in delays related to obtaining approvals from IRBs or ECs and/or regulatory agencies to proceed with clinical studies;
- imposition of a clinical hold by regulatory agencies after review of an IND application or amendment, another equivalent application or amendment, or an inspection of our clinical study operations or study sites;
- delays in recruiting suitable patients to participate in our clinical studies;
- difficulty collaborating with patient groups and investigators;
- failure by our CROs, other third parties, or us to adhere to clinical study requirements;
- failure to perform in accordance with the FDA's and/or ICH's good clinical practices requirements or applicable regulatory guidelines in other countries;
- delays in patients' completion of studies or their returns for post-treatment follow-up;
- patients dropping out of a study;
- adverse events associated with the product candidate occurring that are viewed to outweigh its potential benefits;
- changes in regulatory requirements and guidance that require amending or submitting new clinical protocols;
- greater than anticipated costs associated with clinical studies of our drug candidates;
- clinical studies of our drug candidates producing negative or inconclusive results, which may result in us deciding, or regulators requiring us, to conduct additional clinical or nonclinical studies or to abandon drug development programs;
- competing clinical studies of potential alternative product candidates or investigator-sponsored studies of our product candidates; and
- delays in manufacturing, testing, releasing, validating, or importing/exporting sufficient stable quantities of our product candidates for use in clinical studies or the inability to do any of the foregoing.

Any inability to successfully complete nonclinical and clinical development could result in additional costs to us or negatively impact our ability to generate revenue. In addition, if we make manufacturing or formulation changes to our product candidates, we may need to conduct additional toxicology, comparability or other studies to bridge our modified product candidates to earlier versions. Clinical study delays could also shorten any periods during which our products have commercial exclusivity and may allow our competitors to bring products to market before we do, which could negatively impact our ability to obtain orphan exclusivity and to successfully commercialize our product candidates and may harm our business and results of operations.

If we do not achieve our projected development goals in the timeframes we announce and expect, the commercialization of our products may be delayed and the credibility of our management may be adversely affected and, as a result, our stock price may decline.

For planning purposes, we estimate the timing of the accomplishment of various scientific, clinical, regulatory, and other product development goals, which we sometimes refer to as milestones. These milestones may include the commencement or completion of scientific studies and clinical trials, the timing of patient dosing, the submission or acceptance of regulatory filings, and the potential approval of such regulatory filings. We periodically make public announcements about the expected timing of some of these milestones. All of these milestones are based on a variety of assumptions, but the actual timing of these milestones can vary dramatically from our estimates. If we do not meet these publicly announced milestones, the commercialization of our products may be delayed and the credibility of our management may be adversely affected and, as a result, our stock price may decline.

We may find it difficult to identify and enroll patients in our clinical studies given the limited number of patients who have the diseases for which our product candidates are being studied. Difficulty in enrolling patients could delay or prevent clinical studies of our product candidates.

Identifying and qualifying patients to participate in clinical studies of our product candidates is critical to our success. The timing of our clinical studies depends in part on the speed at which we can recruit patients to participate in testing our product candidates, and we may experience delays in our clinical studies if we encounter difficulties in enrollment.

Each of the conditions for which we plan to evaluate our current product candidates is a rare genetic disease. Accordingly, there are limited patient pools from which to draw for clinical studies. For our current product candidates:

- we estimate that several hundred patients in the United States suffer from TIO, for which Crysvita is being studied;
- we estimate that several thousand patients in the United States suffer from LC-FAOD, for which UX007 is being studied;
- we estimate that approximately 8,000 patients in the developed world suffer from late-onset OTC deficiency, for which DTX301 is being studied, and these all may not be treatable if they are immune to the virus; and
- we estimate that approximately 6,000 patients worldwide suffer from GSD1a, for which DTX401 is being studied, and these all may not be treatable if they are immune to the virus.

In addition to the rarity of these diseases, the eligibility criteria of our clinical studies will further limit the pool of available study participants as we will require patients to have specific characteristics that we can measure or to assure their disease is either severe enough or not too advanced to include them in a study. The process of finding and diagnosing patients may prove costly, especially since the rare diseases we are studying are commonly under diagnosed. We also may not be able to identify, recruit, and enroll a sufficient number of appropriate patients to complete our clinical studies because of demographic criteria for prospective patients, the perceived risks and benefits of the product candidate under study, the proximity and availability of clinical study sites for prospective patients, and the patient referral practices of physicians. The availability and efficacy of competing therapies and clinical studies can also adversely impact enrollment. If patients are unwilling to participate in our studies for any reason, the timeline for recruiting patients, conducting studies, and obtaining regulatory approval of potential products may be delayed, the commercial prospects of our product candidates will be harmed, and our ability to generate product revenue from any of these product candidates could be delayed or prevented. Furthermore, many of the factors that cause, or lead to, a delay in the commencement or completion of clinical studies may also ultimately lead to the denial of regulatory approval of our product candidates. Delays in completing our clinical studies will increase our costs, slow down our product candidate development and approval process, and jeopardize our ability to commence product sales and generate revenue. Any of these occurrences may harm our business, financial condition, and prospects significantly.

The regulatory approval processes of the FDA and comparable foreign authorities are lengthy, time consuming, and inherently unpredictable. Even if we achieve positive results in our pre-clinical and clinical studies, if we are ultimately unable to obtain timely regulatory approval for our product candidates, our business will be substantially harmed.

Our future success is dependent on our ability to successfully commercialize our products and develop, obtain regulatory approval for, and then successfully commercialize one or more product candidates. We are not permitted to market or promote any of our product candidates before we receive regulatory approval from the FDA or comparable foreign regulatory authorities. We have only obtained regulatory approval for two products, and it is possible that none of our existing product candidates or any product candidates we may seek to develop in the future will ever obtain regulatory approval.

