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, 2020

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	Trading Symbol	Name of each exchange on which registered
Common Stock, $0.001 par value	**RARE**	**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 whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, a smaller reporting company, or an 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 has filed a report on and attestation to its management's assessment of the effectiveness of its internal control over financial reporting under Section 404(b) of the Sarbanes-Oxley Act (15 U.S.C. 7262(b)) by the registered public accounting firm that prepared or issued its audit report. ☑

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, 2020 was approximately $4.7 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 8, 2021, the Company had 66,949,244 shares of common stock issued and outstanding.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant's definitive proxy statement relating to its 2021 Annual Meeting of Stockholders, to be held on or about June 24, 2021, are incorporated by reference into Part III of this Annual Report on Form 10-K where indicated. Such proxy statement will be filed with the U.S. Securities and Exchange Commission within 120 days after the end of the fiscal year to which this report relates.

Table of Contents

CAUTIONARY NOTE REGARDING FORWARD-LOOKING STATEMENTS

This Annual Report on Form 10-K, or Annual Report, contains forward-looking statements that involve risks and uncertainties. We make such forward-looking statements pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995 and other federal securities laws. All statements other than statements of historical facts contained in this Annual Report are forward-looking statements. In some cases, you can identify forward-looking statements by words such as "anticipate," "believe," "contemplate," "continue," "could," "estimate," "expect," "forecast," "intend," "may," "plan," "potential," "predict," "project," "seek," "should," "target," "will," "would," or the negative of these words, or other comparable terminology. These forward-looking statements include, but are not limited to, statements about:

- our 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;
- the impact of the COVID-19 pandemic and related health measures on our business, financial condition and liquidity;
- 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 typically no approved therapies treating the underlying disease.

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 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

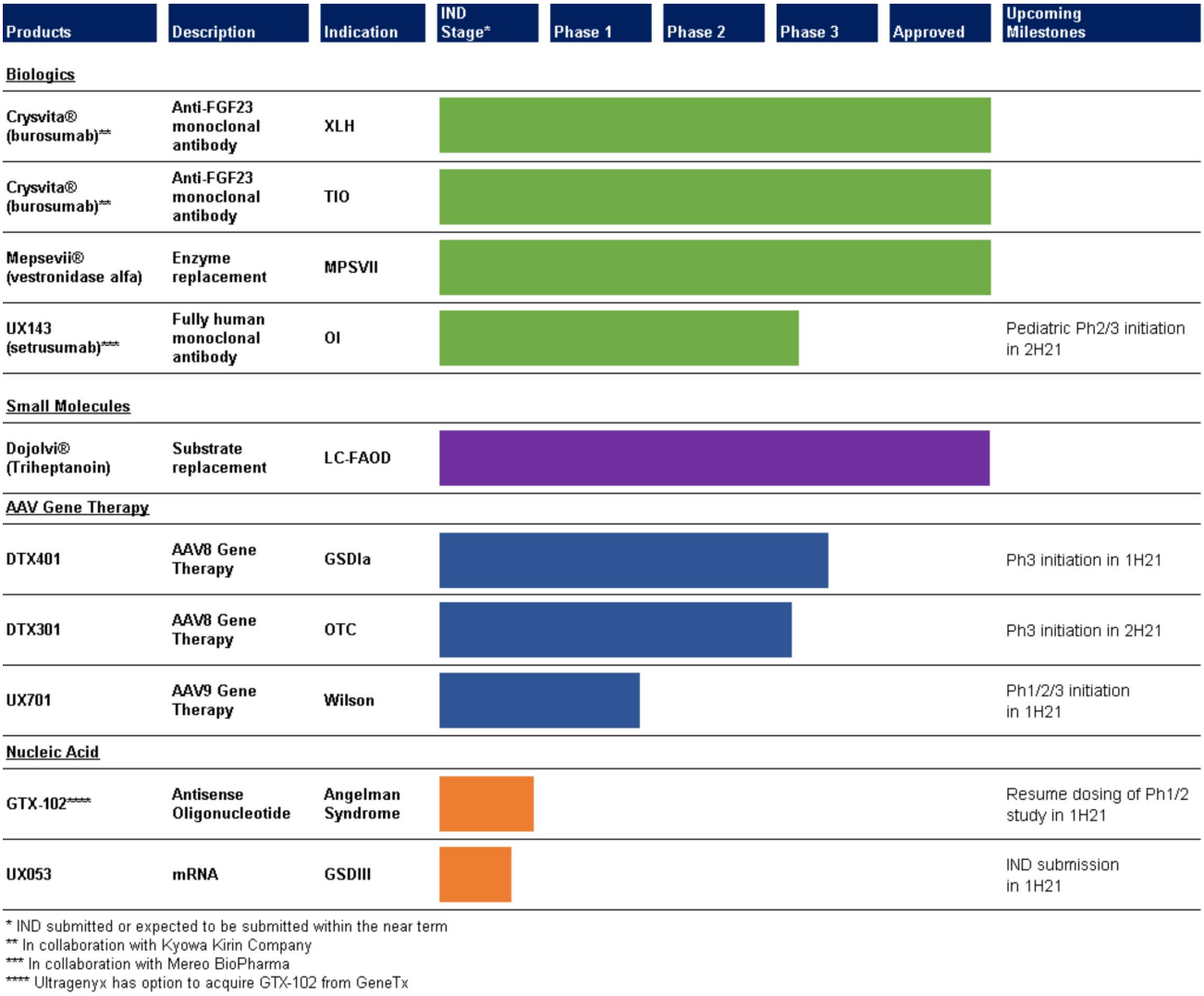
The critical components of our business strategy include the following:

- ***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 that treat the underlying disease. 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 modalities of small molecules, biologics, gene therapy, and nucleic acids 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.
- ***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, and United Kingdom, 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 therapies and clinical-stage pipeline consist of four product categories: biologics, small molecules, gene therapy, and nucleic acid product candidates.

We have three commercially approved products, Crysvita® (burosumab) for the treatment of X-linked hypophosphatemia, or XLH, and tumor-induced osteomalacia, or TIO, Mepsevii® (vestronidase alfa) for the treatment of mucopolysaccharidosis VII, or MPSVII or Sly Syndrome, and Dojolvi® (triheptanoin) for the treatment of long-chain fatty acid oxidation disorders, or LC-FAOD, and we anticipate having six product candidates in the clinical pipeline in 2021. The following table summarizes our approved products and clinical product candidate pipeline:



Approved Products

Crysvita for the treatment of XLH

Crysvita is an antibody administered via subcutaneous injection that targets fibroblast growth factor 23 (FGF23), developed for the treatment of XLH, a rare, hereditary, progressive and lifelong musculoskeletal disorder characterized by renal phosphate wasting caused by excess FGF23 production. There are approximately 48,000 patients with XLH in the developed world, including approximately 36,000 adults and 12,000 children. Crysvita is the only approved treatment that addresses the underlying cause of XLH. Crysvita is approved in the United States and Canada for the treatment of XLH in adult and pediatric patients six months of age and older. In the European Union, or the EU, and the United Kingdom, Crysvita is approved for the treatment of XLH with radiographic evidence of bone disease in children one year of age and older, adolescents, and adults. In Brazil and Mexico, Crysvita is approved for treatment of XLH in adult and pediatric patients one year of age and older. We have submitted regulatory filings in various other Latin American countries.

We are collaborating with Kyowa Kirin Co., Ltd., or KKC (formerly Kyowa Hakko Kirin Co., Ltd., or KHK), and Kyowa Kirin, a wholly owned subsidiary of KKC, on the development and commercialization of Crysvita globally.

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

Tumor-induced osteomalacia (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 June 2020, we and Kyowa Kirin announced the FDA approval of Crysvita for the treatment of FGF23-related hypophosphatemia TIO associated with phosphaturic mesenchymal tumors that cannot be curatively resected or localized in adults and pediatric patients 2 years of age and older.

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

Mepsevii for the treatment of MPS VII

Mepsevii is an intravenous, or IV, enzyme replacement therapy, developed for the treatment of Mucopolysaccharidosis VII, also known as MPS VII or Sly syndrome, a rare lysosomal storage disease that often leads to multi-organ dysfunction, pervasive skeletal disease, and death. MPS VII is one of the rarest MPS disorders, affecting an estimated 200 patients in the developed world. Mepsevii is approved in the United States for the treatment of children and adults with MPS VII. In the EU and the United Kingdom, Mepsevii is approved under exceptional circumstances for the treatment of non-neurological manifestations of MPS VII for patients of all ages. In Brazil and Mexico, Mepsevii is approved for the treatment of MPS VII for patients of all ages.

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

Dojolvi for the treatment of LC-FAOD

Dojolvi is a highly purified, synthetic, 7-carbon fatty acid triglyceride specifically designed to provide medium-chain, odd-carbon fatty acids as an energy source and metabolite replacement for people with long-chain fatty acid oxidation disorders, or LC-FAOD, which is a set of rare metabolic diseases that prevents the conversion of fat into energy and can cause low blood sugar, muscle rupture, and heart and liver disease. Dojolvi is the first FDA-approved therapy as a source of calories and fatty acids for the treatment of pediatric and adult patients with molecularly confirmed LC-FAOD and the product is commercially available in the United States. We have submitted Dojolvi to the Brazilian Health Regulatory Agency (ANVISA) seeking marketing authorization. In Canada, we have been granted priority review and have filed a new drug submission. Discussions with EU regulatory authorities are ongoing. There are approximately 8,000 to 14,000 patients in the developed world with LC-FAOD.

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

Clinical Product Candidates

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

DTX401 is an adeno-associated virus 8, or AAV8, gene therapy clinical candidate for the treatment of patients with glycogen storage disease type Ia, or GSDIa, a disease that arises from a defect in G6Pase, an essential enzyme in glycogen and glucose metabolism. 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. GSDIa is the most common genetically inherited glycogen storage disease, with an estimated 6,000 patients in the developed world affected by GSDIa. DTX401 has been granted Orphan Drug Designation in both the United States and in the EU and the United Kingdom, Regenerative Medicine Advanced Therapy (RMAT) designation and Fast Track designation in the United States.

In May 2020, we announced positive data from the confirmatory cohort in the ongoing Phase 1/2 study at the American Society of Gene & Cell Therapy (ASGCT) annual meeting. The data demonstrated increased time to hypoglycemia and substantial reductions in cornstarch usage. Across all three cohorts in the study, 100 percent of patients had demonstrated meaningful and sustained cornstarch regimens over time and significant increases in time to hypoglycemia. At the data cut-off on April 23, 2020, four of six patients in the first two cohorts had discontinued daytime cornstarch.

In January 2021, we announced positive longer-term safety and efficacy data from the first three cohorts of the ongoing Phase 1/2 study. All nine patients continued to demonstrate improved glucose control while tapering or discontinuing oral glucose replacement with cornstarch and improvements in energy metabolism pathways over the long term. At the primary evaluation timepoint at Week 52, the overall mean reduction in cornstarch was 77% across all three cohorts, including two patients in Cohort 3 showing a reduction of greater than 75%. Follow-up for more than two years for the three patients in Cohort 1 have shown sustained and continued cornstarch reductions with a mean reduction of 91% through weeks 104 and 120.

In Cohort 3, data collected from continuous glucose monitoring (CGM) indicated that glycemic control was maintained and even improved despite the reductions in cornstarch dependence. These reductions in cornstarch dosing have had an impact on energy metabolism and body weight. Seven of nine treated patients had decreases of 5% (5.6 kg) to 21% (10.5 kg) in bodyweight following DTX401 treatment, with a mean decrease of 12% from the mean baseline weight of 82.8 kg in these seven patients. The notable weight loss was attributed to improved glycemic control and potentially increased physical activity reported by patients.

All three patients in a fourth and final Phase 1/2 cohort, which utilized prophylactic steroids, had been dosed at the same dose as Cohorts 2 and 3. Through 11 weeks post-dosing, there had been no treatment related serious adverse events and all three patients were doing well, demonstrating early reduction in daily cornstarch intake.

We have completed Scientific Advice with the EMA and had an End of Phase 2 (EOP2) meeting with the FDA to discuss the Phase 2 data, the Phase 3 design, and endpoints. Based in part on this feedback, we currently plan to conduct a 48-week Phase 3 study in approximately 50 patients, randomized 1:1 to DTX401 dosed at 1.0 x 10^13 GG/kg, as calculated using a new droplet digital PCR (ddPCR) test method, or placebo. All patients in the study are expected to cross over to the therapeutic arm and receive therapy at the end of the initial 48-week follow-up period.

Based on the regulatory discussion and pending finalization with the regulatory authorities, we currently intend to study as primary endpoints glycemic control by assessing the maintenance of glucose control by CGM and the reduction in cornstarch requirements. These primary endpoints are expected to be supported by key secondary endpoints of improvement in percent of time spent in normal glucose control (60-120 mg/dL), time to hypoglycemia in controlled fasting challenge, and the GSDIa functional assessment diary signs and symptom scale. The durability of the treatment would then be supported by the longer-term Phase 1/2 data and early treated Phase 3 patients. Based on the results to date, the therapeutic benefit appears to increase over time during the second year after treatment. We currently expect to initiate the Phase 3 study in the first half of 2021.

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

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

DTX301 is an AAV8 gene therapy product candidate designed for the treatment of patients with ornithine transcarbamylase, or 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 in the EU and the United Kingdom and Fast Track Designation in the United States.

In May 2020, we announced updated positive data from the ongoing Phase 1/2 study at the ASGCT annual meeting. The updated data confirmed that all three patients in the third dose cohort were responders to DTX301 as shown by sustained meaningful increases in the rate of ureagenesis or reductions in ammonia levels. Six of nine patients across all three cohorts have now responded to the gene therapy, including three females and three males. All three complete responders, those who have discontinued all ammonia scavengers and liberalized their diets, remain clinically and metabolically stable after longer-term follow-up, up to 130 weeks for the longest patient.

In January 2021, we announced positive longer-term safety and efficacy data from the first three cohorts. The six responders identified at ASGCT in May 2020 continued to demonstrate durable metabolic control. The three complete responders were stable through 104, 130, and 156 weeks post-treatment with good ammonia control despite discontinuation of their alternative pathway medications and protein-restricted diets. The three other responders also remained stable through Weeks 52 and 130 and were either continuing to taper medications and diet or intended to continue tapering once COVID-19 restrictions are lifted and patients could be more closely followed in clinic. As of January 2021, all responders remained in excellent clinical condition with no significant adverse events, hospitalizations, or other events related to OTC deficiency.

Two of three patients have been dosed in the prophylactic steroid cohort, the final cohort in the Phase 1/2 study, at the same dose as in Cohort 3. Through up to 18 weeks post-dosing, both patients were doing well clinically with good metabolic control and there had been no treatment related serious adverse events.

We completed the initial Scientific Advice process with the EMA regarding the Phase 3 development plan and continue to have discussions with the FDA regarding the Phase 3 study of DTX301. The EOP2 meeting with the FDA is scheduled to occur late in the first quarter of 2021, barring any unforeseen delays.

Based on regulatory feedback to date, the proposed Phase 3 study design is currently expected to include approximately 50 patients, randomized 1:1 to DTX301 dosed at 1.7 x 10^13 GC/kg, as calculated using a new ddPCR test method, or placebo and followed for 48 weeks initially. The change in 24-hour ammonia levels is expected as the primary endpoint. The entry criteria will allow patients with higher baseline ammonia levels than in the Phase 1/2 study to allow sufficient power to assess the change in ammonia. The primary endpoint will be supported by the change in the rate of ureagenesis as a key secondary endpoint that evaluates

the capacity to generate urea from ammonia. Additional secondary endpoints include reduction or discontinuation of scavenger medications and normalization of protein-restricted diet.

The Phase 3 study is expected to begin dosing in the second half of 2021. Placebo patients participating in the study will receive DTX301 at the end of the initial 48-week follow-up period. We will continue to follow patients in the ongoing Phase 1/2 study during the Phase 3 study in order to augment the overall long-term data package supporting the durability of DTX301.

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

UX143 (setrusumab) for the treatment of Osteogenesis Imperfecta (OI), in collaboration with Mereo BioPharma 3 Limited, or Mereo

UX143 is a fully human monoclonal antibody that inhibits sclerostin, a protein that acts on a key bone-signaling pathway and inhibits the activity of bone-forming cells. By blocking inhibitory effects of sclerostin, the anti-sclerostin antibody causes new bone formation, increased production of collagen, and increased bone mineral density and strength. Sclerostin inhibition also reduces excessive bone resorption, further enhancing the impact on bone density. Setrusumab has received orphan drug designation from the FDA and EMA, rare pediatric disease designation from the FDA, and was accepted into the EMA's Priority Medicines program (PRIME). OI is a rare genetic disorder that is characterized by fragile bones and reduced bone mass resulting in bones that break easily, loose joints, and weakened teeth. In severe cases, those with OI may experience hundreds of fractures in a lifetime. In addition, people with OI often suffer muscle weakness, early hearing loss, fatigue, curved bones, scoliosis, respiratory problems, and short stature, leading to significant effects on overall health and quality of life. The majority of cases of OI (estimated at approximately 90%) are caused by a dominant mutation in a gene coding for type I collagen, a key component of healthy bone. Current treatment of OI is supportive, focusing on minimizing fractures and maximizing mobility, but to date, there are no FDA or EU approved treatments. There are an estimated 60,000 patients in the developed world affected by OI.