To obtain regulatory approval in the United States and other jurisdictions, we must comply with numerous and varying requirements regarding safety, efficacy, chemistry, manufacturing and controls, clinical studies (including good clinical practices), commercial sales, pricing, and distribution of our product candidates. Even if we are successful in obtaining approval in one jurisdiction, we cannot ensure that we will obtain approval in any other jurisdictions. In addition, approval policies, regulations, positions of the regulatory agencies on study design and/or endpoints, or the type and amount of clinical data necessary to gain approval may change during the course of a product candidate’s clinical development, which may cause delays in the approval or the decision not to approve an application. Communications with the regulatory agencies during the approval process are also unpredictable; favorable communications early in the process do not ensure that approval will be obtained and unfavorable

communications early on do not guarantee that approval will be denied. If we are unable to obtain approval for our product candidates in multiple jurisdictions, our revenue and results of operations could be negatively affected. Applications for our product candidates could fail to receive regulatory approval, or could be delayed in receiving regulatory approval, for many reasons, including but not limited to the following:

- regulatory authorities may disagree with the design, implementation, or conduct of our clinical studies;
- regulatory authorities may change their guidance or requirements for a development program for a product candidate;
- the population studied in the clinical program may not be sufficiently broad or representative to assure efficacy and safety in the full population for which we seek approval;
- regulatory authorities may disagree with our interpretation of data from nonclinical studies or clinical studies;
- the data collected from clinical studies of our product candidates may not be sufficient to support the submission of an NDA, or biologics license application, or BLA, or other submission or to obtain regulatory approval;
- we may be unable to demonstrate to regulatory authorities that a product candidate’s risk-benefit ratio for its proposed indication is acceptable;

- regulatory authorities may fail to approve the manufacturing processes, test procedures and specifications, or facilities used to manufacture our clinical and commercial supplies;
- the U.S. government may be shut down, which could delay the FDA;
- failure of our nonclinical or clinical development to comply with an agreed upon Pediatric Investigational Plan (PIP), which details the designs and completion timelines for nonclinical and clinical studies and is a condition of marketing authorization in the EU; and
- the approval policies or regulations of regulatory authorities may significantly change in a manner rendering our clinical data insufficient for approval.

Furthermore, the disease states we are evaluating often will not have clear regulatory paths for approval and/or do not have validated outcome measures. In these circumstances, we work closely with the regulatory authorities to define the approval path and may have to qualify outcome measures as part of our development programs. Additionally, many of the disease states we are targeting are highly heterogeneous in nature, which may impact our ability to determine the treatment benefit of our potential therapies. For example, patients with LC-FAOD have a highly heterogeneous disease course, which may impact our ability to determine the true treatment benefit of our product candidates in these patients.

This lengthy and uncertain approval process, as well as the unpredictability of the clinical and nonclinical studies, may result in our failure to obtain regulatory approval to market any of our product candidates, or delayed regulatory approval, which would significantly harm our business, results of operations, and prospects.

The regulatory approval process for novel product candidates, such as our gene therapy product candidates, can be more expensive and take longer than for other product candidates, and may change in the future.

The clinical trial requirements of regulatory authorities and the criteria these regulators use to determine the safety and efficacy of a product candidate vary substantially according to the type, complexity, novelty and intended use and market of the product candidate. As a result, the regulatory approval process for novel product candidates such as our gene therapy product candidates can be more expensive and take longer than for other, better known or more extensively studied product candidates, which can lead to fewer product approvals. To date, very few gene therapy products have received regulatory approval in the United States or Europe.

Additionally, the FDA, Health Canada, and the EMA have each expressed interest in further regulating biotechnology, including gene therapy and genetic testing. For example, the EMA, which governs the development of gene therapies in the EU and may issue new guidelines concerning the development and marketing authorization for gene therapy products, advocates a risk-based approach to the development of a gene therapy product. Agencies at both the federal and state level in the United States, as well as U.S. congressional committees and foreign governments, have also expressed interest in further regulating the biotechnology industry. Different regulatory approaches by jurisdiction can result in different or additional preclinical studies or clinical trials being required to support regulatory approval in each jurisdiction.

Regulatory requirements such as review committees and advisory groups, the new guidelines they promulgate, and new guidance issued by regulatory authorities may lengthen the regulatory review process, require us to perform additional studies or trials, increase our development costs, lead to changes in regulatory positions and interpretations, delay or prevent approval and commercialization of our product candidates or lead to significant post- approval limitations or restrictions. As we advance our product candidates, we will be required to consult with these regulatory and advisory groups and comply with applicable guidelines. If we fail to do so, we may be required to delay or discontinue development of such product candidates. These additional processes may result in a review and approval process that is longer than we otherwise would have expected. Delays as a result of an increased or lengthier regulatory approval process or further restrictions on the development of our product candidates can be costly and could negatively impact our or our collaborators' ability to complete clinical trials and commercialize our current and

future product candidates in a timely manner, if at all.

Our product candidates may cause undesirable side effects or have other properties that could delay or prevent their regulatory approval, limit the commercial profile of an approved label, or result in significant negative consequences following marketing approval, if any.

Undesirable side effects caused by our product candidates could cause us or regulatory authorities to interrupt, delay, or halt clinical studies or further development, and could result in a more restrictive label, the delay or denial of regulatory approval by the FDA or other comparable foreign authorities, or a Risk Evaluation and Mitigation Strategy, or REMS, plan, which could include a medication guide outlining the risks of such side effects for distribution to patients, restricted distribution, a communication plan for healthcare providers, and/or other elements to assure safe use. Some of our product candidates are in the early stages of development and the safety profile has not been established. For example, in a completed Phase 2 study, LC-FAOD patients treated with UX007 experienced treatment-related adverse events, the most common of which were diarrhea, abdominal/gastrointestinal pain and vomiting. There was one treatment-related serious adverse event of moderate gastroenteritis with vomiting. There were two deaths during the LC-FAOD extension study, both deemed to be related to disease progression and not due to treatment with UX007. Gene therapy product candidates using AAV vectors, like DTX301, have been associated with immunologic reaction to the capsid protein or gene at early time points after administration. For example, in our recently discontinued Phase 1/2 clinical trial of DTX101 in hemophilia B, we observed elevated laboratory alanine transaminase levels, or ALTs. In previous clinical trials involving AAV viral vectors for gene therapy, some subjects experienced adverse events, including the development of a T-cell mediated immune response against the vector capsid proteins. In addition, theoretical side effects of AAV vectors include replication and spread of the virus to other parts of the body and insertional oncogenesis, which is the process whereby the insertion of a gene near a gene that is important in cell growth or division results in uncontrolled cell division, which could potentially enhance the risk of malignant transformation or cancer. Potential procedure-related events are similar to those associated with standard coronary diagnostic procedures, and may include vascular injury (e.g., damage to the femoral, radial or brachial arteries at the site of vascular access, or damage to the coronary arteries) or myocardial injury. Future product candidates may also cause these or similar side effects as development proceeds. Results of our studies or investigator-sponsored trials could reveal a high and unacceptable severity and prevalence of these or other side effects. In such an event, our studies could be suspended or terminated, and the FDA or comparable foreign regulatory authorities could order us to cease further development of or deny or withdraw approval of our product candidates for any or all targeted indications.

Drug-related side effects could affect patient recruitment and the ability of enrolled patients to complete a study. Such side effects could also result in potential product liability claims. We currently carry product liability insurance in the amount of $10.0 million per incident and $10.0 million in the aggregate, and we are required to maintain product liability insurance pursuant to certain of our agreements. We believe our product liability insurance coverage is sufficient in light of our current clinical programs; however, we may not be able to maintain insurance coverage at a reasonable cost or in sufficient amounts to protect us against losses due to liability, or losses may exceed the amount of insurance that we carry. A product liability claim or series of claims brought against us could cause our stock price to decline and, if judgments exceed our insurance coverage, could adversely affect our results of operations and business. In addition, regardless of merit or eventual outcome, product liability claims may result in impairment of our business reputation, withdrawal of clinical study participants, costs due to related litigation, distraction of management’s attention from our primary business, initiation of investigations by regulators, substantial monetary awards to patients or other claimants, the inability to commercialize our product candidates, and decreased demand for our product candidates, if approved for commercial sale.

Additionally, even though we received regulatory approval for Crysvita and Mepsevii and even if our product candidates receive marketing approval in the future, if we or others later identify undesirable side effects caused by such products, a number of potentially significant negative consequences could result, including but not limited to:

- regulatory authorities may withdraw approvals of such product;
- regulatory authorities may require additional warnings on the product's label or restrict the product's approved use;
- we may be required to create a REMS plan;
- patients and physicians may elect not to use our products, or reimbursement authorities may elect not to reimburse for them; and
- our reputation may suffer.

Any of these events could prevent us from achieving or maintaining market acceptance of the particular product candidate, if approved, and could significantly harm our business, results of operations, and prospects.

Serious adverse events in clinical trials involving gene therapy product candidates may damage public perception of the safety of our product candidates, increase government regulation, and adversely affect our ability to obtain regulatory approvals for our product candidates or conduct our business.

Gene therapy remains a novel technology. Public perception may be influenced by claims that gene therapy is unsafe, and gene therapy may not gain the acceptance of the public or the medical community. For example, earlier gene therapy trials using other vectors led to several well- publicized adverse events, including cases of leukemia and death. The risk of cancer remains a concern for

gene therapy and we cannot assure you that it will not occur in any of our planned or future clinical studies. In addition, there is the potential risk of delayed adverse events following exposure to gene therapy products due to persistent biological activity of the genetic material or other components of products used to carry the genetic material. Serious adverse events in our clinical trials, or other clinical trials involving gene therapy products, particularly AAV gene therapy products such as candidates based on the same capsid serotypes as our product candidates, or occurring during use of our competitors' products, even if not ultimately attributable to the relevant product candidates, and the resulting publicity, could result in increased government regulation, unfavorable public perception, potential regulatory delays in the testing or approval of our gene therapy product candidates, stricter labeling requirements for those gene therapy product candidates that are approved and a decrease in demand for any such gene therapy product candidates, all of which would have an adverse effect on our business, financial condition, results of operations and prospects.

Even if we obtain regulatory approval for our product candidates, our products will remain subject to regulatory scrutiny.

Our products and any product candidates that are approved will be subject to ongoing regulatory requirements for manufacturing, labeling, packaging, storage, distribution, advertising, promotion, sampling, record-keeping, conduct of post-marketing studies, and submission of safety, efficacy, and other post-market information, including both federal and state requirements in the United States and requirements of comparable foreign regulatory authorities.

Manufacturers and manufacturers' facilities are required to comply with extensive FDA, and comparable foreign regulatory authority, requirements, including ensuring that quality control and manufacturing procedures conform to Good Manufacturing Practices (GMP) regulations. As such, we and our contract manufacturers will be subject to continual review and inspection to assess compliance with GMP and adherence to commitments made in any NDA, BLA, MAA, or other comparable application for approval in another jurisdiction. Accordingly, we and others with whom we work must continue to expend time, money, and effort in all areas of regulatory compliance, including manufacturing, production, and quality control.

Any regulatory approvals that we receive for our product candidates may be subject to limitations on the approved indicated uses for which the product may be marketed or other conditions of approval, or contain requirements for potentially costly post-marketing testing, including Phase 4 clinical studies, and surveillance to monitor the safety and efficacy of the product candidate. We could also be asked to conduct post-marketing clinical studies to verify the safety and efficacy of our products in general or in specific patient subsets. If original marketing approval was obtained via the accelerated approval or conditional marketing authorization pathways, we would be required to conduct a successful post-marketing clinical study to confirm clinical benefit for our products. An unsuccessful post-marketing study or failure to complete such a study could result in the withdrawal of marketing approval. We will be required to report certain adverse events and manufacturing problems, if any, to the FDA and comparable foreign regulatory authorities. Any new legislation addressing drug safety issues could result in delays in product development or commercialization, or increased costs to assure compliance. We will have to comply with requirements concerning advertising and promotion for our products. Promotional communications with respect to prescription drugs are subject to a variety of legal and regulatory restrictions and must be consistent with the information in the product's approved label. As such, we may promote our products only for indications or uses for which they have approval. The holder of an approved NDA, BLA, MAA, or other comparable application must submit new or supplemental applications and obtain approval for certain changes to the approved product, product labeling, or manufacturing process.