On January 25, 2021, after the early termination of the waiting period under the Hart-Scott-Rodino Antitrust Improvements Act of 1976 and satisfaction of other customary closing conditions under our collaboration and license agreement with Mereo, we closed the transactions under the agreement and pursuant to the terms thereof, we made a payment of $50 million to Mereo. We expect to start a pediatric Phase 2/3 study in the second half of 2021. Development plans are being finalized which may include changes to current study designs, and will require discussions with regulatory agencies. The objective of a pediatric Phase 2/3 study would first focus on determining the optimal dose based on increases in collagen production using serum P1NP levels and an acceptable safety profile. Following determination of the dose, we currently intend to adapt the study into a pivotal Phase 3 stage, evaluating fracture reduction over an estimated 15 to 24 months as the primary endpoint, subject to regulatory review. A separate pivotal study is also currently being planned for adults with OI.

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

GTX-102 for the treatment of Angelman Syndrome, partnered with GeneTx

GTX-102 is an antisense oligonucleotide, or ASO, that is being developed for the treatment of Angelman syndrome, a debilitating and rare neurogenetic disorder caused by loss-of-function of the maternally inherited allele of the UBE3A gene. There are an estimated 60,000 patients in the developed world affected by Angelman syndrome. GTX-102 was granted Fast Track designation, Orphan Drug Designation and Rare Pediatric Disease Designation from the FDA. GTX-102 is being developed in collaboration with GeneTx Biotherapeutics LLC (GeneTx).

In March 2020, we, along with our partner GeneTx, announced the initiation of a Phase 1/2 open-label, multiple-dose, dose-escalating study (GTX-102-001) to evaluate the safety, tolerability, and potential efficacy of GTX-102 in pediatric patients with Angelman syndrome. Five patients have received GTX-102 treatment to date and signs of clinical improvement in multiple domains of Angelman syndrome were reported early in dosing, After the fifth patient was dosed, the patient experienced a serious adverse event (SAE) of lower extremity weakness and the companies paused enrollment and dosing in the study. Subsequently, similar SAEs of lower extremity weakness were reported in the other four patients following treatment at the highest doses. The SAEs were assessed as mild or moderate in severity, improved over a period of a few weeks and all have fully resolved. Full safety information has been submitted to the FDA. A formal clinical hold was issued by the FDA on study GTX-102-001 during the fourth quarter of 2020.

In the fourth quarter of 2020, along with our partner GeneTx, we announced positive interim preliminary data from study GTX-102-001 which indicated substantial improvements in all patients in at least two disease domains including communication, behavior, sleep, gross motor function, and fine motor function as measured by the CGI-I-AS for Patients 1 through 4 at day 128, and Patient 5 at Day 86. These improvements were also supported by other scores, including the Bayley Scales of Infant and Toddler Development (Bayley-4), where multiple patients improved on receptive or expressive communication sub-scales. Also in the Observed Reported Communication Ability (ORCA) measure of expressive, receptive, and pragmatic communication, three patients, ages 5, 10, and 15, demonstrated clinically relevant increases at day 128 and two patients did not have notable changes.

In December 2020, a substantial information amendment was submitted to the FDA including follow-up safety information for the five patients dosed and toxicology data in nonhuman primates that demonstrated no evidence of the safety issue described above at higher repeat dosing. The amendment also included a safety evaluation of the SAEs, which supported that causality of the SAEs could be due to local contact toxicity. An amended dosing and administration plan has been proposed to the FDA. The changes reflected in the amended plan are designed to reduce the local contact time and concentration of the drug; the amended dosing plan is within the dosing range for which clinical activity was observed but below doses associated with the SAEs. As of January 2021 the study remains on clinical hold, but is currently expected to resume enrollment and dosing in the first half of 2021, assuming resolution of FDA requests and approval to proceed. Once the study has resumed, we currently expect additional interim data from the study in the second half of 2021. A Clinical Trial Application (CTA) was accepted in Canada in March 2020 and a protocol and a revised protocol incorporating the new dosing and administration plan will be submitted. The companies are also in the process of expanding the study to other countries using the amended dosing and administration plan.

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

UX701 for the treatment of Wilson Disease

UX701 is an investigational AAV type 9 gene therapy designed to deliver stable expression of a truncated version of the ATP7B copper transporter following a single intravenous infusion. It has been shown in preclinical studies to improve copper distribution and excretion from the body and reverse pathological findings of Wilson liver disease. UX701 was granted Orphan Drug Designation in the United States and EU. Wilson disease is 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.

In January 2021, we announced that the FDA has cleared the IND application for UX701. We currently expect enrollment in a seamless single-protocol Phase 1/2/3 study to begin in the first half of 2021.

In February 2021, UX701 received Fast Track Designation from the FDA. This allows for early and frequent communication throughout the entire drug development and review process and reflects the serious, unmet need for patients with Wilson disease.

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

Our preclinical candidate UX053 is being developed 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. We currently expect UX053 to be our first mRNA program in the clinic, with an IND planned for the first half of 2021 and initiation of the trial in the second half of 2021.

Please see "—License and Collaboration Agreements—Preclinical Pipeline—Arcturus" for a description of our collaboration agreement with Arcturus.

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 and TIO, it is possible that competitors may produce, develop, and commercialize therapeutics, or utilize other approaches such as gene therapy, to treat XLH and TIO. 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 Dojolvi, although we are not aware of any other compounds currently in clinical development for LC-FAOD, LC-FAOD is commonly treated with diet therapy and MCT oil. Dojolvi may compete with this approach. Although we believe that Dojolvi 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. In addition, Reneo Pharmaceuticals is developing REN001, a PPAR delta agonist, in Phase 1b for LC-FAOD and other genetic myopathies.

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

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. A novel formulation of sodium phenylbutyrate, ACER-001, is in Phase 2 clinical testing by Acer Therapeutics. 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, Kaleido Biosciences is developing KB195, a synthetic glycan, in Phase 2 for urea cycle disorders, including OTC deficiency, and Arcturus Therapeutics is developing ARCT-810, a messenger RNA therapy, in Phase 1b for OTC deficiency.

With respect to GTX-102, there are currently no approved drugs for Angelman syndrome. Many patients take general treatments to try to manage specific symptoms, such as seizures or sleep disturbances, but there are no treatments available that address the underlying biology of the disease. We are aware of other ASOs in preclinical and clinical development for Angelman syndrome, including a program from Roche in a Phase 1 study, as well as preclinical gene therapy programs. In addition, Neuren is developing NNZ-2591, an IGF-1 analog, in Phase 1 for Angelman syndrome.

With respect to UX701, there are no currently approved treatments that address the underlying cause of Wilson disease. Many patients are on chelator therapies, but these fail to address the mutated ATP7B copper transporter gene. We are aware of another gene therapy, VTX-801, that is in development by Vivet Therapeutics, in collaboration with Pfizer, for Wilson disease.

License and Collaboration Agreements

Our products and some of our current product candidates 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 Kirin Co., Ltd.

In August 2013, we entered into a collaboration and license agreement with KKC. Under the terms of this collaboration and license agreement, as amended, we and KKC currently 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, United Kingdom, and Switzerland, or the European territory, and we 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 KKC, we are the lead party for development activities in the profit-share territory and in the European territory until the applicable transition date; we are also 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 KKC. We 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 KKC and KKC is responsible for 100% of the costs for development activities in Japan and Korea. In April 2023, which is the transition date for the profit-share territory, and following the applicable transition date for the European territory, KKC 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 KKC. Crysvita was approved in the EU in February 2018 and was approved by the FDA in April 2018. As described below, we and KKC share commercial responsibilities and profits in the profit-share territory until April 2023, KKC has the commercial responsibility in the European territory, and we are responsible for commercializing burosumab in Latin America.

In the profit-share territory, KKC books sales of products and we have the sole right to promote the products for a specified period of time, with KKC having the right to increasingly participate in the promotion of the products until the transition date of April 2023, which is five years from commercial launch. After April 2023, KKC will have the right to promote the products, subject to a limited promotion right retained by us. See "Item I.A. Risk Factors" for additional information on the risks related to the expiration of our exclusive right to promote Crysvita in the profit-share territory. In the European territory, KKC books sales of products and has the sole right to promote and sell the products. In Latin America, we book sales of products and have the sole right to promote and sell the products.

KKC manufactures and supplies all quantities of product for clinical studies. KKC also supplies all quantities of product for commercial sales in the profit-share territory and in Latin America. The supply price in the profit-share territory and Latin America is 35% of the net sales price through December 31, 2022 and 30% thereafter.

The remaining profit or loss from commercializing products in the profit-share territory is shared between us and KKC on a 50/50 basis until April 2023. 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. KKC is also required to pay a royalty of up to 10% based on net sales in the European territory. We sold our interest in the European territory royalty to Royalty Pharma in December 2019. In Latin America, we pay to KKC a low single-digit royalty on net sales. Our and KKC's obligations to pay royalties will continue on a country-by-country basis for so long as we or KKC, as applicable, are selling products in such country.

In May 2017, we signed an agreement with a wholly-owned subsidiary of KKC pursuant to which we were granted the right to commercialize Crysvita in Turkey. KKC'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.

KKC 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, KKC 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 KKC 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 KKC, unless such termination is the result of KKC'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 KKC 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 KKC, 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 the license agreement, we are obligated to pay to SLU a low single-digit royalty on net sales of the licensed products in the United States, Europe, or Japan, subject to certain potential deductions. Our obligation to pay royalties to SLU in these territories continues until the 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 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 expiration of any orphan drug exclusivity in the United States, Europe, or Japan, at which point our license becomes fully paid.

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 Dojolvi. The license includes patents, patent applications, know-how, and intellectual property related to the composition and formulation of Dojolvi 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 $2.5 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.

Clinical Product Candidates

REGENXBIO Inc.

In October 2013, we entered into an exclusive license agreement with REGENXBIO Inc., or REGENX, under which we were granted an option to develop products to treat hemophilia A, OTC deficiency and GSDIa. 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 pursuant to which we have an exclusive worldwide license to make, have made, use, import, sell, and offer for sale licensed products to treat Wilson disease and CDKL5 deficiency. 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.

In March 2020, we entered into a license agreement with REGENX, for an exclusive, sublicensable, worldwide license to REGENX's NAV AAV8 and AAV9 vectors for the development and commercialization of gene therapy treatments for a rare metabolic disorder. In return for these rights, we made an upfront payment and pay or will pay certain annual fees, milestone payments and royalties on any net sales of products incorporating the licensed intellectual property that range from a high single-digit to low double-digit.

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, which was amended and restated in June 2019. 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 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.

GeneTx

In August 2019, we entered into an agreement with GeneTx to collaborate on the development of GeneTx's GTX-102. Under the terms of the agreement, we made an upfront payment of $20.0 million which included an exclusive option to acquire GeneTx. This option may be exercised any time prior to 30 days following notice of FDA acceptance of the IND for GTX-102. In February 2020, we paid $25.0 million following acceptance of the IND to maintain the option to acquire GeneTx until the earlier of 30 months from the first dosing of a patient in a planned Phase 1/2 study (subject to extensions) or 90 days after results are available from that study. If we exercise the purchase option, we will pay a purchase price to acquire GeneTx, payments upon achieving regulatory and commercial milestones, and royalties on any product sales.

Mereo

In December 2020, we entered into a License and Collaboration Agreement with Mereo to collaborate on the development of setrusumab. Under the terms of the agreement, we will lead future global development of setrusumab in both pediatric and adult patients with OI and were granted an exclusive license to develop and commercialize setrusumab in the U.S., Turkey, and the rest of the world, excluding the European Economic Area, United Kingdom, and Switzerland, or the Mereo Territory, where Mereo retains commercial rights. Each party will be responsible for post-marketing commitments and commercial supply in their respective territories.

Upon the closing of the transactions under the License and Collaboration Agreement with Mereo in January 2021, we made a payment of $50.0 million to Mereo and will be required to make payments of up to $254.0 million upon the achievement of certain clinical, regulatory, and commercial milestones. We will pay for all global development costs as well as tiered double-digit percentage royalties to Mereo on net sales in the U.S., Turkey, and the rest of the world, and Mereo will pay us a fixed double-digit percentage royalty on net sales in the Mereo Territory.

Preclinical Pipeline

Arcturus

In October 2015, we entered into a Research Collaboration and License Agreement with Arcturus Therapeutics Holdings Inc., or Arcturus, to develop mRNA therapeutics for select rare disease targets. The Arcturus collaboration may help us address a wider range of rare diseases than possible with current approaches. As part of the collaboration, we may use Arcturus' LUNAR® nanoparticle delivery platform to develop mRNA therapeutics for the treatment of various rare disease targets, subject to certain exclusions and restrictions.

In June 2019, we announced the expansion of our research and collaboration arrangement with Arcturus, to discover and develop mRNA, DNA and siRNA therapeutics for up to 12 rare disease targets pursuant to the terms of an amendment to the 2015 Research Collaboration and License Agreement, or 2015 license agreement, and equity purchase agreement. In connection with the amendment to the 2015 license agreement, we made a $6.0 million cash upfront payment to Arcturus and also purchased 2,400,000 shares of Arcturus' common stock at a stated value of $10.00 per share. In May 2020, we exercised an option to purchase an additional 600,000 shares of Arcturus' common stock at $16.00 per share. In December 2020, we sold 800,000 shares at a weighted-average price of $100.81. As of December 31, 2020, we held 2,200,000 shares of Arcturus common stock. Arcturus is entitled to preclinical, clinical, regulatory, and sales milestone payments for each product developed under the collaboration. Under the amended license agreement, certain early-stage milestone payments are reduced and the total potential milestone payments are increased due to the expanded number of targets. Arcturus is also entitled to reimbursement of related research expenses and royalties on commercial sales.

Solid Biosciences Inc.

In October 2020, we entered into a strategic Collaboration and License Agreement with Solid Biosciences Inc., or Solid, and received an exclusive license for any pharmaceutical product that expresses Solid's proprietary microdystrophin construct from AAV8 and variants thereof in clade E for use in the treatment of Duchenne muscular dystrophy and other diseases resulting from lack of functional dystrophin, including Becker muscular dystrophy. We will collaborate to develop products that combine Solid's differentiated microdystrophin construct, our HeLa producer cell line (PCL) manufacturing platform, and our AAV8 variants. Solid will also provide development support and was granted an exclusive option to co-invest in products we develop for profit share participation in certain territories. Pursuant to the terms of the Stock Purchase Agreement with Solid that was entered into in October 2020 in connection with the collaboration, we also purchased 7,825,797 shares of Solid's common stock for an aggregate price of $40.0 million.

Other

Daiichi

In March 2020, we entered into a License and Technology Access Agreement, or the License Agreement with Daiichi Sankyo Co., Ltd., or Daiichi Sankyo, pursuant to which, we granted Daiichi Sankyo a non-exclusive license to intellectual property, including know-how and patent applications, with respect to our HeLa PCL and HEK293 transient transfection manufacturing technology platforms for AAV-based gene therapy products. We retained the exclusive right to use the manufacturing technology for our current target indications and additional indications identified now and in the future. We are providing certain technical assistance and technology transfer services during the technology transfer period of three years to enable Daiichi Sankyo to use the technologies for its internal gene therapy programs. Daiichi Sankyo has an option to extend the technology transfer period including know-how improvements by two additional one-year periods by paying a fixed amount for each additional year. Daiichi Sankyo will be responsible for the manufacturing, development, and commercialization of their products manufactured with the licensed technology; however, we have the option to co-develop and co-commercialize rare disease products at the IND stage. We may also provide strategic consultation to Daiichi Sankyo on the development of both AAV-based gene therapy products and other products for rare diseases.

Under the terms of the License Agreement, Daiichi Sankyo made an upfront payment of $125.0 million and is obligated to pay an additional $25.0 million milestone upon the successful completion of the technology transfer of the HeLa PCL and HEK293 platforms, as well as single-digit royalties on net sales of products manufactured in either system. Daiichi Sankyo is reimbursing us for all costs associated with the transfer of the manufacturing technology.

We also entered into a Stock Purchase Agreement, or SPA, with Daiichi Sankyo, pursuant to which Daiichi Sankyo purchased 1,243,913 shares of our common stock in exchange for $75.0 million in cash during the first quarter of 2020. Daiichi Sankyo is subject to a three-year standstill and restrictions on sale of the shares (subject to customary exceptions or release).