If we fail to comply with applicable regulatory requirements, or there are safety or efficacy problems with a product, a regulatory agency or enforcement authority may, among other things:

- issue warning or notice of violation letters;
- impose civil or criminal penalties;
- suspend or withdraw regulatory approval;
- suspend any of our ongoing clinical studies;
- refuse to approve pending applications or supplements to approved applications submitted by us;
- impose restrictions on our operations, including closing our contract manufacturers' facilities;
- seize or detain products, or require a product recall; or
- require entry into a consent decree.

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

If we are unable to identify, source, and develop effective predictive biomarkers, or our collaborators are unable to successfully develop and commercialize companion diagnostics for our product candidates, or experience significant delays in doing so, we may not realize the full commercial potential of our product candidates.

We currently anticipate that we will need to develop diagnostic tests to identify the right patients for certain of our product candidates and to monitor response to treatment. In certain cases, diagnostic tests may need to be developed as companion diagnostics and regulatory approval obtained in order to commercialize some product candidates. We expect to use predictive biomarkers to identify the right patients for certain of our product candidates. For example, to evaluate therapeutic response of DTX301, we plan to measure ammonia levels and other biomarkers, including ^{13}C-acetate, which are established measures of OTC deficiency disease status and ureagenesis. We cannot assure you that ^{13}C-acetate or any other future potential biomarker will in fact prove predictive, be reliably sourced, or be accepted by the FDA or other regulatory authorities. In addition, our success may depend, in part, on the development and commercialization of companion diagnostics. We also expect the FDA will require the development and regulatory approval of a companion diagnostic assay as a condition to approval of DTX301. There has been limited success to date industrywide in developing and commercializing these types of companion diagnostics. Development and manufacturing of companion diagnostics is complex and there are limited manufacturers with the necessary expertise and capability. Even if we are able to find a qualified collaborator, it may not be able to manufacture the companion diagnostics at a cost or in quantities or on timelines necessary for use with our product candidates. To be successful, we need to address a number of scientific, technical and logistical challenges. We have not yet initiated development and commercialization of companion diagnostics. We have little experience in the development and commercialization of diagnostics and may not be successful in developing and commercializing appropriate diagnostics to pair with any of our product candidates that receive marketing approval. University of Pennsylvania School of Medicine currently conducts some of our clinical assays pursuant to a sponsored research agreement, one of which is required for our ongoing Phase 1/2 clinical trial. We intend to enter into agreements with third parties for the automation, characterization and validation, of our companion diagnostic and the manufacture of its critical reagents. However, we may be unable to enter into any such agreement on favorable terms, or at all.

Companion diagnostics are subject to regulation by FDA and similar regulatory authorities outside the United States as medical devices and require regulatory clearance or approval prior to commercialization. In the United States, companion diagnostics are cleared or approved through FDA’s 510(k) premarket notification or premarket approval, or PMA, process. Changes in marketing approval policies during the development period, changes in or the enactment of additional statutes or regulations, or changes in regulatory review for each submitted 510(k) premarket notification, PMA or equivalent application types in jurisdictions outside the United States, may cause delays in the approval, clearance or rejection of an application. Given our limited experience in developing and commercializing diagnostics, we expect to rely in part or in whole on third parties for companion diagnostic design and commercialization. We and our collaborators may encounter difficulties in developing and obtaining approval or clearance for the companion diagnostics, including issues relating to selectivity/specificity, analytical validation, reproducibility, or clinical validation. Any delay or failure by us or our collaborators to develop or obtain regulatory approval of the companion diagnostics could delay or prevent approval of our product candidates.

Risks Related to our Reliance on Third Parties

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

We have relied upon and plan to continue to rely upon third parties, including CROs, collaborative partners, and independent investigators to analyze, collect, monitor, and manage data for our ongoing nonclinical and clinical programs. We rely on third parties for execution of our nonclinical and clinical studies, and for estimates regarding costs and efforts completed, and we control only certain aspects of their activities. For example, we will rely on our partner Arcturus for the design and optimization of initial product candidates under our messenger RNA collaboration. Nevertheless, we are responsible for ensuring that each of our studies is conducted in accordance with the applicable protocol, legal, regulatory, and scientific standards, and our reliance on the CROs and other third parties does not relieve us of our regulatory responsibilities. We and our CROs and other vendors and partners are required to comply with GMP, GCP, and GLP, which are regulations and guidelines enforced by the FDA, the Competent Authorities of the Member States of the European Economic Area, and comparable foreign regulatory authorities for all of our product candidates in development. Regulatory authorities enforce these regulations through periodic inspections of study sponsors, principal investigators, study sites, and other contractors. If we or any of our CROs or other vendors and partners, including the sites at which clinical studies are conducted, fail to comply with applicable regulations, the data generated in our nonclinical and clinical studies may be deemed unreliable and the FDA, EMA, or comparable foreign regulatory authorities may deny approval and/or require us to perform additional nonclinical and clinical studies before approving our marketing applications, which would delay the approval process. We cannot make assurances that upon inspection by a given regulatory authority, such regulatory authority will determine that any of our clinical studies comply with GCP regulations or that nonclinical studies comply with GLP regulations. In addition, our clinical studies must be conducted with products produced under GMP regulations. If the regulatory authorities determine that we have failed to comply with GLP, GMP, or GCP regulations, they may deny approval of our product candidates and/or we may be required to repeat clinical or nonclinical studies, which would delay the regulatory approval process.

Our CROs and other vendors and partners are not our employees, and except for remedies available to us under our agreements with such third parties, we cannot control whether or not they devote sufficient time and resources to our on-going nonclinical and clinical programs. If our vendors and partners do not successfully carry out their contractual duties or obligations or meet expected deadlines, if they need to be replaced, or if the quality or accuracy of the data they obtain is compromised due to the failure to adhere to our protocols, regulatory requirements, or for other reasons, our clinical studies may be extended, delayed, or terminated, and we may not be able to obtain regulatory approval for or successfully commercialize our product candidates. CROs and other vendors and partners may also generate higher costs than anticipated as a result of changes in scope of work or otherwise. As a result, our results of operations and the commercial prospects for our product candidates would be harmed, our costs could increase, and our ability to generate revenue could be delayed.

If any of our relationships with these third parties terminate, we may not be able to enter into arrangements with alternative vendors or do so on commercially reasonable terms. Switching or adding additional vendors involves additional cost and requires management time and focus. In addition, there is a natural transition period when a new vendor commences work. As a result, delays may occur, which can materially impact our ability to meet our desired clinical development timelines. Though we carefully manage our relationships with our vendors and partners, there can be no assurance that we will not encounter similar challenges or delays in the future or that these delays or challenges will not have a material adverse impact on our business, financial condition, and business prospects.

We also rely on third parties in other ways, including efforts to support patient diagnosis and identify patients, to assist our finance and legal departments, and to provide other resources for our business. Use of these third parties could expose us to sub-optimal quality, missed deadlines, and non-compliance with applicable laws, all of which could result in reputational harm to us and negatively affect our business.

We are dependent on KHK for the clinical and commercial supply of Crysvita for all major markets and for the development and commercialization of Crysvita in certain major markets, and KHK's failure to provide an adequate supply of Crysvita or to commercialize Crysvita in those markets could result in a material adverse effect on our business and operating results.

Under our agreement with KHK, KHK has the sole right to commercialize Crysvita in Europe and, at a specified time, in the United States, Canada, and Turkey, subject to a limited promotion right we retained. Our development partnership with KHK may not be successful, and we may not realize the expected benefits from such partnership, due to a number of important factors, including but not limited to the following:

- KHK has no obligation under our agreement to use diligent efforts to commercialize Crysvita in Europe. The timing and amount of any royalty payments we may receive under our agreement will depend on, among other things, the efforts, allocation of resources, and successful commercialization of Crysvita by KHK in Europe.

- the timing and amount of any royalty payments we may receive under our agreement with KHK will depend on, among other things, the efforts, allocation of resources, and successful commercialization of Crysvita by KHK in the United States and Canada under our agreement;
- KHK may change the focus of its commercialization efforts or pursue higher-priority programs;
    - KHK may make decisions regarding the indications for our product candidates in countries where it has the sole right to commercialize the product candidates that limit commercialization efforts in those countries or in countries where we have the right to commercialize our product candidates;
- KHK may make decisions regarding market access and pricing in countries where it has the sole right to commercialize our product candidates which can negatively impact our commercialization efforts in countries where we have the right to commercialize our product candidates;
- KHK may fail to manufacture or supply sufficient drug product of Crysvita in compliance with applicable laws and regulations or otherwise for our development and clinical use, which could result in program delays;
- KHK may fail to manufacture or supply sufficient drug product of Crysvita in compliance with applicable laws and regulations or otherwise for our commercial use, which could result in lost revenue;
- KHK may elect to develop and commercialize Crysvita indications with a larger market than XLH and at a lower price, thereby reducing the profit margin on sales of Crysvita for any orphan indications, including XLH;
    - if KHK were to breach or terminate the agreement with us, we would no longer have any rights to develop or commercialize Crysvita or such rights would be limited to non-terminated countries;
- KHK may terminate its agreement with us, adversely affecting our potential revenue from licensed products; and
- the timing and amounts of expense reimbursement that we may receive are uncertain, and the total expenses for which we are obligated to reimburse KHK may be greater than anticipated.

We rely on third parties to manufacture our products and most of our product candidates. Our business could be harmed if those third parties fail to provide us with sufficient quantities of drug product, or fail to do so at acceptable quality levels or cost.

We have limited infrastructure or capability internally to manufacture our products and product candidates, and we lack the resources and the capability to manufacture most of our product candidates on a clinical or commercial scale. We rely on our manufacturers to purchase from third-party suppliers the materials necessary to produce our product candidates for our clinical studies. There are a limited number of suppliers for raw materials that we use to manufacture our drugs, placebos, or active controls, and there may be a need to identify alternate suppliers to prevent a possible disruption of the manufacture of the materials necessary to produce our products and our product candidates for our clinical studies, and, if approved, ultimately for commercial sale. We do not have any control over the process or timing of the acquisition of these raw materials by our manufacturers. Although we generally do not begin a clinical study unless we believe we have a sufficient supply of a product candidate to complete such study, any significant delay or discontinuity in the supply of a product candidate, or the raw material components thereof, for an ongoing clinical study due to, among other things, the failure of a manufacturer to provide a drug substance or drug product of sufficient quantity or quality, or the need to replace a third-party manufacturer could considerably delay completion of our clinical studies, product testing, and potential regulatory approval of our product candidates, and could also impair named patient sale supply of our product candidates, which could harm our business and results of operations.

We have no experience as a company developing a manufacturing facility and may not be able to do so successfully if we determine to expand or develop our manufacturing capability and infrastructure.

We expect our future manufacturing strategy to involve the use of one or more CMOs as well as our own capabilities and infrastructure, including at our Woburn, MA facility or new facilities we may develop. We expect that development of our own process development facility will provide us with enhanced control of material supply for both clinical trials and the commercial market, enable the more rapid implementation of process changes, and allow for better long-term margins. However, we have no experience as a company in developing a manufacturing facility

and may never be successful in developing our own manufacturing facility or capability. Additionally, given that cGMP gene therapy manufacturing is a nascent industry, there are a small number of CMOs with the experience necessary to manufacture our gene therapy product candidates and we may have difficulty finding or maintaining relationships with such CMOs or hiring experts for internal manufacturing and accordingly, our production capacity may be limited. We may establish multiple manufacturing facilities as we expand our commercial footprint to multiple geographies, which may lead to regulatory delays or prove costly. Even if we are successful, our manufacturing capabilities could be affected by cost-overruns, unexpected delays, equipment failures, lack of capacity, labor shortages, natural disasters, power failures and numerous other factors that could prevent us from realizing the intended benefits of our manufacturing strategy and have a material adverse effect on our business.

Gene therapy and mRNA product candidates are novel, complex, expensive and difficult to manufacture. We could experience manufacturing problems that result in delays in developing and commercializing these programs or otherwise harm our business.

The manufacturing process used to produce our gene therapy and mRNA product candidates is novel, complex, and has not been validated for commercial use. Several factors could cause production interruptions, including equipment malfunctions, regulatory inspections, facility contamination, raw material shortages or contamination, natural disasters, disruption in utility services, human error or disruptions in the operations of our suppliers.