In June 2020, we executed a subsequent license agreement, or the Sublicense Agreement, with Daiichi Sankyo for transfer of certain technology in consideration for a payment of $8.0 million and annual maintenance fees, milestone payments, and royalties on any net sales of products incorporating the licensed intellectual property.

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 our products, product candidates, processes, 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 processes. Our policy is to patent or in-license the technologies, inventions and improvements that we consider important to the development of our business. In addition to patent protection, we rely on trade secrets, know-how, and continuing innovation to develop and maintain our competitive position.

We also use other means to protect our products and product candidates, 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 — Biosimilars and Exclusivity," "Government Regulation—U.S. Government Regulation — Abbreviated New Drug Applications for Generic Drugs and New Chemical Entity Exclusivity," "Government Regulation—U.S. Government Regulation — Patent Term Restoration," "Government Regulation—EU Regulation — Orphan Designation and Exclusivity," and "Government Regulation—EU Regulation — New Chemical Entity Exclusivity" below for additional information.

We seek regulatory approval for our products and 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. We also 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 products, product candidates, or processes. For more information, please see "Item I.A. Risk Factors Risks Related to Our Intellectual Property."

As of December 31, 2020, we own, jointly own, or have exclusive rights to more than 140 issued and in-force patents (not including individually validated national patents in European Patent Convention member countries) that cover one or more of our products or product candidates, methods of their use, or methods of their manufacture, including more than 45 in-force patents issued by the U.S. Patent and Trademark Office (the USPTO). Furthermore, as of December 31, 2020, we own, jointly own, or have exclusive rights to more than 250 pending patent applications, including more than 50 pending U.S. applications.

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 as of December 31, 2020 for our commercial products and our clinical-stage product candidates are summarized below.

Crysvita (Burosumab) Exclusivity

We have in-licensed rights from KKC to patents and patent applications relating to Crysvita and its use for the treatment of XLH, TIO, and various other hypophosphatemic conditions. Pursuant to this license, we have rights to a number of issued patents and pending applications, including six 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, TIO, and related conditions. The patent terms for the issued patents in the U.S. are from 2022 to 2035, while the issued patents outside the U.S. expire between 2021 and 2035. For patents covering the Crysvita composition of matter, KKC has applied to extend the patent term in the U.S. from 2029 to 2032 and in Europe from 2028 to 2033. In addition to the foregoing patent protections, Crysvita is protected in the U.S. by regulatory exclusivity until 2030 and by orphan drug exclusivity for treating XLH and TIO until 2025 and 2027, respectively.

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 exclusivity until 2029 and by orphan drug exclusivity for treating MPS VII until 2024. Outside the U.S., we own issued patents expiring in 2035 in Australia, Canada, China, Colombia, Europe, Japan, Korea, Mexico, Russia, Singapore, and Taiwan, as well as pending patent applications in other territories, which cover Mepsevii and its use in the treatment of MPS VII.

Dojolvi (Triheptanoin) Exclusivity

We have an exclusive license from the BRI to patents and patent applications relating to Dojolvi and its use for the treatment of FAOD. The in-licensed BRI patent portfolio includes issued patents in the U.S and Mexico that expire in 2025 and cover Dojolvi, as well as an issued patent in Canada that expires in 2025 and covers the use of Dojolvi for the treatment of FAOD. In the U.S., we have applied to extend the term of a BRI patent covering Dojolvi from 2025 to 2029. Beyond the aforementioned BRI patents and patent applications, we own a pending U.S. patent application, corresponding foreign patent applications, and issued patents in Australia, Malaysia, and Taiwan relating to our pharmaceutical-grade Dojolvi composition; these owned patents and any additional patents issuing from these owned applications are expected to expire in 2034. Dojolvi is also protected in the U.S. by regulatory exclusivity until 2025 and orphan drug exclusivity for treating FAOD until 2027.

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 University of Pennsylvania (UPENN) and sublicensed to us by REGENX 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 extension of patent term) and corresponding foreign patents and 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.

DTX301 Exclusivity

We have in-licensed patents and patent applications owned by 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 REGENX 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 two issued U.S. patents expiring in 2035 (without extension of patent term) and corresponding foreign patents and patent applications covering the codon-optimized version of the OTC gene used in DTX301. 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.

UX143 (Setrusumab) Exclusivity

We have in-licensed rights from Mereo to patents and patent applications relating to setrusumab and its use for the treatment of OI. Pursuant to our license from Mereo, we have exclusive rights outside of Europe to a first Mereo patent family that includes three issued U.S. patents and corresponding issued foreign patents that relate to the setrusumab antibody, nucleic acids encoding the setrusumab antibody, and setrusumab's use as a medicament. Patents emanating from the first patent family expire in 2028 (without extension of patent term). We also have exclusive rights outside of Europe to two additional Mereo patent families relating to the use of anti-sclerostin antibodies including setrusumab for the treatment of OI. We expect any patents emanating from these two latter patent families to expire in 2037 (without extension of patent term).

Trademarks

We own registered trademarks covering the Ultragenyx word mark in the U.S. and multiple other jurisdictions. In addition, we own a registered trademark in the U.S. covering a stylized design of our Ultragenyx Pharmaceutical logo. We also own registered trademarks in the U.S. and other territories relating to our Mepsevii and Dojolvi brand names for vestronidase alfa and triheptanoin, respectively. We additionally have a license from KKC to registered trademarks 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. 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 and QC lab capabilities focused on the gene therapy and nucleic acid technologies. The use of contracted manufacturing and reliance on collaboration partners 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.

While our third-party manufacturers have met our current manufacturing requirements, we are building our own GMP gene therapy manufacturing plant to attempt to mitigate potential program timeline delays, control manufacturing costs and reduce manufacturing lead times. For the other non-gene therapy modalities, we primarily use third-party manufacturers 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. We are transferring the fill and finish activities for the manufacture of Mepsevii to a new site as the Rentschler manufacturing site in Laupheim, Germany is being discontinued. In preparation of this activity, we intend to maintain sufficient inventory levels as we identify an alternative supplier and transfer the fill and finish activities for Mepsevii to such supplier. See “Item IA. Risk Factors” for additional information on the risks associated with the transfer of the Mepsevii finish and fill activities to an alternative supplier.

Crysvita

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

Dojolvi

The pharmaceutical-grade drug substance for Dojolvi 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. The drug product for Dojolvi is manufactured by Aenova Haupt Pharma Wolfratshausen GmbH, or Haupt Pharma, pursuant a Master Services Agreement, for the non-exclusive manufacture and supply of product. The agreement was executed in April 2019 with an initial three year term and automatically renews at the end of the current term for an indefinite period unless we provide written notice of termination to Haupt Pharma no later than 60 days prior to the expiration of the initial term. After the initial term, either party may terminate the agreement without cause with at least 12 months' notice. Additionally, if a party materially breaches certain obligations under the agreement and does not cure such breach within 30 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. Either party may also terminate the agreement with immediate effect if the other party breaches certain specified obligations as set forth in the agreement.

Product Candidates

DTX401

Similar to DTX301, the drug substance and drug product for DTX401 are manufactured on a non-exclusive basis by a contract manufacturing organization, or 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.

DTX301

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

DTX301 is currently manufactured using HEK293 mammalian cells. 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 to a cell-based suspension bioreactor format.

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. Our intention is to expand our product portfolio and its geographic accessibility, whether via acquisitions, strategic partnerships, or through the continued development of our proprietary pipeline. We may elect to utilize strategic partners, distributors, or contract management organizations to assist in the commercialization of our products in certain geographies. 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, distribution team and managed care 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 commercial and medical affairs teams focus 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 stakeholders such as managed care organizations, group-purchasing organizations, specialty pharmacies, and government payers as well as single national payers in some countries outside the US. 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 other 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 information 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 liaisons, 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 that has a significant impact on our capital expenditures and results of operations.

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.

Furthermore, the FDA has made available expedited programs to sponsors of regenerative medicine therapies that have been granted designation as a regenerative medicine advanced therapy (RMAT). Regenerative medicine therapies include cell therapies, therapeutic tissue engineering products and human cell and tissue products. A sponsor may seek RMAT designation if its regenerative medicine product is intended for a serious condition and preliminary clinical evidence indicates that the regenerative medicine therapy has the potential to address unmet medical needs for such condition.

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 27 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

We are 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. Complying with these requirements may have a significant impact on our capital expenditures and results of operations.

Customers

Our customers include collaboration partners, drug wholesalers, and retail pharmacy distributors. For the year ended December 31, 2020, more than half of our total revenues were generated under our collaboration agreement with KKC.

Human Capital

As of December 31, 2020, we had 893 total employees, of which 613 are in research and development and 280 are in sales, general, and administrative. Further, 825 are based out of the United States, including facilities at Novato, California, Brisbane, California, Cambridge, Massachusetts, and Woburn, Massachusetts, and 68 are based out of our international locations. The majority of new employees hired during the year ended December 31, 2020 were to support and extend our clinical and preclinical pipeline as well as our commercialization activities, with hires in commercial, clinical development and operations, research, manufacturing, and general and administrative functions. We believe our relationship with our employees to be generally good. We have not experienced any material employment-related issues or interruptions of services due to labor disagreements and are not a party to any collective bargaining agreements.

We expect to continue to add employees in 2021 with a focus on expanding our in-house manufacturing capacity through construction of our gene therapy manufacturing facility, as well as increasing expertise and bandwidth in clinical and preclinical research and development and commercialization activities. The Company continually evaluates the business need and opportunity and balances in house expertise and capacity with outsourced expertise and capacity. Currently, we outsource substantial clinical trial work to clinical research organizations and certain drug manufacturing to contract manufacturers.

We maintain a safety culture grounded on the premise of eliminating workplace incidents, risks and hazards. In response to COVID-19, we have implemented and continue to enhance safety measures in all our facilities, including:

- Adding work from home flexibility for our workforce;
- Reducing density and increasing physical distancing in workspaces for essential employees working onsite;
- Establishing clear and regular COVID-19 policies, safety protocols, and updates to all employees;
- Increasing cleaning and sanitization protocols across all locations;
- Providing additional personal protective equipment and cleaning supplies;
- Implementing protocols to address actual and suspected COVID-19 cases and potential exposure;
- Providing routine COVID-19 testing for essential employees working onsite;
- Implementing daily health attestations and capacity management via online app;
- Including healthcare professionals on staff to administer testing and a health declaration process;
- Prohibiting all domestic and international non-essential travel for all employees; and
- Requiring face coverings to be worn in all locations.

We believe our company's success depends on our ability to attract, develop and retain key personnel. We invest in the growth and development of our employees through various training and development programs that build and strengthen employees' leadership and professional skills, including leadership development programs for new leaders which continued virtually during the pandemic. We also have a talent management framework and process in place that regularly conducts activities like performance management, succession and workforce planning in order to support our employees in their growth and development and ensure we provide learning opportunities.

To continually assess and improve our employee retention and engagement, we conduct an engagement survey on an annual basis, the results of which are discussed with our board of directors, at all hands employee meetings and in individual functions. We take actions to address areas of employment concern and follow-up routinely to share with employees what we are doing. Retention of our key contributors and the results from our annual engagement survey were also included as our corporate goals for fiscal year 2020 and as part of our corporate goals for 2021.

We strive toward having a diverse team of employees and are committed to equality, inclusion and workplace diversity. To accomplish this, we have included questions in our engagement survey to measure employee perception of inclusive culture. Business units review diversity data related to hiring, promotions, and retention on an ongoing basis. In 2020, we established an Inclusion and Diversity Action Team (I&D Action Team) comprised of 11 employee representatives throughout our company. Amongst other initiatives, our I&D Action Team engages in continual discussions across the various business functions to identify potential actions to address areas of improvement and is focused on building accountability across the organization to ensure we meet our diversity objectives.

General Information

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 Annual Reports on Form 10-K, 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 material 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. The risks and uncertainties described below are not the only ones we face. Additional risk and uncertainties not presently known to us or that we presently deem less significant may also impair our business operations. 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. Our company's business, financial condition and operating results can be affected by a number of factors, whether currently known or unknown, including but not limited to those described below, any one or more of which could, directly or indirectly, cause our actual financial condition and operating results to vary materially from past, or from anticipated future, financial condition and operating results. Any of these factors, in whole or in part, could materially and adversely affect our business, prospects, financial condition, operating results and stock price.

Because of the following factors, as well as other factors affecting our financial condition and operating results, past financial performance should not be considered to be a reliable indicator of future performance, and investors should not use historical trends to anticipate results or trends in future periods.

Risk Factor Summary

- We have a history of operating losses and anticipate that we will continue to incur losses for the foreseeable future.
- We have limited experience in generating revenue from product sales.
- We expect we will likely need to raise additional capital to fund our activities.
- Clinical drug development is a lengthy and expensive process with uncertain outcomes.
- If we do not achieve our projected development goals in the time frames we announce and expect, we may experience delays in commercialization of our products and the reputation of our management may be adversely affected.
- We may experience difficulty in enrolling patients, which could delay or prevent clinical studies of our product candidates.
- The regulatory approval processes of the FDA and comparable foreign authorities are lengthy and inherently unpredictable.
- Our product candidates, including our gene therapy product candidates, may cause undesirable or serious side effects that could delay or prevent their regulatory approval, limit the commercial profile of an approved label, or result in other negative consequences following marketing approval, if any.
- Our products will remain subject to regulatory scrutiny even if we obtain regulatory approval.
- We may not realize the full commercial potential of our product candidates if we are unable to source and develop effective biomarkers.
- We rely on third parties to conduct our nonclinical and clinical studies and perform other tasks for us.
- We are dependent on KKC for the clinical and commercial supply of Crysvita for all major markets and for the development and commercialization of Crysvita in certain major markets.
- We have no experience as a company developing a manufacturing facility.
- We rely on third parties to manufacture our products and product candidates and face a multitude of manufacturing risks.
- The loss of, or failure to supply by, any of any of our single-source suppliers for our drug substance and drug product could adversely affect our business.
- The actions of distributors and specialty pharmacies could affect our ability to sell or market products profitably.
- A competitor could misappropriate or disclose our trade secrets.
- Our revenue may be adversely affected if the market opportunities for our products and product candidates are smaller than expected.
- Our competitors may develop therapies that are similar, more advanced, or more effective than ours.
- We may not successfully manage expansion of our company, including building an integrated commercial organization.
- Our exclusive right to promote Crysvita in the United States and Canada expires in 2023.

- Commercial success of our products depends on the degree of market acceptance by physicians, patients, third-party payors, and others in the medical community
- We face uncertainty related to insurance coverage and reimbursement status of our newly approved products.
- We may be adversely affected by the United Kingdom's withdrawal from the EU.
- If we, or our third party partners, are unable to maintain effective proprietary rights for our products, product candidates, or any future product candidates, we may not be able to compete effectively in our markets.
- Claims of intellectual property infringement may prevent or delay our development and commercialization efforts.
- We may not be successful in obtaining or maintaining necessary rights to our product candidates through acquisitions and in-licenses.
- We may face competition from biosimilars or from generic versions of Dojolvi or our small-molecule product candidates, which may result in a material decline in sales of affected products.
- We could lose license rights that are important to our business if we fail to comply with our obligations in the agreements under which we license intellectual property and other rights from third parties.
- We may become involved in lawsuits to protect or enforce our patents or the patents of our licensors, or be subject to claims that challenge the inventorship or ownership of our patents.
- Changes in U.S. patent law could diminish the value of patents in general, thereby impairing our ability to protect our products.
- We may not be able to protect our intellectual property rights throughout the world.
- The ongoing COVID-19 pandemic has impacted our operations and could materially and adversely affect our business and operating results.
- Our success depends in part on our ability to retain our President and Chief Executive Officer and other qualified personnel.
- Our revenue may be impacted if we fail to obtain or maintain orphan drug exclusivity for our products.
- Our operating results may be adversely impacted if our intangible assets become impaired.
- We may not be successful in identifying, licensing, discovering, developing, or commercializing additional product candidates or we may fail to capitalize on opportunities that may be more profitable or for which there is a greater likelihood of success.
- We may fail to comply with laws and regulations or changes in laws and regulations could adversely affect our business.
- We are exposed to risks related to international expansion of our business outside of the United States.
- Our business may be adversely affected in the event of computer system failures or security breaches.
- We or our third party partners may be adversely affected by earthquakes or other serious natural disasters that are not adequately protected by business continuity and disaster recovery plans.
- We may incur various costs and expenses and risks related to acquisition of companies or products or strategic transactions.
- The market price of our common stock is highly volatile.
- Future sales and issuances of our common stock could dilute the percentage ownership of our current stockholders and result in a decline in stock price.
- We do not intend to pay dividends on our common stock so any returns will be limited to the value of our stock.
- Provisions in our amended and restated certificate of incorporation and by-laws, as well as provisions of Delaware law, could make it more difficult for a third-party to acquire us or increase the cost of acquiring us or could limit our stockholders' ability to obtain a favorable judicial forum for disputes with us or our directors, officers or employees.
- We face general risks related to our ability to maintain effective internal controls over financial reporting, additional tax liabilities related to our operations, our ability to use our net operating loss carryforwards and costs of litigation

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;
- expand upon or build our own manufacturing-related facilities and capabilities, including construction of our own GMP gene therapy manufacturing plant;
- 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.

We have limited experience in generating 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, 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 they receive regulatory approval.

We expect we will likely 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, 2020, our available cash, cash equivalents, and marketable debt securities were $1,212.0 million. We expect we will likely 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 (including whether we exercise our option to acquire GeneTx pursuant to the terms of our Unitholder Option Agreement with them), and other arrangements that we may establish, including any required milestone, royalty, and reimbursements or other payments thereunder.

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. We have in the past sought and may in the future seek funds through a sale of future royalty payments similar to our transaction with Royalty Pharma or through collaborative partnerships, strategic alliances, and licensing or other arrangements, such as our transaction with Daiichi Sankyo, 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 or fail 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 delaying or 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, messenger RNA (mRNA), DNA, small interfering RNA (siRNA) 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 time frames 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 example,

- we estimate that approximately 10,000 patients in the developed world suffer from OTC deficiency, of which 80% are classified as late-onset for which DTX301 is being studied, and these all may not be treatable if they are immune to the AAV viral vector;
- we estimate that approximately 6,000 patients worldwide suffer from GSDIa, for which DTX401 is being studied, and these all may not be treatable if they are immune to the AAV viral vector; and.
- we estimate that approximately 10,000 patients worldwide suffer from GSDIII, for which UX053 is being studied.

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 is 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.

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 three 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. Further, as 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 candidates, 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, leading to fewer product approvals. To date, very few gene therapy products have received regulatory approval in the United States or Europe.

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, as described above in “Item 1. Business – Government Regulation”. 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. 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.

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.

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. Our product candidates are in development and the safety profile has not been established. Further, as one of the goals of Phase 1 and/or 2 clinical trials is to identify the highest dose of treatment that can be safely provided to study participants, adverse side effects, including serious adverse effects, have occurred in certain studies as a result of changes to the dosing regimen during such studies. For instance, patients in our Phase 1/2 study of GTX-102 experienced a serious adverse event of lower extremity weakness believed to be related to local inflammation due to GTX-102 at the highest doses of the product. 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 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. There can be no assurance that our product liability insurance, which provides coverage in the amount of $10.0 million per incident and $10.0 million in the aggregate, will be sufficient in light of our current or planned clinical programs. 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, Mepsevii, and Dojolvi 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, certain gene therapy trials using AAV8 vectors (although at significantly higher doses than those used in our gene therapy product candidates) and other vectors led to several well-publicized adverse events, including cases of leukemia and death. The risk of cancer or death 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 are 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, as described above in "Item 1. Business – Government Regulation".

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 are 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. Regulatory authorities may, at any time, audit or inspect a manufacturing facility involved with the preparation of our products, product candidates or the associated quality systems for compliance with the regulations applicable to the activities being conducted. If we, our collaborators, such as KKC, 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, the temporary or permanent suspension of a clinical study or commercial sales, recalls or seizures of product or the temporary or permanent closure of a facility or withdrawal of product approval. If supply from one approved manufacturer is interrupted due to failure to maintain regulatory compliance, 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 delays in product supply. 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. Accordingly, we and others with whom we work are required 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. 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 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 are developing companion 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 currently use and expect to continue to use biomarkers to identify the right patients for certain of our product candidates. We may also need to develop predictive biomarkers in the future. For example, to evaluate therapeutic response of DTX301, we are measuring ammonia levels and other biomarkers, including ^{13}C-acetate, which are established measures of OTC deficiency disease status and ureagenesis. We offer no assurances that ^{13}C-acetate or any other future potential biomarker will in fact prove predictive, be reliably measured, or be accepted as a measure of efficacy 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 our gene therapy product candidates. 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 successfully develop companion diagnostics, we 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 are currently working with a third party to develop companion diagnostics, however, we have little experience in the development and commercialization of diagnostics and may not ultimately 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 also use third parties for the automation, characterization and validation, of our bioanalytical assays, companion diagnostics and the manufacture of its critical reagents.

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, pursuant to the terms of our collaboration with GeneTx on the development of GeneTx's GTX-102, an antisense oligonucleotide (ASO) for the treatment of Angelman syndrome, subject to certain limited rights we have, GeneTx retains the decision-making authority on all matters in connection with the research, development, manufacturing and regulatory activities with respect to the program. With respect to our collaboration with Arcturus, we rely on our partner Arcturus for the design and optimization of initial product candidates under our mRNA, DNA and siRNA collaborations. 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 we cannot control whether or not they devote sufficient time and resources to our on-going nonclinical and clinical programs, except for the limited remedies available to us under our agreements with such third parties. 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. Our efforts to manage our relationships with our vendors and partners can provide 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 KKC 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 KKC'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 KKC, KKC 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 partnership with KKC 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:

- KKC has no obligation under our agreement to use diligent efforts to commercialize Crysvita in Europe. The timing and amount of any royalty payments that are made by KKC based on sales of Crysvita in Europe will depend on, among other things, the efforts, allocation of resources, and successful commercialization of Crysvita by KKC in Europe.
- the timing and amount of any payments we may receive under our agreement with KKC will depend on, among other things, the efforts, allocation of resources, and successful commercialization of Crysvita by KKC in the United States and Canada under our agreement;
- KKC may change the focus of its commercialization efforts or pursue higher-priority programs;
- KKC 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;
- KKC 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;
- KKC 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 or commercial use (including as a result of the COVID-19 pandemic), which could result in program delays or lost revenue;
- KKC 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 KKC 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;
- KKC 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 KKC may be greater than anticipated.

We have no experience as a company developing a manufacturing facility and may experience unexpected costs or delays or ultimately be unsuccessful in developing a facility.

During the fourth quarter 2020, we completed our purchase of land located in the Town of Bedford, Massachusetts for construction of our gene therapy manufacturing facility and began construction of the base building for the facility. We expect that the new 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 for our gene therapy products. We currently anticipate construction of the facility to be completed in 2023. We do not have experience as a company, however, in developing a manufacturing facility and we may experience unexpected costs or delays or ultimately be unsuccessful in developing the facility or capability. As we expand our commercial footprint to multiple geographies, we may establish multiple manufacturing facilities, 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, program 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, DNA and siRNA 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, mRNA, DNA and siRNA 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. Further, given that cGMP gene therapy, mRNA, DNA and siRNA 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.

Our gene therapy, mRNA, DNA and siRNA 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, mRNA, DNA and siRNA 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 rely on third parties to manufacture our products and our product candidates and we are subject to a multitude of manufacturing risks, any of which could substantially increase our costs and limit the supply of our product and product candidates.

As we currently lack the resources and the capability to manufacture our products and most of our product candidates on a clinical or commercial scale, we rely on third parties to manufacture our products and product candidates. 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. See "-*Even if we obtain regulatory approval for our product candidates, our products will remain subject to regulatory scrutiny"* risk factor above. Further, we depend on our manufacturers to purchase from third-party suppliers the materials necessary to produce our products and product candidates. 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 also do not have any control over the process or timing of the acquisition of these raw materials by our manufacturers. We may also experience interruptions in supply of product if the product or raw material components fail to meet our quality control standards or the quality control standards of our suppliers.

Further, manufacturers that produce our products and product candidates may not have experience producing our products and product candidates at commercial levels and may not produce our products and product candidates at the cost, quality, quantities, locations, and timing needed to support profitable commercialization. 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 acceptable manufacturing processes that provide the necessary quantities of our products and product candidates in a compliant and timely manner, 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. For instance, KKC is our sole supplier of commercial quantities of Crysvita. The supply price to us for commercial sales of Crysvita in Latin America and the transfer price for commercial sales of the product in the United States and Canada is 35% of net sales through December 31, 2022 and 30% thereafter, which is higher than the typical cost of goods sold by companies focused on rare diseases.

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.
- 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. For instance, during the fourth quarter of 2019, we experienced disruptions from our third-party supplier related to the fill and finish activities for the manufacture of Mepsevii, which negatively impacted our inventory of the product. 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. If any single source supplier breaches an agreement with us, or terminates the agreement in response to an alleged breach by us or otherwise becomes unable to fulfill its supply obligations, we would not be able to manufacture and distribute the product or product candidate until a qualified alternative supplier is identified, which could significantly impair our ability to commercialize such product or delay the development of such product candidate. The drug substance and drug product for Crysvita are made by KKC pursuant to our license and collaboration agreement with KKC. The drug substance and drug product for Mepsevii are manufactured by Rentschler under a commercial supply and services agreement, accompanying purchase orders, and other agreements. The pharmaceutical-grade drug substance for Dojolvi is manufactured by IOI Oleo pursuant to our supply agreement with IOI Oleo, and the drug product for Dojolvi is prepared by Haupt Pharma AG and CPM ContractPharma GmbH & Co. pursuant to a services agreement and accompanying 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 expense or delay in the commercialization of our products or the development of our product candidates. For instance, we experienced disruptions from our third-party supplier related to the fill and finish activities for the manufacture of Mepsevii during the fourth quarter of 2019 and as a result, we have identified an alternative supplier to conduct such activities. It may take a significant amount of time and expense to qualify such alternative supplier and to transfer activities to such supplier, which are currently ongoing. If we fail to qualify our alternative supplier in a timely manner, we could experience delays or disruptions in the supply of Mepsevii, which would negatively impact sales of the product. Additionally, we may not be able to enter into supply arrangements with our alternative supplier on commercially reasonable terms or at all. The terms of any new agreement, such as any agreement with our alternative supplier for Mepsevii, may also be less favorable or more costly than the terms we have with our current supplier. 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.

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

We rely on commercial distributors and specialty pharmacies for a considerable portion of our product sales and such sales are concentrated within a small number of distributors and specialty pharmacies. The financial failure of any of these parties 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 buying or distribution patterns of such distributors and specialty pharmacies. 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, 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.

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. See "Item 1. Business – Competition" above.

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 may not be able to effectively manage the expansion of our organization, including building 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 products and product candidates, as needed, we may be unable to increase our revenue.

We expect we will need additional managerial, operational, marketing, financial, legal, and other resources to support our development and commercialization plans and strategies. In order to successfully commercialize our products as well as any additional products that may result from our development programs, we are building and expanding our 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. Our management may need to divert a disproportionate amount of its attention away from our day-to-day activities and devote a substantial amount of time to managing these growth activities. We may not be able to effectively manage the expansion of our operations, which may result in weaknesses in our infrastructure, operational mistakes, loss of business opportunities, loss of employees, and reduced productivity among remaining employees. Our expected growth could require significant capital expenditures and may divert financial resources from other projects, such as the development of additional product candidates. If our management is unable to effectively manage our growth, our expenses may increase more than expected, our ability to generate and/or grow revenue could be reduced, and we may not be able to implement our business strategy. Our future financial performance and our ability to commercialize product candidates and compete effectively will depend, in part, on our ability to effectively manage any future growth.

We, as a company, have limited, recent experience selling and marketing our product and only some of our employees have prior experience promoting other similar products in the past while employed at other companies. As we launch additional products or as demand for our products change, 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 products and product candidates or we may incur excess costs in an effort to optimize the hiring of commercial personnel. 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.

Our exclusive right to promote Crysvita in the United States and Canada expires in 2023.

Pursuant to the terms of our collaboration and license agreement with KKC, we have the sole right to promote Crysvita in the United States and Canada, or the profit-share territory, for a specified period of time, with KKC increasingly participating in the promotion of the product until the transition date of April 2023, which is the fifth anniversary of the commercial launch of the product in the United States. After the transition date, KKC will have the right to promote the product, subject to a limited promotion right retained by us. We cannot assure that we will have adequate commercial activity to support our North America field force and other aspects of our commercial infrastructure in the territory after the transition date. After the transition date, we will also solely bear the expenses related to the promotion of Crysvita in the profit-share territory pursuant to our limited promotion right, rather than share such expenses with KKC. Collaboration with KKC may not result in a seamless transition of responsibilities for KKC to promote the product in the profit-share territory after the transition date and the commercial success of Crysvita in the profit-share territory after the transition date will depend on, among other things, the efforts and allocation of resources of KKC.

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 to educate the medical community and payors on the benefits of the product candidates require significant resources and may never be successful. If our current and future products fail to achieve an adequate level of acceptance by physicians, patients, payors, and others in the medical community, we will not be able to generate sufficient revenue to become or remain profitable.

The insurance coverage and reimbursement status of newly approved products is uncertain. Failure to obtain or maintain adequate coverage and reimbursement for new or current products could limit our ability to market those products and decrease our ability to generate revenue.

Our target patient populations are small, and accordingly the pricing, coverage, and reimbursement of our products and product candidates, if approved, must be adequate to support our commercial infrastructure. Our per-patient prices must be sufficient to recover our development and manufacturing costs and potentially achieve profitability. We expect the cost of a single administration of gene therapy products, such as those we are developing, to be substantial, when and if they achieve regulatory approval. Accordingly, the availability and adequacy of coverage and reimbursement by governmental and private payors are essential for most patients to afford expensive treatments such as ours, assuming approval. Sales of our products and product candidates, if approved, will depend substantially, both domestically and abroad, on the extent to which their costs will be paid for by health maintenance, managed care, pharmacy benefit, and similar healthcare management organizations, or reimbursed by government authorities, private health insurers, and other payors. If coverage and reimbursement are not available, are available only to limited levels, or are not available on a timely basis, we may not be able to successfully commercialize our products and product candidates, if approved. For example, deteriorating economic conditions and political instability in certain Latin American countries and in Turkey may cause us to experience significant delays in receiving approval for reimbursement for our products and consequently impact our product commercialization timelines in such regions. Even if coverage is provided, the approved reimbursement amount may not be high enough to allow us to establish or maintain pricing sufficient to sustain our overall enterprise.

There is significant uncertainty related to the insurance coverage and reimbursement of newly approved products. In the United States, the Centers for Medicare & Medicaid Services, or CMS, an agency within the U.S. Department of Health and Human Services, decides whether and to what extent a new drug will be covered and reimbursed under Medicare. Private payors tend to follow the coverage reimbursement policies established by CMS to a substantial degree. It is difficult to predict what CMS or private payors will decide with respect to reimbursement for products such as ours, especially our gene therapy product candidates as there is a limited body of established practices and precedents for gene therapy products.

Outside the United States, international operations are generally subject to extensive governmental price controls and other market regulations, and we believe the increasing emphasis on cost-containment initiatives in Europe, Canada, and other countries will put pressure on the pricing and usage of our products and product candidates. In many countries, the prices of medical products are subject to varying price control mechanisms as part of national health systems. Other countries allow companies to fix their own prices for medicinal products, but monitor and control company profits. Additional foreign price controls or other changes in pricing regulation could restrict the amount that we are able to charge for our product candidates. Accordingly, in markets outside the United States, the reimbursement for our products may be reduced compared with the United States and may be insufficient to generate commercially reasonable revenue and profits.

Moreover, increasing efforts by governmental and third-party payors in the United States and abroad to cap or reduce healthcare costs may cause such organizations to limit both coverage and the level of reimbursement for new products and, as a result, they may not cover or provide adequate payment for our products and product candidates. We expect to experience pricing pressures in connection with the sale of any of our products and product candidates due to the trend toward managed healthcare, the increasing influence of health maintenance organizations, additional legislative changes, and statements by elected officials. For example, proposals have been discussed to tie U.S. drug prices to the cost in other countries, several states in the U.S. have introduced legislation to require pharmaceutical companies to disclose their costs to justify the prices of their products, and an “Affordable Drug Pricing Task-Force” has been formed in the U.S. House of Representatives with the goal of combating the increased costs of prescription drugs. Drug pricing is also expected to remain a focus for the new Presidential Administration and Congress. The downward pressure on healthcare costs in general, and with respect to prescription drugs, surgical procedures, and other treatments in particular, has become very intense. As a result, increasingly high barriers are being erected to the entry of new products.

The United Kingdom's withdrawal from the EU may have a negative effect on our business, global economic conditions, and financial markets.

On January 30, 2020, the United Kingdom formally withdrew from the EU, commonly referred to as Brexit, and the United Kingdom and EU subsequently entered into a trading agreement effective January 1, 2021. In anticipation of Brexit, we had previously adjusted our product inventory and storage plans and as such, our business and operations to date have not been materially or adversely impacted by Brexit. However, the full effects of Brexit and the impact from the trade agreement and other formal agreements between the United Kingdom and EU that may impact the regulatory framework and supply chain in Europe remain uncertain. For instance, we expect that Brexit could lead to additional processes and steps with respect to certain regulatory applications and activities, which may impact the timing of approvals or result in additional costs. Further, if the United Kingdom were to significantly alter its regulations affecting the biotechnology or pharmaceutical industries, we could face significant additional costs. It may also be time-consuming and expensive for us to alter our internal operations in order to comply with new regulations. Any of these factors could have a material adverse effect on our business, financial condition and results of operations and affect our strategy in the U.K. and EU biotech market.