Our gene therapy and mRNA product candidates require processing steps that are more complex than those required for most small molecule drugs. Moreover, unlike small molecules, the physical and chemical properties of a biologic such as gene therapy and mRNA product candidates generally cannot be fully characterized. As a result, assays of the finished product candidate may not be sufficient to ensure that the product candidate is consistent from lot to lot or will perform in the intended manner. Accordingly, we employ multiple steps to control the manufacturing process to assure that the process works reproducibly and the product candidate is made strictly and consistently in compliance with the process. Problems with the manufacturing process, even minor deviations from the normal process, could result in product defects or manufacturing failures that result in lot failures, noncompliance with regulatory requirements, product recalls, product liability claims or insufficient inventory. We may encounter problems achieving adequate quantities and quality of clinical-grade materials that meet FDA, the EMA or other applicable standards or specifications with consistent and acceptable production yields and costs.

In addition, FDA, the EMA and other foreign regulatory authorities may require us to submit samples of any lot of any approved product together with the protocols showing the results of applicable tests at any time. Under some circumstances, FDA, the EMA or other foreign regulatory authorities may require that we not distribute a lot until the agency authorizes its release. Slight deviations in the manufacturing process, including those affecting quality attributes and stability, may result in unacceptable changes in the product that could result in lot failures or product recalls. Lot failures or product recalls could cause us to delay product launches or clinical trials, which could be costly to us and otherwise harm our business, financial condition, results of operations and prospects.

We also may encounter problems hiring and retaining the experienced scientific, quality-control and manufacturing personnel needed to operate our gene therapy and mRNA manufacturing processes, which could result in delays in production or difficulties in maintaining compliance with applicable regulatory requirements. We may be unable to scale up existing or new facilities, including our facility in Woburn, MA, and such facilities may not enable the expansion of our internal manufacturing process discovery and development to the extent we anticipate, or at all.

We are subject to a multitude of manufacturing risks, any of which could substantially increase our costs and limit the supply of our product candidates.

The process of manufacturing our products and product candidates is complex, highly regulated, and subject to several risks, including but not limited to those listed below.

- The process of manufacturing our products and product candidates is extremely susceptible to product loss due to contamination, equipment failure or improper installation or operation of equipment, or vendor or operator error. Even minor deviations from normal manufacturing processes for our products and any of our product candidates could result in reduced production yields, product defects, and other supply disruptions. If microbial, viral, or other contaminations are discovered in our products and product candidates or in the manufacturing facilities in which our products and product candidates are made, such manufacturing facilities may need to be closed for an extended period of time to investigate and remedy the contamination.
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The manufacturing facilities in which our products and product candidates are made could be adversely affected by equipment failures, labor shortages, raw material shortages, natural disasters, power failures, and numerous other factors.

Any adverse developments affecting manufacturing operations for our products and product candidates may result in shipment delays, inventory shortages, lot failures, withdrawals or recalls, or other interruptions in the supply of our products and product candidates. Due to their stage of development, small volume requirements, and infrequency of batch production runs, we carry limited amounts of safety stock for our products and product candidates. We may also have to take inventory write-offs and incur other charges and expenses for products and product candidates that fail to meet specifications, undertake costly remediation efforts, or seek more costly manufacturing alternatives.

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

We acquire most of the drug substances and drug products for our products and product candidates from single sources. The drug substance and drug product for Crysvita are made by KHK pursuant to our license and collaboration agreement with KHK. The drug substance and drug product for Mepsevii are manufactured by Rentschler under a commercial supply and services agreement and accompanying purchase orders. The pharmaceutical-grade drug substance for UX007 is manufactured by IOI Oleo pursuant to our supply agreement with IOI Oleo, and the drug product for UX007 is prepared by Haupt Pharma AG and CPM pursuant to purchase orders. Single source suppliers are also used for our gene therapy programs. We have not currently secured any other suppliers for the drug substance or drug product of our products and product candidates and, although we believe that there are alternate sources of supply that could satisfy our clinical and commercial requirements, we cannot provide assurance that identifying alternate sources and establishing relationships with such sources would not result in significant delay in the commercialization of our products or the development of our product candidates. Additionally, we may not be able to enter into supply arrangements with alternative suppliers on commercially reasonable terms or at all. A delay in the commercialization of our products or the development of our product candidates or having to enter into a new agreement with a different third-party on less favorable terms than we have with our current suppliers could have a material adverse impact upon on our business.

We and our collaborators and contract manufacturers are subject to significant regulation with respect to manufacturing our product candidates. The manufacturing facilities on which we rely may not continue to meet regulatory requirements or may not be able to meet supply demands.

All entities involved in the preparation of therapeutics for clinical studies or commercial sale, including our existing contract manufacturers and collaboration partners for our product candidates, are subject to extensive regulation. Components of a finished therapeutic product approved for commercial sale or used in clinical studies must be manufactured in accordance with GMP. These regulations govern manufacturing processes and procedures (including record keeping) and the implementation and operation of quality systems to control and assure the quality of investigational products and products approved for sale. Poor control of production processes can lead to the introduction of contaminants or to inadvertent changes in the properties or stability of our products and product candidates that may not be detectable in final product testing. We, our collaborators, or our contract manufacturers must supply all necessary documentation in support of an NDA, BLA, MAA, or other application for regulatory approval, on a timely basis and must adhere to GLP, GMP, and similar regulations enforced by the FDA and other regulatory agencies through their facilities inspection programs. Some of our contract manufacturers have never produced a commercially approved pharmaceutical product and therefore have not obtained the requisite regulatory authority approvals to do so. The facilities and quality systems of some or all of our collaborators and third-party contractors must pass a pre-approval inspection for compliance with the applicable regulations as a condition of regulatory approval of our product candidates or any of our other potential products. In addition, the regulatory authorities may, at any time, audit or inspect a manufacturing facility involved with the preparation of our product candidates or our other potential products or the associated quality systems for compliance with the regulations applicable to the activities being conducted. Although we oversee the contract manufacturers, we cannot control the manufacturing process of, and are substantially dependent on, our contract manufacturing partners for compliance with the regulatory requirements. If these facilities cannot schedule manufacturing to meet inspectional demands or do not pass a pre-approval plant inspection, regulatory approval of the products may not be granted or may be substantially delayed until any violations are corrected to the satisfaction of the regulatory authority, if ever.