Risks Related to Our Intellectual Property

If we are unable to obtain and maintain effective patent rights for our products, product candidates, or any future product candidates, we may not be able to compete effectively in our markets.

We rely upon a combination of patents, trade secret protection, and confidentiality agreements to protect the intellectual property related to our technologies, our products, and our product candidates. Our success depends in large part on our and our licensors' ability to obtain and maintain patent and other intellectual property protection in the United States and in other countries with respect to our proprietary technologies, our products, and our product candidates.

We have sought to protect our proprietary position by filing patent applications in the United States and abroad related to our novel technologies, products and product candidates that are important to our business. This process is expensive and time consuming, and we may not be able to file and prosecute all necessary or desirable patent applications at a reasonable cost or in a timely manner. It is also possible that we will fail to identify patentable aspects of our research and development output before it is too late to obtain patent protection.

The patent position of biotechnology and pharmaceutical companies generally is highly uncertain and involves complex legal and factual questions for which legal principles remain unsolved. The patent applications that we own or in-license may fail to result in issued patents with claims that cover our products or product candidates in the United States or in other foreign countries. There is no assurance that all potentially relevant prior art relating to our patents and patent applications has been found, which can invalidate a patent or prevent a patent from issuing from a pending patent application. Even if patents do successfully issue, and even if such patents cover our products or product candidates, third parties may challenge their validity, enforceability, or scope, which may result in such patents being narrowed, found unenforceable, or invalidated. Furthermore, even if the patents and patent applications we own or in-license are unchallenged, they may not adequately protect our intellectual property, provide exclusivity for our products or product candidates, or prevent others from designing around our claims. Any of these outcomes could impair our ability to prevent competition from third parties, which may have an adverse impact on our business.

We, independently or together with our licensors, have filed several patent applications covering various aspects of our products or product candidates. We cannot offer any assurances about which, if any, patents will issue, the breadth of any such patent or whether any issued patents will be found invalid and unenforceable or will be threatened by third parties. Any successful opposition to these patents could impair the exclusivity position of our products or deprive us of rights necessary for the successful commercialization of any product candidates that are approved. Further, if we encounter delays in regulatory approvals, the period of time during which we could market a product candidate under patent protection could be reduced.

Our current patents or applications covering methods of use and certain compositions of matter do not provide complete patent protection for our products and product candidates in all territories. For example, there are no issued patents covering the Crysvita composition of matter in Latin America where we have rights to commercialize the compound. Therefore, a competitor could develop the same antibody or a similar antibody as well as other approaches that target FGF23 for potential commercialization in Latin America, subject to any intellectual property rights or regulatory exclusivities awarded to us. If we cannot obtain and maintain effective patent rights for our products or product candidates, we may not be able to compete effectively and our business and results of operations would be harmed.

We may not have sufficient patent terms to effectively protect our products and business.

Patents have a limited lifespan. In the United States, the natural expiration of a patent is generally 20 years after its effective filing date. Although various extensions may be available, the life of a patent, and the protection it affords, is limited. Even if patents covering our product candidates are obtained, once the patent life has expired for a product, we may be open to competition from generic or biosimilar medications.

Patent term extensions under the Hatch-Waxman Act in the United States and under supplementary protection certificates in Europe may not be available to extend the patent exclusivity term for our products and product candidates, and we cannot provide any assurances that any such patent term extension will be obtained and, if so, for how long. Furthermore, we may not receive an extension if we fail to apply within applicable deadlines, fail to apply prior to expiration of relevant patents or otherwise fail to satisfy applicable requirements. Moreover, the length of the extension could be less than we request. If we do not have sufficient patent terms or regulatory exclusivity to protect our products, our business and results of operations may be adversely affected.

Patent policy and rule changes could increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our issued patents.

Changes in either the patent laws or interpretation of the patent laws in the United States and other countries may diminish the value of our patents or narrow the scope of our patent protection. The laws of foreign countries may not protect our rights to the same extent as the laws of the United States. Publications of discoveries in the scientific literature often lag behind the actual discoveries, and patent applications in the United States and other jurisdictions are typically not published until 18 months after filing, or in some cases not at all. We therefore cannot be certain that we or our licensors were the first to make the invention claimed in our owned and in-licensed patents or pending applications, or that we or our licensor were the first to file for patent protection of such inventions.

In 2011, the Leahy-Smith America Invents Act (the Leahy-Smith Act) was signed into law and introduced significant changes to the prosecution of U.S. patent applications and to the procedures for challenging U.S. patents. The effects of these changes still remain unclear owing to the evolving nature of the law and the lengthy timelines associated with court system review and interpretation. However, the Leahy-Smith Act and its implementation could increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our issued patents, all of which could have a material adverse effect on our business and financial condition.

If we are unable to maintain effective proprietary rights for our products, product candidates, or any future product candidates, we may not be able to compete effectively in our markets.

In addition to the protection afforded by patents, we rely on trade secret protection and confidentiality agreements to protect proprietary know-how that is not patentable or that we elect not to patent, processes for which patents are difficult to enforce and any other elements of our products or product candidate discovery and development processes that involve proprietary know-how, information, or technology that is not covered by patents. However, trade secrets can be difficult to protect. The confidentiality agreements entered into with our employees, consultants, scientific advisors, and contractors may not be sufficient to protect our proprietary technology and processes. The physical security of our premises and physical and electronic security of our information technology systems may not preserve the integrity and confidentiality of our data and trade secrets. These individuals, organizations and systems, agreements or security measures may be breached, and we may not have adequate remedies for any breach. In addition, our trade secrets may otherwise become known or be independently discovered by competitors.

The assignment agreements we enter into with our employees and consultants to assign their inventions to us, and the confidentiality agreements we enter into with our employees, consultants, advisors, and any third parties who have access to our proprietary know-how, information, or technology may not have been duly executed and we cannot assure that our trade secrets and other confidential proprietary information will not be disclosed or that competitors will not otherwise gain access to our trade secrets or independently develop substantially equivalent information and techniques. Misappropriation or unauthorized disclosure of our trade secrets could impair our competitive position and may have a material adverse effect on our business. Additionally, if the steps taken to maintain our trade secrets are deemed inadequate, we may have insufficient recourse against third parties for misappropriating the trade secret.

Claims of intellectual property infringement may prevent or delay our development and commercialization efforts.

Our commercial success depends in part on our avoiding infringement of the patents and proprietary rights of others. There have been many lawsuits and other proceedings involving patent and other intellectual property rights in the biotechnology and pharmaceutical industries, including patent infringement lawsuits, interferences, *inter partes* reviews, post grant reviews, oppositions, and reexamination proceedings before the USPTO and corresponding foreign patent offices. Numerous U.S. and foreign issued patents and pending patent applications, which are owned by other parties, exist in the fields in which we are developing product candidates. As the biotechnology and pharmaceutical industries expand and more patents are issued, the risk increases that our products or product candidates may be subject to claims of infringement of the patent rights of these other parties.

Other parties may assert that we are employing their proprietary technology without authorization. There may be patents or patent applications with claims to materials, formulations, methods of manufacture, or methods for treatment related to the use or manufacture of our products or product candidates. We have conducted freedom to operate analyses with respect only to our products and certain of our product candidates, and therefore we do not know whether there are any patents of other parties that would impair our ability to commercialize all of our product candidates. We also cannot guarantee that any of our analyses are complete and thorough, nor can we be sure that we have identified each and every patent and pending application in the United States and abroad that is relevant or necessary to the commercialization of our products or product candidates. Because patent applications can take many years to issue, there may be currently pending patent applications that may later result in issued patents that our products or product candidates may infringe.

We are aware of certain U.S. and foreign patents owned by third parties that a court might construe to be relevant to one or more of our gene therapy product candidates, certain methods that may be used in their manufacture, or certain formulations comprising one or more of our gene therapy candidates. We are also aware of certain U.S. and foreign patents owned by third parties that relate to anti-sclerostin antibodies and their use, and which a court might construe to be relevant to setrusumab. There is a risk that one or more of these third parties may choose to engage in litigation with us to enforce or to otherwise assert their patent rights against us. Even if we believe such claims are without merit, a court of competent jurisdiction could hold that one or more of these patents is valid, enforceable, and infringed, in which case the owners of any such patents may be able to block our ability to commercialize a product candidate unless we obtained a license under the applicable patents, or until such patents expire. However, such a license may not be available on commercially reasonable terms or at all.

Parties making claims against us may obtain injunctive or other equitable relief, which could effectively block our ability to continue commercialization of our products, or block our ability to develop and commercialize one or more of our product candidates. Defense of these claims, regardless of their merit, would involve substantial litigation expense and would be a substantial diversion of employee resources from our business. In the event of a successful claim of infringement against us, we may have to pay substantial damages, including treble damages and attorneys' fees for willful infringement, pay royalties, redesign our infringing products, or obtain one or more licenses from third parties, which may be impossible or require substantial time and monetary expenditure.

We may not be successful in obtaining or maintaining necessary rights to our product candidates through acquisitions and in-licenses.

We currently have rights to the intellectual property, through licenses from third parties and under patents that we own, to commercialize our product candidates. Because our programs may require the use of proprietary rights held by third parties, the growth of our business will likely depend in part on our ability to acquire, in-license, or use these proprietary rights. For example, our product candidates may require specific formulations to work effectively and efficiently and the rights to these formulations may be held by others. We may be unable to acquire or in-license any compositions, methods of use, processes, or other third-party intellectual property rights from third parties that we identify as necessary for our product candidates. The licensing and acquisition of third-party intellectual property rights is a competitive area, and a number of more established companies are also pursuing strategies to license or acquire third-party intellectual property rights that we may consider attractive. These established companies may have a competitive advantage over us due to their size, cash resources, and greater clinical development and commercialization capabilities. In addition, companies that perceive us to be a competitor may be unwilling to assign or license rights to us. We also may be unable to license or acquire third-party intellectual property rights on terms that would allow us to make an appropriate return on our investment.

We sometimes collaborate with U.S. and foreign academic institutions to accelerate our preclinical research or development under written agreements with these institutions. Typically, these institutions provide us an option to negotiate a license to any of the institution's rights in technology resulting from the collaboration. Regardless of such option, we may be unable to negotiate a license within the specified timeframe or under terms that are acceptable to us. If we are unable to do so, the institution may offer the intellectual property rights to other parties, potentially blocking our ability to pursue our program.

If we are unable to successfully obtain rights to required third-party intellectual property rights or maintain the existing intellectual property rights we have, we may have to abandon development of that program and our business and financial condition could suffer.

We may face competition from biosimilars, which may have a material adverse impact on the future commercial prospects of our biological products and product candidates.

Even if we are successful in achieving regulatory approval to commercialize a product candidate faster than our competitors, we may face competition from biosimilars with respect to our biological products (Crysvita and Mepsevii) and our biological product candidates. In the United States, the Biologics Price Competition and Innovation Act of 2009, or BPCI Act, was included in the Affordable Care Act and created an abbreviated approval pathway for biological products that are demonstrated to be "highly similar," or biosimilar, to or "interchangeable" with an FDA-approved biological product. The BPCI Act prohibits the FDA from approving a biosimilar or interchangeable product that references a brand biological product until 12 years after the licensure of the reference product, but permits submission of an application for a biosimilar or interchangeable product to the FDA four years after the reference product was first licensed. The BPCI Act does not prevent another company from developing a product that is highly similar to the innovative product, generating its own data, and seeking approval. Moreover, it is not known whether the BPCI Act will survive in whole or in part if the Affordable Care Act is repealed by Congress or held unconstitutional by courts. As a result, its ultimate impact, implementation, meaning, and long-term existence are subject to uncertainty. Elimination or modification of the BPCI Act, or changes to the FDA's interpretation or implementation of the BPCI Act, could have a material adverse effect on the future commercial prospects for our biological products and product candidates.

In Europe, the European Commission has granted marketing authorizations for several biosimilars pursuant to a set of general and product class-specific guidelines for biosimilar approvals issued over the past few years. In Europe, a competitor may reference data supporting approval of an innovative biological product, but will not be able to get on the market until 10 years after the time of approval of the innovative product. This 10-year marketing exclusivity period will be extended to 11 years if, during the first eight of those 10 years, the marketing authorization holder obtains an approval for one or more new therapeutic indications that bring significant clinical benefits compared with existing therapies. In addition, companies may be developing biosimilars in other countries that could compete with our products.

If competitors are able to obtain marketing approval for biosimilars referencing our products, our products may become subject to competition from such biosimilars, with the attendant competitive pressure and consequences.

Competitors could enter the market with generic versions of Dojolvi or our small-molecule product candidates, which may result in a material decline in sales of affected products.

Under the Hatch-Waxman Act, a pharmaceutical manufacturer may file an abbreviated new drug application, or ANDA, seeking approval of a generic copy of an approved innovator product. Under the Hatch-Waxman Act, a manufacturer may also submit an NDA under section 505(b)(2) that references the FDA's finding of safety and effectiveness of a previously approved drug. A 505(b)(2) NDA product may be for a new or improved version of the original innovator product. Innovative small molecule drugs may be eligible for certain periods of regulatory exclusivity (*e.g.*, five years for new chemical entities, three years for changes to an approved drug requiring a new clinical study, and seven years for orphan drugs), which preclude FDA approval (or in some circumstances, FDA filing and review of) an ANDA or 505(b)(2) NDA relying on the FDA's finding of safety and effectiveness for the innovative drug. In addition to the benefits of regulatory exclusivity, an innovator NDA holder may have patents claiming the active ingredient, product formulation or an approved use of the drug, which would be listed with the product in the "Orange Book." If there are patents listed in the Orange Book, a generic applicant that seeks to market its product before expiration of the patents must include in the ANDA or 505(b)(2) what is known as a "Paragraph IV certification," challenging the validity or enforceability of, or claiming non-infringement of, the listed patent or patents. Notice of the certification must be given to the innovator, too, and if within 45 days of receiving notice the innovator sues to enforce its patents, approval of the ANDA is stayed for 30 months, or as lengthened or shortened by the court.

Accordingly, competitors could file ANDAs for generic versions of our small-molecule product, Dojolvi, or 505(b)(2) NDAs that reference Dojolvi. For the patents listed for Dojolvi in the Orange Book, those ANDAs and 505(b)(2) NDAs would be required to include a certification as to each listed patent indicating whether the ANDA applicant does or does not intend to challenge the patent. We cannot predict how any generic competitor would address such patents, whether we would sue on any such patents, or the outcome of any such suit.

We may not be successful in securing or maintaining proprietary patent protection for products and technologies we develop or license. Moreover, if any patents that are granted and listed in the Orange Book are successfully challenged by way of a Paragraph IV certification and subsequent litigation, the affected product could more immediately face generic competition and its sales would likely decline materially. Should sales decline, we may have to write off a portion or all of the intangible assets associated with the affected product and our results of operations and cash flows could be materially and adversely affected.

The patent protection and patent prosecution for some of our products and product candidates is dependent on third parties.

While we normally seek and gain the right to fully prosecute the patents relating to our products or product candidates, there may be times when patents relating to our products or product candidates are controlled by our licensors. This is the case with our agreement with KKC, who is primarily responsible for the prosecution of certain patents and patent applications covering Crysvita which are licensed to us under the collaboration agreement.

In addition, we have in-licensed patents and patent applications owned by the University of Pennsylvania, relating to the AAV8 vector used in DTX301 and DTX401. These patents and patent applications are licensed or sublicensed by REGENXBIO and sublicensed to us. We do not have the right to control the prosecution of these patent applications, or the maintenance of any of these patents. In addition, under our agreement with REGENXBIO, we do not have the first right to enforce the licensed patents, and our enforcement rights are subject to certain limitations that may adversely impact our ability to use the licensed patents to exclude others from commercializing competitive products. Moreover, REGENXBIO and the University of Pennsylvania may have interests which differ from ours in determining whether and the manner in which to enforce such patents.

If KKC, the University of Pennsylvania, or any of our future licensing partners fail to appropriately prosecute, maintain, and enforce patent protection for the patents covering any of our products or product candidates, our ability to develop and commercialize those products or product candidates may be adversely affected and we may not be able to prevent competitors from making, using, and selling competing products. In addition, even where we now have the right to control patent prosecution of patents and patent applications we have licensed from third parties, we may still be adversely affected or prejudiced by actions or inactions of our licensors and their counsel that took place prior to us assuming control over patent prosecution.

If we fail to comply with our obligations in the agreements under which we license intellectual property and other rights from third parties or otherwise experience disruptions to our business relationships with our licensors, we could lose license rights that are important to our business.

We are a party to a number of intellectual property license agreements that are important to our business and expect to enter into additional license agreements in the future. Our existing license agreements impose, and we expect that future license agreements will impose, various diligence, milestone payment, royalty, and other obligations on us. If we fail to comply with our obligations under these agreements, or we are subject to a bankruptcy, we may be required to make certain payments to the licensor, we may lose the exclusivity of our license, or the licensor may have the right to terminate the license, in which event we would not be able to develop or market products covered by the license. Additionally, the milestone and other payments associated with these licenses will make it less profitable for us to develop our product candidates.

In certain cases, we control the prosecution of patents resulting from licensed technology. In the event we breach any of our obligations related to such prosecution, we may incur significant liability to our licensing partners. Licensing of intellectual property is of critical importance to our business and involves complex legal, business, and scientific issues. Disputes may arise regarding intellectual property subject to a licensing agreement, including but not limited to:

- the scope of rights granted under the license agreement and other interpretation-related issues;
- the extent to which our technology and processes infringe on intellectual property of the licensor that is not subject to the licensing agreement;
- the sublicensing of patent and other rights;
- our diligence obligations under the license agreement and what activities satisfy those diligence obligations;
- the ownership of inventions and know-how resulting from the joint creation or use of intellectual property by our licensors and us and our collaborators; and
- the priority of invention of patented technology.

If disputes over intellectual property and other rights that we have licensed prevent or impair our ability to maintain our current licensing arrangements on acceptable terms, we may be unable to successfully develop and commercialize the affected product candidates.

We may become involved in lawsuits to protect or enforce our patents or the patents of our licensors, or be subject to claims that challenge the inventorship or ownership of our patents or other intellectual property, which could be expensive, time consuming, and result in unfavorable outcomes.

Competitors may infringe our patents or the patents of our licensors. If we or one of our licensing partners were to initiate legal proceedings against a third party to enforce a patent covering our products or one of our product candidates, the defendant could counterclaim that the patent covering our product or product candidate is invalid and/or unenforceable. In patent litigation in the United States, defendant counterclaims alleging invalidity and/or unenforceability are commonplace. Grounds for a validity challenge could be an alleged failure to meet any of several statutory requirements, including lack of novelty, obviousness, or non-enablement. Grounds for an unenforceability assertion could be an allegation that someone connected with prosecution of the patent withheld relevant information from the USPTO, or made a misleading statement, during prosecution. The outcome following legal assertions of invalidity and unenforceability is unpredictable.

Interference proceedings or derivation proceedings now available under the Leahy-Smith Act provoked by third parties or brought by us or declared or instituted by the USPTO may be necessary to determine the priority of inventions with respect to our patents or patent applications or those of our licensors. An unfavorable outcome could require us to cease using the related technology or to attempt to license rights to it from the prevailing party. Our business could be harmed if the prevailing party does not offer us a license on commercially reasonable terms. In addition, the validity of our patents could be challenged in the USPTO by one of the new post grant proceedings (*i.e., inter partes* review or post grant review) now available under the Leahy-Smith Act. Our defense of litigation, interference proceedings, or post grant proceedings under the Leahy-Smith Act may fail and, even if successful, may result in substantial costs and distract our management and other employees.

We may in the future also be subject to claims that former employees, collaborators, or other third parties have an interest in our patents as an inventor or co-inventor. In addition, we may have ownership disputes arise from conflicting obligations of consultants or others who are involved in developing our product candidates. Litigation may be necessary to defend against these and other claims challenging inventorship or ownership. If we fail to successfully defend against such litigation or claims, in addition to paying monetary damages, we may lose valuable intellectual property rights, such as exclusive ownership of, or right to use, valuable intellectual property.

Even if we are successful in defending against such litigation and claims, such proceedings could result in substantial costs and distract our management and other employees. Because of the substantial amount of discovery required in connection with intellectual property litigation, there is a risk that some of our confidential information could be compromised by disclosure during litigation. There could also be public announcements of the results of hearings, motions, or other interim proceedings or developments related to such litigation or claims. If securities analysts or investors perceive these results to be negative, it could have a material adverse effect on the price of our common stock.

We may be subject to claims that our employees, consultants, or independent contractors have wrongfully used or disclosed confidential information of third parties or that our employees have wrongfully used or disclosed alleged trade secrets of their former employers.

We employ certain individuals who were previously employed at universities or other biotechnology or pharmaceutical companies, including our competitors or potential competitors. Our efforts to vet our employees, consultants, and independent contractors and prevent their use of the proprietary information or know-how of others in their work for us may not be successful, and we may in the future be subject to claims that our employees, consultants, or independent contractors have wrongfully used or disclosed confidential information of third parties. If we fail in defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights or personnel, which could adversely impact our business. Even if we are successful in defending against such claims, litigation could result in substantial costs and distract management and other employees.

Changes in U.S. patent law could diminish the value of patents in general, thereby impairing our ability to protect our products.

As is the case with other biotechnology and pharmaceutical companies, our success is heavily dependent on intellectual property, particularly patents. Obtaining and enforcing patents in the biotechnology and pharmaceutical industries involves both technological and legal complexity. Therefore, obtaining and enforcing such patents is costly, time consuming, and inherently uncertain. In addition, the United States has recently enacted and is currently implementing wide-ranging patent reform legislation. Recent U.S. Supreme Court rulings have narrowed the scope of patent protection available in certain circumstances and weakened the rights of patent owners in certain situations. For example, in *Association for Molecular Pathology v. Myriad Genetics, Inc.*, the Supreme Court ruled that a "naturally occurring DNA segment is a product of nature and not patent eligible merely because it has been isolated," invalidating Myriad Genetics' patents on the BRCA1 and BRCA2 genes. Certain claims of our licensed U.S. patents covering DTX301 and DTX401 relate to isolated AAV8 vectors, capsid proteins, or nucleic acids. To the extent that such claims are deemed to be directed to natural products, or to lack an inventive concept above and beyond an isolated natural product, a court may decide the claims are invalid under *Myriad*. Additionally, there have been recent proposals for additional changes to the patent laws of the United States and other countries that, if adopted, could impact our ability to obtain patent protection for our proprietary technology or our ability to enforce our proprietary technology. Depending on future actions by the U.S. Congress, the U.S. courts, the USPTO and the relevant law-making bodies in other countries, the laws and regulations governing patents could change in unpredictable ways that would weaken our ability to obtain new patents or to enforce our existing patents and patents that we might obtain in the future.

We may not be able to protect our intellectual property rights throughout the world.

Filing, prosecuting, and defending patents on our products or product candidates in all countries throughout the world would be prohibitively expensive, and our intellectual property rights in some countries outside the United States can be less extensive than those in the United States. In addition, the laws of some foreign countries do not protect intellectual property rights to the same extent as federal and state laws in the United States. Further, licensing partners such as KKC may not prosecute patents in certain jurisdictions in which we may obtain commercial rights, thereby precluding the possibility of later obtaining patent protection in these countries. Consequently, we may not be able to prevent third parties from practicing our inventions in all countries outside the United States, or from selling or importing products made using our inventions in and into the United States or other jurisdictions. Competitors may use our technologies in jurisdictions where we have not obtained patent protection to develop their own products and may also export infringing products to territories where we have patent protection, but enforcement is not as strong as that in the United States. These products may compete with our products, and our patents or other intellectual property rights may not be effective or sufficient to prevent them from competing.

Many companies have encountered significant problems in protecting and defending intellectual property rights in foreign jurisdictions. The legal systems of certain countries, particularly certain developing countries, do not favor the enforcement of patents, trade secrets, and other intellectual property protection, particularly those relating to biotechnology products, which could make it difficult for us to stop the infringement of our patents or marketing of competing products in violation of our proprietary rights generally. Proceedings to enforce our patent rights in foreign jurisdictions, whether or not successful, could result in substantial costs and divert our efforts and attention from other aspects of our business, could put our patents at risk of being invalidated or interpreted narrowly, could put our patent applications at risk of not issuing, and could provoke third parties to assert claims against us. We may not prevail in any lawsuits that we initiate and the damages or other remedies awarded, if any, may not be commercially meaningful. Accordingly, our efforts to enforce our intellectual property rights around the world may be inadequate to obtain a significant commercial advantage from the intellectual property that we develop or license.

Risks Related to Our Business Operations

Actual or threatened public health epidemics or outbreaks, including the ongoing COVID-19 pandemic, could materially and adversely impact our business and operating results.

A public health epidemic or outbreak, and the public and governmental efforts to mitigate the spread of such disease, could materially and adversely impact the commercialization of our products, development and regulatory approval of our product candidates and our clinical trial operations and significantly disrupt our business operations as well as those of our third party suppliers, CRO and collaboration partners that we rely on. In December 2019, a new strain of novel coronavirus (COVID-19) emerged in Wuhan, Hubei Province, China. In March 2020, the World Health Organization declared COVID-19 a pandemic.

Our clinical trial activities, including the initiation and completion of such activities and the timing thereof, have been and are expected to continue to be significantly delayed or disrupted by COVID-19. For instance, enrollment of patients in certain of our clinical trials for our gene therapy product candidates have been disrupted and dosing was delayed in one of our trials. Changes in local regulations in response to COVID-19 have also required us to change the way our clinical trials are conducted and certain data from our clinical trials were delayed as a result. Further, healthcare resources have been and may continue to be diverted away from the conduct of clinical trials, such as the diversion of hospitals serving as our clinical trial sites, in response to the COVID-19 pandemic. We have also had difficulties in recruiting clinical site investigators and clinical staff for our studies, and may continue to experience such difficulties. Any of these events, including if we are required to initiate new or additional sites in response to such events, could require us to incur substantial increased expenses, delay the development and commercialization of our product candidates, delay the timing of anticipated data releases, and impact our operating results.

The COVID-19 pandemic has also impacted the timing of review of our submissions. The FDA has delayed certain key meetings or discussions with us related to one of our product candidates, which may adversely impact the progression of our clinical study for such product candidate. The pandemic has also significantly impacted our commercialization efforts for our products. Social distancing measures and travel limitations have prevented our field sales and medical teams from meeting with health care professionals, customers and patients in person and it has become increasingly difficult to maintain consistent contact with our current patients or identify new patients for our commercialized products and product candidates. Further, certain of our patients may experience interruptions in insurance coverage due to job loss or change in employment status due to the economic impact from the pandemic, which would limit patient access to our products. Effects from government budgetary constraints, either in the United States or internationally, due to the economic impact of the pandemic, such as changes to state coverage rules under Medicaid programs in the United States, could also impact continued insurance coverage and reimbursement for our products. Any of these events could impact our ability to commercialize our products and adversely affect our operating results and revenue.

The continuing spread of the COVID-19 pandemic has caused delays in delivery of ancillary clinical trial materials to us and may also impact the ability of our other suppliers to deliver drug product or raw materials on a timely basis, if at all, or result in increased costs or expenses. Facility shutdowns or operational restrictions imposed by government-imposed mandates could result in supply disruptions that could impact the availability of drug product for our clinical trials as well as our commercialized products. For instance, certain of our third party manufacturers or suppliers have prioritized and allocated more resources and capacity to supply materials to other companies engaged in the study of potential treatments or vaccinations for COVID-19, which has resulted in delays or shortages in supply of such materials to us. Any of these events could adversely impact our clinical trial activities and our ability to meet commercial demand for our product and product candidates and result in loss of revenue. In response to these events, we are currently seeking alternative sources of supply of drug product or raw materials in an attempt to avoid future potential delays in supply of product, which may result in additional expenses.

In an effort to protect the health of our employees, their families and our communities, and in accordance with shelter-in-place direction from state and local government authorities, we have restricted access to our facilities to personnel and third parties who must perform critical activities that must be completed on-site, limited the number of such personnel that can be present at our facilities at any one time, and requested that most of our personnel work remotely, including significant limitations on access to our laboratory space. The effects of the shelter-in-place and our remote working policies may negatively impact productivity and disrupt our business operations. Further, notwithstanding these measures, the COVID-19 pandemic could affect the health and availability of our workforce, including members of our management. If members of our management and other key personnel in critical functions across our organization are unable to perform their duties or have limited availability due to illness from COVID-19, we may not be able to execute on our business strategy and/or our operations may be negatively impacted. Further, the safety protocols we may implement may not prevent employees from contracting COVID-19 at the workplace if and when we ease restrictions to our facilities and our employees return to work on-site. The magnitude of the adverse effect on our business operations will depend, in part, on the length and severity of the restrictions and other limitations on our ability to conduct our business in the ordinary course.

The COVID-19 pandemic has negatively impacted the global economy, disrupted global supply chains and created significant volatility and disruption of financial markets, which could adversely impact our operating results. For instance, delays or defaults in payments by our customer and third-party partners could adversely impact our accounts receivables. The value of our investments currently held in a variety of accounts could also be negatively impacted by the volatility in certain markets, such as the fixed income market, and impact our sources of liquidity. The stock market in general and the stock price of biopharmaceutical companies, in particular, have also experienced extreme price and volume fluctuations. Broad market and industry factors, including worsening economic conditions or a recession resulting from the ongoing COVID-19 pandemic, may adversely impact the value of our common stock and our ability to raise capital. If we do raise additional capital and issue equity securities when the value of our common stock is depressed, the dilutive impact on our stockholders may be greater compared to when the value of our common stock is higher.

The COVID-19 pandemic has already impacted our operations and those of our third-party partners. The magnitude and extent to which the outbreak may impact or continue to impact our business operations, clinical trial activities, product candidate approvals, supply chain and commercialization of our products and product candidates will continue to remain highly dependent on future developments, which are very uncertain and cannot be predicted with confidence, such as the duration of the outbreak, the scope and magnitude of any resurgence in the outbreak due to virus mutations or other factors, the timing and availability of treatments and vaccines against the virus, the duration of, or implementation of additional, restrictions to contain the outbreak and the effectiveness of other actions taken in the United States and other countries to contain and address the pandemic. This pandemic may also amplify many of the other risks described throughout the “Risk Factors” section of this Annual Report on Form 10-K.

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

We are dependent on Emil D. Kakkis, M.D., Ph.D., our Founder, President, and Chief Executive Officer, the loss of whose services may adversely impact the achievement of our objectives. Dr. Kakkis could leave our employment at any time, as he is an “at will” employee. Recruiting and retaining other qualified employees, consultants, and advisors for our business, including scientific and technical personnel, will also be critical to our success. There is currently a shortage of skilled personnel in our industry, which is likely to continue. As a result, competition for skilled personnel is intense and the turnover rate can be high. Our investments and efforts in human capital management may not attract and retain personnel on acceptable terms given the competition among numerous pharmaceutical and biotechnology companies for individuals with similar skill sets. In addition, failure to succeed in preclinical or clinical studies may make it more challenging to recruit and retain qualified personnel. The inability to recruit and retain qualified personnel, or the loss of the services of Dr. Kakkis, may impede the progress of our research, development, and commercialization objectives.

If we fail to obtain or maintain orphan drug exclusivity for our products, our competitors may sell products to treat the same conditions and our revenue will be reduced.

Our business strategy focuses on the development of drugs that are eligible for FDA and EU orphan drug designation. 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. In addition, if a product receives the first FDA approval for the indication for which it has orphan designation, the product 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, except in limited circumstances, such as a showing of clinical superiority over the product with orphan exclusivity or where the manufacturer is unable to assure sufficient product quantity. In the EU, orphan drug designation entitles a party to financial incentives such as reduction of fees or fee waivers and ten years of market exclusivity following drug or biological 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.

Because the extent and scope of patent protection for our products may in some cases be limited, orphan drug designation is especially important for our products for which orphan drug designation may be available. For eligible drugs, we plan to rely on the exclusivity period under the Orphan Drug Act to maintain a competitive position. If we do not obtain orphan drug exclusivity for our drug products and biologic products that do not have broad patent protection, our competitors may then sell the same drug to treat the same condition sooner than if we had obtained orphan drug exclusivity, and our revenue will be reduced.

Even though we have orphan drug designation for Dojolvi for the treatment of fatty acid oxidation disorders in the United States and for various subtypes of LC-FAOD in Europe, as well as for Crysvita, Mepsevii, DTX301, DTX401 and UX701 in the United States and Europe, we may not be the first to obtain marketing approval for any particular orphan indication due to the uncertainties associated with developing pharmaceutical products. Further, even if we obtain orphan drug exclusivity for a product, that exclusivity may not effectively protect the product from competition because different drugs with different active moieties can be approved for the same condition or the same drug can be approved for a different indication unless there are other exclusivities such as new chemical entity exclusivity preventing such approval. Even after an orphan drug is approved, the FDA or EMA can subsequently approve the same drug with the same active moiety for the same condition if the FDA or EMA concludes that the later drug is safer, more effective, or makes a major contribution to patient care. Orphan drug designation neither shortens the development time or regulatory review time of a drug nor gives the drug any advantage in the regulatory review or approval process.

Our operating results would be adversely impacted if our intangible assets become impaired.