The regulatory authorities also may, at any time following approval of a product for sale, audit the manufacturing facilities of our collaborators, such as KHK, and third-party contractors. If any such inspection or audit identifies a

failure to comply with applicable regulations or if a violation of our product specifications or applicable regulations occurs independent of such an inspection or audit, we or the relevant regulatory authority may require remedial measures that may be costly and/or time consuming for us or a third-party to implement, and that may include the temporary or permanent suspension of a clinical study or commercial sales or the temporary or permanent closure of a facility. Any such remedial measures imposed upon us, our collaborators, or third parties with whom we contract could materially harm our business.

If we, our collaborators, including KHK, or any of our third-party manufacturers fail to maintain regulatory compliance, the FDA or other applicable regulatory authority can impose regulatory sanctions including, among other things, refusal to approve a pending application for a new drug product or biologic product, withdrawal of an approval, or suspension of production. As a result, our business, financial condition, and results of operations may be materially harmed.

Additionally, if supply from one approved manufacturer is interrupted, an alternative manufacturer would need to be qualified through an NDA or BLA supplement or MAA variation, or equivalent foreign regulatory filing, which could result in further delay. The regulatory agencies may also require additional studies if a new manufacturer is relied upon for commercial production. Switching manufacturers may involve substantial costs and is likely to result in a delay in our desired clinical and commercial timelines.

These factors could cause us to incur higher costs and could cause the delay or termination of clinical studies, regulatory submissions, required approvals, or commercialization of our product candidates. Furthermore, if our suppliers fail to meet contractual requirements and we are unable to secure one or more replacement suppliers capable of production at a substantially equivalent cost, our clinical studies may be delayed or we could lose potential revenue.

The actions of distributors could affect our ability to sell or market products profitably. Fluctuations in buying or distribution patterns by such distributors could adversely affect our revenues, financial condition, or results of operations.

We intend to rely on commercial distributors for a considerable portion of our product sales and we expect such sales to be concentrated within a small number of distributors. The financial failure of any of these distributors could adversely affect our revenues, financial condition or results of operations. Our revenues, financial condition or results of operations may also be affected by fluctuations in distributor buying or distribution patterns. These fluctuations may result from seasonality, pricing, wholesaler inventory objectives, or other factors.

Our reliance on third parties requires us to share our trade secrets, which increases the possibility that a competitor will discover them or that our trade secrets will be misappropriated or disclosed.

Because we rely on third parties in connection with the development and manufacture of our products and product candidates and will likely rely on third parties in connection with the commercialization of our approved products, we must, at times, share trade secrets with them. We seek to protect our proprietary technology in part by entering into confidentiality agreements and, if applicable, material transfer agreements, collaborative research agreements, consulting agreements, letters of engagement, or other similar agreements with our collaborators, advisors, employees, and consultants prior to beginning research or disclosing proprietary information. These agreements typically limit the rights of the third parties to use or disclose our confidential information, such as trade secrets. Despite the contractual provisions employed when working with third parties, the need to share trade secrets and other confidential information increases the risk that such trade secrets become known by our competitors, are inadvertently incorporated into the technology of others, or are disclosed or used in violation of these agreements. Given that our proprietary position is based, in part, on our know-how and trade secrets, a competitor’s discovery of our trade secrets or other unauthorized use or disclosure would impair our competitive position and may have a material adverse effect on our business.

Risks Related to Commercialization of Our Products and Product Candidates

If the market opportunities for our products and product candidates are smaller than we believe they are, our revenue may be adversely affected, and our business may suffer. Because the target patient populations of our products and product candidates are small, and the addressable patient population potentially even smaller, we must be able to successfully identify patients and acquire a significant market share to achieve profitability and growth.

We focus our research and product development on treatments for rare and ultra-rare genetic diseases. Given the small number of patients who have the diseases that we are targeting, it is critical to our ability to grow and become profitable that we continue to successfully identify patients with these rare and ultra-rare genetic diseases. Some of our current clinical programs may be most appropriate for patients with more severe forms of their disease. For instance, our Phase 2 study of UX007 in LC-FAOD enrolled patients with more severe disease. In addition, while adults make up the majority of the XLH patients, they often have less severe disease that may reduce the penetration of Crysvita in the adult population relative to the pediatric population. Given the overall rarity of the diseases we target, it is difficult to project the prevalence of the more severe forms, or the other subsets of patients that may be most suitable to address with our products and product candidates, which may further limit the addressable patient population to a small subset. Our projections of both the number of people who have these diseases, as well as the

subset of people with these diseases who have the potential to benefit from treatment with our products and product candidates, are based on our beliefs and estimates. These estimates have been derived from a variety of sources, including the scientific literature, surveys of clinics, patient foundations, or market research, and may prove to be incorrect. Further, new studies may change the estimated incidence or prevalence of these diseases. The number of patients may turn out to be lower than expected. The effort to identify patients with diseases we seek to treat is in early stages, and we cannot accurately predict the number of patients for whom treatment might be possible. Additionally, the potentially addressable patient population for each of our products and product candidates may be limited or may not be amenable to treatment with our products and product candidates, and new patients may become increasingly difficult to identify or access, which would adversely affect our results of operations and our business. Further, even if we obtain significant market share for our products and product candidates, because the potential target populations are very small we may never become or remain profitable nor generate sufficient revenue growth to sustain our business.

Manufacturers that produce our products and product candidates may not have experience producing our products and product candidates at commercial levels and may not achieve the necessary regulatory approvals or produce our products and product candidates at the cost, quality, quantities, locations, and timing needed to support profitable commercialization.