As a result of the accounting for our acquisition of Dimension Therapeutics, Inc. (Dimension) in November 2017, we have recorded on our balance sheet intangible assets for in-process research and development (IPR&D) related to DTX301 and DTX401. Following the FDA approval of Dojolvi in June 2020, we have also recorded contract-based intangible assets related to our license from third parties for certain assets related to the product. We test the intangible assets for impairment annually during the fourth quarter and more frequently if events or changes in circumstances indicate that it is more likely than not that the asset is impaired. If the associated research and development effort is abandoned, the related assets will be written-off and we will record a noncash impairment loss on our statement of operations. We have not recorded any impairments related to our intangible assets through the end of December 31, 2020.

We may not be successful in our efforts to identify, license, discover, develop, or commercialize additional product candidates.

The success of our business depends upon our ability to identify, license, discover, develop, or commercialize additional product candidates in addition to the continued clinical testing, potential approval, and commercialization of our existing product candidates. Research programs to identify and develop new product candidates, such as those under our collaboration with Arcturus, require substantial technical, financial, and human resources. We may focus our efforts and resources on potential programs or product candidates that ultimately prove to be unsuccessful. Our research programs or licensing efforts may fail to yield additional product candidates for clinical development and commercialization for a number of reasons, including but not limited to the following:

- our research or business development methodology or search criteria and process may be unsuccessful in identifying potential product candidates;
- we may not be able or willing to assemble sufficient technical, financial or human resources to acquire or discover additional product candidates;
- we may face competition in obtaining and/or developing additional product candidates;
- our product candidates may not succeed in research, discovery, preclinical or clinical testing;
- our potential product candidates may be shown to have harmful side effects or may have other characteristics that may make the products unmarketable or unlikely to receive marketing approval;
- competitors may develop alternatives that render our product candidates obsolete or less attractive;

- product candidates we develop may be covered by third parties' patents or other exclusive rights;
- the market for a product candidate may change during our program so that such a product may become unreasonable to continue to develop;
- a product candidate may not be capable of being produced in commercial quantities at an acceptable cost or at all; and
- a product candidate may not be accepted as safe and effective by regulatory authorities, patients, the medical community, or payors.

If any of these events occur, we may be forced to abandon our development efforts for a program or programs, or we may not be able to identify, license, discover, develop, or commercialize additional product candidates, which would have a material adverse effect on our business and could potentially cause us to cease operations.

We may expend our limited resources to pursue a particular product, product candidate or indication and fail to capitalize on products, product candidates or indications that may be more profitable or for which there is a greater likelihood of success.

Because we have limited financial and managerial resources, we focus our sales, marketing and research programs on certain products, product candidates or for specific indications. As a result, we may forego or delay pursuit of opportunities with other products or product candidates or other indications that later prove to have greater commercial potential. Our resource allocation decisions may cause us to fail to capitalize on viable commercial products or profitable market opportunities. Our spending on current and future research and development programs and product candidates may not yield any commercially viable products. If we do not accurately evaluate the commercial potential or target market for a particular product or product candidate, we may relinquish valuable rights through collaboration, licensing, or other royalty arrangements in cases in which it would have been advantageous for us to retain sole development and commercialization rights or we may allocate internal resources to a product candidate in a therapeutic area in which it would have been more advantageous to enter into a partnering arrangement.

Changes to healthcare and FDA laws, regulations, and policies may have a material adverse effect on our business and results of operations.

As described above under "Item 1. Business - Government Regulation" and in the Risk Factor above entitled " – *The insurance coverage and reimbursement status of newly approved products is uncertain*" there have been and continue to be a number of legislative initiatives to contain healthcare costs and to modify the regulation of drug and biologic products. We expect that additional state and federal healthcare reform measures and regulations will be adopted in the future, including proposals to reduce the exclusivity protections provided to already approved biological products and to provide biosimilar and interchangeable biologic products an easier path to approval. Any of these measures and regulations could limit the amounts that federal and state governments will pay for healthcare products and services, result in reduced demand for our product candidates or additional pricing pressures and affect our product development, testing, marketing approvals and post-market activities.

Failure to comply with laws and regulations could harm our business and our reputation.

Our business is subject to regulation by various federal, state, local and foreign governmental agencies, including agencies responsible for monitoring and enforcing employment and labor laws, workplace safety, and tax laws and regulations. In certain jurisdictions, these regulatory requirements may be more stringent than those in the United States, and in other circumstances these requirements may be more stringent in the United States.

In particular, our operations are directly, and indirectly through our customers, subject to various federal and state fraud and abuse laws, including, without limitation, the federal Anti-Kickback Statute, the federal False Claims Act, and physician sunshine laws and regulations and patient privacy regulations, including the EU General Data Protection Regulation and the California Consumer Privacy Act (CCPA), as described above under "Item 1. Business – Government Regulation". Because of the breadth of these laws and the narrowness of the statutory exceptions and safe harbors available, it is possible that some of our business activities could be subject to challenge under one or more of such laws. For instance, as we and our employees increasingly use social media tools as a means of communication with the public, there is a risk that the use of social media by us or our employees to communicate about our products or business may cause to be found in violation of applicable laws, despite our attempts to monitor such social media communications through company policies and guidelines. In addition, our employees may knowingly or inadvertently make use of social media in ways that may not comply with our company policies or other legal or contractual requirements, which may give rise to liability, lead to the loss of trade secrets or other intellectual property, or result in public exposure of personal information of our employees, clinical trial patients, customers, and others. If our operations are found to be in violation of any of the laws described above or any other governmental regulations that apply to us, we may be subject to penalties, including civil and criminal penalties, damages, fines, exclusion from participation in government health care programs, such as Medicare and Medicaid, imprisonment, disgorgement of profits, and the curtailment or restructuring of our operations. If any governmental sanctions, fines or penalties are imposed, or if we do not prevail in any possible civil or criminal litigation, our business, operating results, financial condition and our reputation could be harmed. In addition, responding to any action will likely result in a significant diversion of management's attention and resources and an increase in professional fees.

Our research and development activities, including our process and analytical development activities in our quality control laboratory, and our and our third-party manufacturers' and suppliers' activities involve the controlled storage, use, and disposal of hazardous materials, including the components of our product candidates, such as viruses, and other hazardous compounds, which subjects us to laws and regulations governing such activities. In some cases, these hazardous materials and various wastes resulting from their use are stored at our or our manufacturers' facilities pending their use and disposal. We cannot eliminate the risk of contamination, which could cause an interruption of our commercialization efforts, research and development efforts, and business operations or environmental damage that could result in costly clean-up and liabilities under applicable laws and regulations governing the use, storage, handling, and disposal of these materials and specified waste products. We cannot guarantee that the safety procedures utilized by us and our third-party manufacturers for handling and disposing of these materials comply with the standards prescribed by these laws and regulations, or eliminate the risk of accidental contamination or injury from these materials. In such an event, we may be held liable for any resulting damages—and such liability could exceed our resources—and state or federal or other applicable authorities may curtail our use of certain materials and/or interrupt our business operations. Furthermore, environmental laws and regulations are complex, change frequently, and have tended to become more stringent. We cannot predict the impact of such changes and cannot be certain of our future compliance. We do not currently carry biological or hazardous waste insurance coverage.

International expansion of our business exposes us to business, regulatory, political, operational, financial, and economic risks associated with doing business outside of the United States.

Our business strategy includes international expansion. We currently conduct clinical studies and regulatory activities and we also commercialize products outside of the United States. Doing business internationally involves a number of risks, including but not limited to:

- multiple, conflicting, and changing laws and regulations such as privacy and data regulations, transparency regulations, tax laws, export and import restrictions, employment laws, regulatory requirements, and other governmental approvals, permits, and licenses;
- introduction of new health authority requirements and/or changes in health authority expectations;
- failure by us to obtain and maintain regulatory approvals for the use of our products in various countries;
- additional potentially relevant third-party patent rights;
- complexities and difficulties in obtaining protection for, and enforcing, our intellectual property;
- difficulties in staffing and managing foreign operations;
- complexities associated with managing multiple payor reimbursement regimes, government payors, or patient self-pay systems;
- limits on our ability to penetrate international markets;
- financial risks, such as longer payment cycles, difficulty collecting accounts receivable, the impact of local and regional financial crises on demand and payment for our products, and exposure to foreign currency exchange rate fluctuations;
- natural disasters and political and economic instability, including wars, terrorism, political unrest, results of certain elections and votes, actual or threatened public health emergencies and outbreak of disease (including for example, the COVID-19 pandemic), boycotts, adoption or expansion of government trade restrictions, and other business restrictions;

- certain expenses including, among others, expenses for travel, translation, and insurance;
- regulatory and compliance risks that relate to maintaining accurate information and control over commercial operations and activities that may fall within the purview of the U.S. Foreign Corrupt Practices Act, or FCPA, its books and records provisions, or its anti-bribery provisions, including those under the U.K. Bribery Act and similar foreign laws and regulations; and
- regulatory and compliance risks relating to doing business with any entity that is subject to sanctions administered by the Office of Foreign Assets Control of the U.S. Department of the Treasury.

Any of these factors could significantly harm our future international expansion and operations and, consequently, our results of operations.

Risks generally associated with a company-wide implementation of an enterprise resource planning (ERP) system may adversely affect our business and results of operations or the effectiveness of our internal controls over financial reporting.

We are in the process of implementing a company-wide ERP system to upgrade certain existing business, operational, and financial processes. Our ERP implementation is a complex and time-consuming project that we expect will require multiple years to complete. Our results of operations could be adversely affected if we experience time delays or cost overruns during the ERP implementation process, or if the ERP system or associated process changes do not give rise to the benefits that we expect. This project has required and may continue to require investment of capital and human resources, the re-engineering of processes of our business, and the attention of many employees who would otherwise be focused on other aspects of our business. Any deficiencies in the design and implementation of the new ERP system could result in potentially much higher costs than we had incurred and could adversely affect our ability to develop and launch solutions, provide services, fulfill contractual obligations, file reports with the SEC in a timely manner, operate our business or otherwise affect our controls environment. Any of these consequences could have an adverse effect on our results of operations and financial condition.

Our business and operations may be materially adversely affected in the event of computer system failures or security breaches.

Our security measures, internal computer systems, and those of our CROs and other third parties on which we rely, are vulnerable to damage from computer viruses, unauthorized access, cyber-attacks, natural disasters, fire, terrorism, war, and telecommunication and electrical failures. Risks of unauthorized access and cyber-attacks have increased as most of our personnel, and the personnel of many third-parties with which we do business, have adopted remote working arrangements as a result of the COVID-19 pandemic. Improper or inadvertent employee behavior, including data privacy breaches by employees, contractors and others with permitted access to our systems, may also pose a risk that sensitive data may be exposed to unauthorized persons or to the public. If a system failure or security breach occurs and interrupts our operations or the operations at one of our third-party vendors, it could result in intellectual property and other proprietary or confidential information being lost or stolen or a material disruption of our drug development programs. For example, the loss of clinical trial data from ongoing or planned clinical trials could result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce the data. To the extent that any disruption or security breach results in a loss of or damage to our data or applications, loss of trade secrets or inappropriate disclosure of confidential or proprietary information, including protected health information or personal data of employees or former employees, access to our clinical data, or disruption of the manufacturing process, we could incur liability and the further development of our drug candidates could be delayed. We may also be vulnerable to cyber-attacks by hackers or other malfeasance. This type of breach of our cybersecurity may compromise our confidential information and/or our financial information and adversely affect our business or reputation or result in legal or regulatory proceedings.

We or the third parties upon whom we depend may be adversely affected by earthquakes or other natural disasters and our business continuity and disaster recovery plans may not adequately protect us from a serious disaster.

Our corporate headquarters and one of our laboratories are located in the San Francisco Bay Area, and our collaboration partner for Crysvita, KKC, is located in Japan, which have both in the past experienced severe earthquakes and other natural disasters. We do not carry earthquake insurance. Earthquakes or other natural disasters could severely disrupt our operations or those of our collaborators, and have a material adverse effect on our business, results of operations, financial condition, and prospects. If a natural disaster, power outage, or other event occurred that prevented us from using all or a significant portion of our headquarters, that damaged critical infrastructure (such as the manufacturing facilities of our third-party contract manufacturers) or that otherwise disrupted operations, it may be difficult or, in certain cases, impossible for us to continue our business for a substantial period of time. The disaster recovery and business continuity plans we have in place currently are limited and are may be inadequate in the event of a serious disaster or similar event. We may incur substantial expenses as a result of the limited nature of our disaster recovery and business continuity plans, which, particularly when taken together with our lack of earthquake insurance, could have a material adverse effect on our business.

We may acquire companies or products or engage in strategic transactions, which could divert our management's attention and cause us to incur various costs and expenses, or result in fluctuations with respect to the value of such investment, which could impact our operating results.

We may acquire or invest in businesses or products that we believe could complement or expand our business or otherwise offer growth opportunities. For example, we acquired Dimension in November 2017 and during the third quarter 2019, we entered into an agreement with GeneTx to collaborate on the development of a product for the treatment of Angelman Syndrome which included an exclusive option to acquire GeneTx. The pursuit of potential acquisitions or investments may divert the attention of management and may cause us to incur various costs and expenses in identifying, investigating, and pursuing them, whether or not they are consummated. We may not be able to identify desirable acquisitions or investments or be successful in completing or realizing anticipated benefits from such transactions. In addition, we may receive inquiries relating to potential strategic transactions, including collaborations, licenses, and acquisitions. Such potential transactions may divert the attention of management and may cause us to incur various costs and expenses in investigating and evaluating such transactions, whether or not they are consummated.

The value of our investments in other companies or businesses may also fluctuate significantly and impact our operating results quarter to quarter or year to year. For instance, in June 2019, we purchased 2.4 million shares of common stock of Arcturus and in May 2020, we exercised our option to purchase an additional 600,000 shares of Arcturus' common stock pursuant to the terms of our equity purchase agreement with Arcturus; we subsequently sold an aggregate of 800,000 shares in December 2020. We also purchased 7,825,797 shares of common stock of Solid in October 2020. We have elected to apply the fair value option to account for our equity investments in Arcturus and Solid. As a result, increases or decreases in the stock price of Arcturus and Solid common stock will result in accompanying changes in the fair value of our investments, and cause substantial volatility in, our operating results for the reporting period. For instance, the changes in fair value of the Arcturus and Solid investments recognized in the Consolidated Statements of Operations for the years ended December 31, 2020 and 2019 was a $170.4 million and $13.4 million increase, respectively, primarily due to the higher Arcturus and Solid stock price as of December 31, 2020 and 2019 compared to the prior year for Arcturus and the acquisition date for Solid. The gains in fair value of the equity investments for the years ended December 31, 2020 and 2019 decreased the amount of our net loss during those periods. If the Arcturus or Solid stock price had been lower at December 31, 2020 and 2019 compared to the prior year or the acquisition date, as applicable, we would have reported an even greater net loss for the years ended December 31, 2020 and 2019. As the fair value of our investments in Arcturus and Solid is dependent on the stock price of Arcturus and Solid, which has recently seen wide fluctuations, the value of our investments and the impact on our operating results may similarly fluctuate significantly from quarter to quarter and year to year such that period-to-period comparisons may not be a good indication of the future value of the investments and our future operating results.

Risks Related to Ownership of Our Common Stock

The market price of our common stock may be highly volatile.

The market price of our common stock has been, and is likely to continue to be, volatile, including for reasons unrelated to changes in our business. Our stock price could be subject to wide fluctuations in response to a variety of factors, including but not limited to the following:

- adverse results or delays in preclinical or clinical studies;
- any inability to obtain additional funding;
- any delay in filing an IND, NDA, BLA, MAA, or other regulatory submission for any of our product candidates and any adverse development or perceived adverse development with respect to the applicable regulatory agency's review of that IND, NDA, BLA, MAA, or other regulatory submission;
- the perception of limited market sizes or pricing for our products and product candidates;
- decisions by our collaboration partners with respect to the indications for our products and product candidates in countries where they have the right to commercialize the products and product candidates;
- decisions by our collaboration partners regarding market access and pricing in countries where they have the right to commercialize our products and product candidates;
- failure to successfully develop and commercialize our products and product candidates;
- the level of revenue we receive from our commercialized products or from named patient sales;
- post-marketing safety issues;
- failure to maintain our existing strategic collaborations or enter into new collaborations;
- failure by us or our licensors and strategic collaboration partners to prosecute, maintain, or enforce our intellectual property rights;
- changes in laws or regulations applicable to our products;

- any inability to obtain adequate product supply for our products and product candidates or the inability to do so at acceptable prices;
- adverse regulatory decisions;
- introduction of new products, services, or technologies by our competitors;
- changes in or failure to meet or exceed financial projections or other guidance we may provide to the public;
- changes in or failure to meet or exceed the financial projections or other expectations of the investment community;
- the perception of the pharmaceutical industry or our company by the public, legislatures, regulators, and the investment community;
- the perception of the pharmaceutical industry's approach to drug pricing;
- announcements of significant acquisitions, strategic partnerships, joint ventures, or capital commitments by us, our strategic collaboration partners, or our competitors;
- the integration and performance of any businesses we have acquired or may acquire;
- disputes or other developments relating to proprietary rights, including patents, litigation matters, and our ability to obtain patent protection for our technologies;
- additions or departures of key scientific or management personnel;
- significant lawsuits, including patent or stockholder litigation;
- securities or industry analysts' reports regarding our stock, or their failure to issue such reports;
- changes in the market valuations of similar companies;
- general market or macroeconomic conditions, including the impact from the COVID-19 pandemic;
- sales of our common stock by us or our stockholders in the future; and
- trading volume of our common stock.