We rely on third-party manufacturers to produce our products and product candidates. These manufacturers may not have the experience or ability to produce our products and product candidates at commercial levels. We may run into technical or scientific issues related to manufacturing or development that we may be unable to resolve in a timely manner or with available funds. We also have not completed all of the characterization and validation activities necessary for commercialization and regulatory approvals for all of our product candidates. If our manufacturing partners are not able to conduct all such necessary activities in accordance with applicable regulations, our commercialization efforts will be harmed. We have not yet secured manufacturing capabilities for commercial quantities of all of our product candidates and may be unable to negotiate binding agreements with manufacturers to support our commercialization activities on commercially reasonable terms.

Even if our third-party product manufacturers develop an acceptable manufacturing process, if such third-party manufacturers are unable to produce the necessary quantities of our products and product candidates, are unable to comply with GMP or other pertinent regulatory requirements, or are unable to produce our products and product candidates within our planned timeframe and cost parameters, the development and sales of our products and product candidates, if approved, may be materially harmed.

Additionally, the cost to us for the supply of our products and product candidates manufactured by such third parties may be high and could limit our profitability, even if our third-party product manufacturers develop acceptable manufacturing processes that provide the necessary quantities of our products and product candidates in a compliant and timely manner. Furthermore, KHK is our sole supplier of commercial quantities of Crysvita. The supply price to us for commercial sales of Crysvita, which is determined on a fixed double-digit percentage of net sales, is higher than the typical cost of goods sold by companies focused on rare diseases.

We face intense competition and rapid technological change and the possibility that our competitors may develop therapies that are similar, more advanced, or more effective than ours, which may adversely affect our financial condition and our ability to successfully commercialize our product candidates.

The biotechnology and pharmaceutical industries are intensely competitive and subject to rapid and significant technological change. We are currently aware of various existing treatments that may compete with our products and product candidates. For example, XLH is treated with oral phosphate and vitamin D therapy, which may compete with Crysvita; LC-FAOD is treated with diet therapy and medium-chain triglyceride oil, which may compete with UX007; OTC deficiency is currently treated with nitrogen scavenging drugs and severe limitations in dietary protein, which may compete with DTX301; and GSD1a is currently treated with corn starch, which may compete with DTX401. Triheptanoin is available in food-grade form, which may compete with our pharmaceutical-grade product. Furthermore, investigator-sponsored trials evaluating triheptanoin in multiple indications are ongoing. Gene therapy, gene correction, RNA-based therapies, and other approaches may also emerge for the treatment of any of the disease areas in which we focus.

We have competitors both in the United States and internationally, including major multinational pharmaceutical companies, specialty pharmaceutical companies, biotechnology companies, startups, academic research institutions, government agencies, and public and private research institutions. Many of our competitors have substantially greater financial, technical, and other resources, such as larger research and development staff and experienced marketing and manufacturing organizations. Additional mergers and acquisitions in the biotechnology and pharmaceutical industries may result in even more resources being concentrated in our competitors. As a result, these companies may obtain

regulatory approval more rapidly than we are able to and may be more effective in selling and marketing their products as well. Smaller or early-stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large, established companies. Competition may increase further as a result of advances in the commercial applicability of technologies and greater availability of capital for investment in these industries. Our competitors may succeed in developing, acquiring, or licensing on an exclusive basis, products that are more effective or less costly than any product candidate that we may develop, or achieve earlier patent protection, regulatory approval, product commercialization, and market penetration than we do. Additionally, technologies developed by our competitors may render our potential products and product candidates uneconomical or obsolete, and we may not be successful in marketing our products and product candidates against competitors.

We continue to build and evolve an integrated commercial organization. If we are unable to expand our existing commercial infrastructure or enter into agreements with third parties to market and sell our product candidates, as needed, we may be unable to generate significant revenue.

In preparation to successfully commercialize Crysvita and Mepsevii as well as any additional products that may result from our development programs, we are building a commercial infrastructure in North America, Europe and Latin America. This infrastructure consists of both office based as well as field teams with technical expertise, and will be expanded as we approach the potential approval dates of additional products that result from our development programs. This will be expensive and time consuming. Any failure or delay in the expansion of this infrastructure may adversely impact the commercialization of our approved products.

Although our employees may have promoted other similar products in the past while employed at other companies, we, as a company, have limited, recent experience selling and marketing our product. Further, given our limited experience in marketing and selling biopharmaceutical products, our initial estimate of the size of the required field force may be materially more or less than the size of the field force actually required to effectively commercialize our product candidates. As such, we may be required to hire large teams to adequately support the commercialization of our product candidates or we may incur excess costs as a result of hiring more commercial personnel than necessary. With respect to certain geographical markets, we may enter into collaborations with other entities to utilize their local marketing and distribution capabilities, but we may be unable to enter into such agreements on favorable terms, if at all. If our future collaborators do not commit sufficient resources to commercialize our future products, if any, and we are unable to develop the necessary marketing capabilities on our own, we will be unable to generate sufficient product revenue to sustain our business. We may be competing with companies that currently have extensive and well-funded marketing and sales operations. Without a large internal team or the support of a third-party to perform key commercial functions, we may be unable to compete successfully against these more established companies.

The commercial success of any current or future product will depend upon the degree of market acceptance by physicians, patients, third-party payors, and others in the medical community.

Even with the requisite approvals from the FDA and comparable foreign regulatory authorities, the commercial success of our current and future products will depend in part on the medical community, patients, and payors accepting our current and future products as medically useful, cost-effective, and safe. Any product that we bring to the market may not gain market acceptance by physicians, patients, payors, and others in the medical community. The degree of market acceptance of any of our current and future products will depend on a number of factors, including:

- the efficacy of the product as demonstrated in clinical studies and potential advantages over competing treatments;
- the prevalence and severity of any side effects, including any limitations or warnings contained in a product's approved labeling;
- the clinical indications for which approval is granted;
- relative convenience and ease of administration;
- the cost of treatment, particularly in relation to competing treatments;
- the willingness of the target patient population to try new therapies and of physicians to prescribe these therapies;
- the effectiveness of our field forces and marketing efforts;
- the strength of marketing and distribution support and timing of market introduction of competitive products;
- publicity concerning our products or competing products and treatments; and
- sufficient third-party insurance coverage and reimbursement.

Even if a potential product displays a favorable efficacy and safety profile in nonclinical and clinical studies, market acceptance of the product will not be fully known until after it is launched. Our efforts t