In addition, biotechnology and biopharmaceutical companies in particular have experienced extreme price and volume fluctuations that have often been unrelated or disproportionate to the operating performance of these companies. Broad market and industry factors may negatively affect the market price of our common stock, regardless of our actual operating performance.

Future sales and issuances of our common stock or rights to purchase common stock, including pursuant to our equity incentive plans, could result in additional dilution of the percentage ownership of our stockholders and could cause our stock price to fall.

We will need additional capital in the future to continue our planned operations. To the extent we raise additional capital by issuing equity securities, our stockholders may experience substantial dilution. We may sell common stock, convertible securities, or other equity securities in one or more transactions at prices and in a manner we determine from time to time. If we sell common stock, convertible securities, or other equity securities in more than one transaction, investors may be materially diluted by subsequent sales. These sales may also result in material dilution to our existing stockholders, and new investors could gain rights superior to our existing stockholders.

Pursuant to our 2014 Incentive Plan, or the 2014 Plan, our management is authorized to grant stock options and other equity-based awards to our employees, directors, and consultants. At December 31, 2020, 2,980,163 shares were available for future grants under the 2014 Plan. Through January 1, 2024, the number of shares available for future grant under the 2014 Plan will automatically increase on January 1 of each year by the lesser of 2,500,000 shares or 4% of all shares of our capital stock outstanding as of December 31 of the prior calendar year, subject to the ability of our compensation committee to take action to reduce the size of the increase in any given year.

Pursuant to our 2014 Employee Stock Purchase Plan, or 2014 ESPP, eligible employees can acquire shares of our common stock at a discount to the prevailing market price. At December 31, 2020, 3,248,367 shares were available for issuance under the 2014 ESPP. Through January 1, 2024, the number of shares available for issuance under the 2014 ESPP will automatically increase on January 1 of each year by the lesser of 1,200,000 shares or 1% of all shares of our capital stock outstanding as of December 31 of the prior calendar year, subject to the ability of our compensation committee to take action to reduce the size of the increase in any given year.

In February 2021, our board of directors adopted an employment inducement plan with a maximum of 500,000 shares available for grant under the plan. We plan to register all the shares under our inducement plan. In addition, we currently plan to register the increased number of shares available under the 2014 Plan and the 2014 ESPP each year. If our board of directors elects to increase the number of shares available for future grant under the 2014 Plan, the 2014 ESPP or the inducement plan, our stockholders may experience additional dilution, which could cause our stock price to fall.

We do not intend to pay dividends on our common stock so any returns will be limited to the value of our stock.

We have never declared or paid any cash dividends on our common stock. We currently intend to retain all available funds and any future earnings, if any, for the development, operation, and expansion of our business and do not anticipate declaring or paying any cash dividends for the foreseeable future. Any return to stockholders will therefore be limited to the appreciation of their stock.

Provisions in our amended and restated certificate of incorporation and by-laws, as well as provisions of Delaware law, could make it more difficult for a third-party to acquire us or increase the cost of acquiring us, even if doing so would benefit our stockholders, or remove our current management.

Our amended and restated certificate of incorporation, amended and restated by-laws, and Delaware law contain provisions that may have the effect of delaying or preventing a change in control of us or changes in our management. Our amended and restated certificate of incorporation and by-laws include provisions that:

- authorize "blank check" preferred stock, which could be issued by our board of directors without stockholder approval and may contain voting, liquidation, dividend, and other rights superior to our common stock;
- create a classified board of directors whose members serve staggered three-year terms;
- specify that special meetings of our stockholders can be called only by our board of directors or the chairperson of our board of directors;
- prohibit stockholder action by written consent;
- establish an advance notice procedure for stockholder approvals to be brought before an annual meeting of our stockholders, including proposed nominations of persons for election to our board of directors;
- provide that our directors may be removed only for cause;
- provide that vacancies on our board of directors may be filled only by a resolution adopted by the board of directors;
- expressly authorize our board of directors to modify, alter or repeal our amended and restated by-laws; and
- require holders of 75% of our outstanding common stock to amend specified provisions of our amended and restated certificate of incorporation and amended and restated by-laws.

These provisions, alone or together, could delay, deter, or prevent hostile takeovers and changes in control or changes in our management.

In addition, because we are incorporated in Delaware, we are governed by the provisions of Section 203 of the Delaware General Corporation Law, which limits the ability of stockholders owning in excess of 15% of our outstanding voting stock to merge or combine with us. Further, no stockholder is permitted to cumulate votes at any election of directors because this right is not included in our amended and restated certificate of incorporation.

Any provision of our amended and restated certificate of incorporation or amended and restated by-laws or Delaware law that has the effect of delaying or deterring a change in control could limit the opportunity for our stockholders to receive a premium for their shares of our common stock, and could also affect the price that some investors are willing to pay for our common stock.

Our amended and restated certificate of incorporation provides that the Court of Chancery of the State of Delaware is the sole and exclusive forum for substantially all disputes between us and our stockholders, which could limit our stockholders' ability to obtain a favorable judicial forum for disputes with us or our directors, officers or employees.

Our amended and restated certificate of incorporation provides that the Court of Chancery of the State of Delaware is the sole and exclusive forum for (1) any derivative action or proceeding brought on our behalf, (2) any action asserting a claim of breach of fiduciary duty owed by any of our directors, officers, or other employees to us or to our stockholders, (3) any action asserting a claim against us arising under the Delaware General Corporation Law or under our amended and restated certificate of incorporation or bylaws, or (4) any action against us asserting a claim governed by the internal affairs doctrine. The choice of forum provision may limit a stockholder's ability to bring a claim in a judicial forum that it finds favorable for disputes with us or our directors, officers, or other employees, which may discourage such lawsuits against us and our directors, officers, and other employees. Alternatively, if a court were to find the choice of forum provision contained in our amended and restated certificate of incorporation to be inapplicable or unenforceable in an action, we may incur additional costs associated with resolving such action in other jurisdictions, which could harm our business, operating results and financial condition.

General Risk Factors

If we are unable to maintain effective internal control over financial reporting, investors may lose confidence in the accuracy and completeness of our financial reports and the market price of our stock may decrease.

The Sarbanes-Oxley Act requires, among other things, that we maintain effective internal controls for financial reporting and disclosure controls and procedures. In particular, we are required to perform system and process evaluation and testing of our internal controls over financial reporting to allow management to report on the effectiveness of our internal controls over financial reporting, as required by Section 404(a) of the Sarbanes-Oxley Act. Section 404(b) of the Sarbanes-Oxley Act also requires our independent auditors to attest to, and report on, this management assessment. Ensuring that we have adequate internal controls in place so that we can produce accurate financial statements on a timely basis is a costly and time-consuming effort that will need to be evaluated frequently. If we are not able to comply with the requirements of Section 404 or if we or our independent registered public accounting firm are unable to attest to the effectiveness of our internal control over financial reporting, investors may lose confidence in the accuracy and completeness of our financial reports, the market price of our stock could decline and we could be subject to sanctions or investigations by Nasdaq, the SEC, or other regulatory authorities, which would require additional financial and management resources.

We may incur additional tax liabilities related to our operations.

We have a multinational tax structure and are subject to income tax in the United States and various foreign jurisdictions. Our effective tax rate is influenced by many factors including changes in our operating structure, changes in the mix of our earnings among countries, our allocation of profits and losses among our subsidiaries, our intercompany transfer pricing agreements and rules relating to transfer pricing, the availability of U.S. research and development tax credits, and future changes in tax laws and regulations in the U.S. and foreign countries. Significant judgment is required in determining our tax liabilities including management's judgment for uncertain tax positions. The Internal Revenue Service, other domestic taxing authorities, or foreign taxing authorities may disagree with our interpretation of tax laws as applied to our operations. Our reported effective tax rate and after-tax cash flows may be materially and adversely affected by tax assessments in excess of amounts accrued for our financial statements. This could materially increase our future effective tax rate thereby reducing net income and adversely impacting our results of operations for future periods.

Our ability to use our net operating loss carryforwards and certain other tax attributes may be limited.

We have incurred substantial losses during our history. To the extent that we continue to generate taxable losses, unused taxable losses will, subject to certain limitations, carry forward to offset future taxable income, if any, until such unused losses expire. Under Sections 382 and 383 of the Internal Revenue Code of 1986, as amended, or the IRC, if a corporation undergoes an "ownership change," generally defined as a greater than 50% change (by value) in its equity ownership over a three-year period, the corporation's ability to use its pre-change net operating loss carryforwards, or NOL carryforwards, and other pre-change tax attributes (such as research tax credits) to offset its post-change income may be limited. An analysis to determine limitations upon our NOL carryforwards and other pre-change tax attributes for ownership changes that have occurred previously has been performed, resulting in a permanent decrease of federal and state NOL carryforwards in the amount of $7.2 million and a permanent decrease in federal research tax credit carryforwards in the amount of $0.2 million. As a result of these decreases and others that may occur as a result of future ownership changes, our ability to use our pre-change NOL carryforwards and other tax attribute carryforwards to offset U.S. federal taxable income and tax liabilities is limited and may become subject to even greater limitations, which could potentially accelerate or permanently increase future federal tax liabilities for us. In addition, there may be periods during which the use of state income tax NOL carryforwards and other state tax attribute carryforwards (such as state research tax credits) are suspended or otherwise limited, which could potentially accelerate or permanently increase future state tax liabilities for us.

Litigation may substantially increase our costs and harm our business.

We have been, and may in the future become, party to lawsuits including, without limitation, actions and proceedings in the ordinary course of business relating to our directors, officers, stockholders, intellectual property, and employment matters, which will cause us to incur legal fees and other costs related thereto, including potential expenses for the reimbursement of legal fees of officers and directors under indemnification obligations. The expense of defending against such litigation may be significant and there can be no assurance that we will be successful in any defense. Further, the amount of time that may be required to resolve such lawsuits is unpredictable, and these actions may divert management's attention from the day-to-day operations of our business, which could adversely affect our business, results of operations, and cash flows. Litigation is subject to inherent uncertainties, and an adverse result in such matters that may arise from time to time could have a material adverse effect on our business, results of operations, and financial condition.

Item 1B. ***Unresolved Staff Comments***

None.

Item 2. ***Properties***

Our primary operations are conducted at the leased facilities summarized in the below table. During the fourth quarter of 2020, we completed our purchase of land located in Bedford, Massachusetts and began construction of our gene therapy manufacturing facility. We believe our facilities are adequate and suitable for our current needs, and that we will be able to obtain new or additional leased space in the future when necessary.

Property Location	Use	Lease Expiration Date
Novato, California	Headquarters and office	December 2024
Novato, California	Laboratory and office	November 2028
Brisbane, California	Office	June 2026
South San Francisco, California	Laboratory and office	March 2025
Cambridge, Massachusetts	Laboratory and office	December 2023
Woburn, Massachusetts	Laboratory and office	April 2025
Woburn, Massachusetts	Laboratory and office	October 2026
Bedford, Massachusetts	Manufacturing facility	Owned property

Item 3. ***Legal Proceedings***

We are not currently a party to any material legal proceedings. We may, however, in the ordinary course of business face various claims brought by third parties or government regulators and we may, from time to time, make claims or take legal actions to assert our rights, including claims relating to our directors, officers, stockholders, intellectual property rights, employment matters and the safety or efficacy of our products. Any of these claims could subject us to costly litigation and, while we generally believe that we have adequate insurance to cover many different types of liabilities, our insurance carriers may deny coverage, may be inadequately capitalized to pay on valid claims, or our policy limits may be inadequate to fully satisfy any damage awards or settlements. If this were to happen, the payment of any such awards could have a material adverse effect on our consolidated operations, cash flows and financial position. Additionally, any such claims, whether or not successful, could damage our reputation and business.

Item 4. ***Mine Safety Disclosures***

Not applicable.

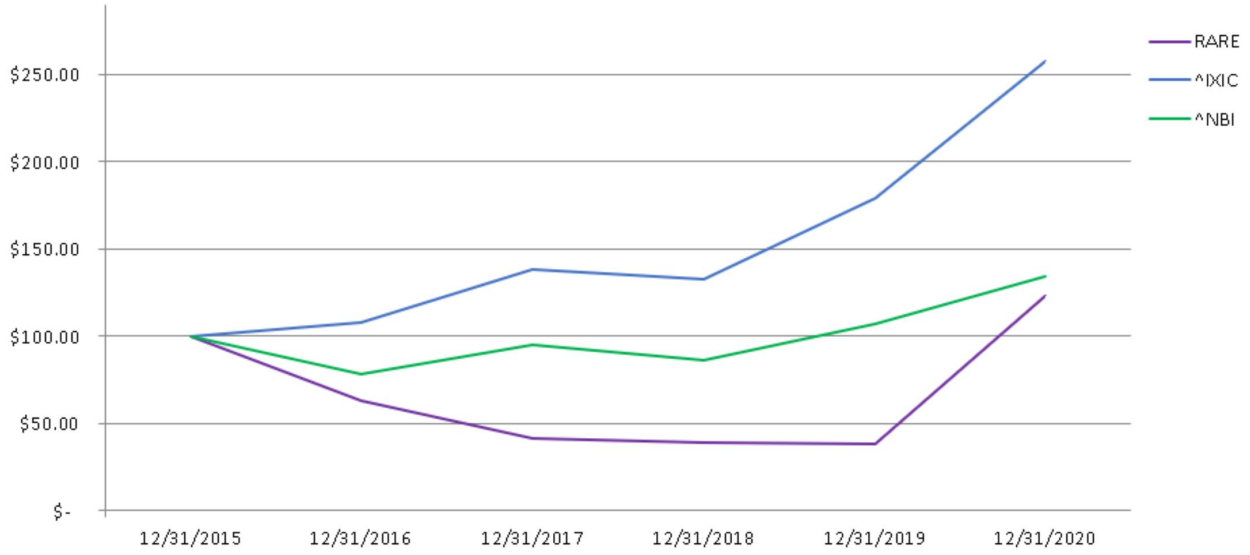
PART II

Item 5. ***Market for Registrant's Common Equity, Related Stockholder Matters and Issuer Purchases of Equity Securities***

Our common stock has been traded on The Nasdaq Global Select Market since January 31, 2014 under the symbol "RARE". As of February 8, 2021, we had 5 holders of record of our common stock. Certain shares are held in "street" name and, accordingly, the number of beneficial owners of such shares is not known or included in the foregoing number.

STOCK PRICE PERFORMANCE GRAPH

The following stock performance graph compares our total stock return with the total return for (i) the Nasdaq Composite Index and the (ii) the Nasdaq Biotechnology Index for the period from December 31, 2015 through December 31, 2020. The figures represented below assume an investment of $100 in our common stock at the closing price of $112.18 on December 31, 2015 and in the Nasdaq Composite Index and the Nasdaq Biotechnology Index on December 31, 2015 and the reinvestment of dividends into shares of common stock. The comparisons in the table are required by the SEC and are not intended to forecast or be indicative of possible future performance of our common stock. This graph shall not be deemed "soliciting material" or be deemed "filed" for purposes of Section 18 of the Securities Exchange Act of 1934, as amended, or the Exchange Act, or otherwise subject to the liabilities under that section, and shall not be deemed to be incorporated by reference into any of our filings under the Securities Act of 1933, as amended, or the Securities Act, whether made before or after the date hereof and irrespective of any general incorporation language in any such filing.



$100 investment in stock or index	Ticker	December 31, 2015	December 31, 2016	December 31, 2017	December 31, 2018	December 31, 2019	December 31, 2020
Ultragenyx Pharmaceutical Inc.	RARE	$ 100.00	$ 62.68	$ 41.34	$ 38.76	$ 38.07	$ 123.40
NASDAQ Composite Index	^IXIC	$ 100.00	$ 107.50	$ 137.86	$ 132.51	$ 179.19	$ 257.38
NASDAQ Biotechnology Index	^NBI	$ 100.00	$ 78.32	$ 94.81	$ 85.97	$ 106.95	$ 134.42

Dividend Policy

We have never declared or paid cash dividends on our common stock. We currently intend to retain all available funds and any future earnings, if any, to fund the development, operation, and expansion of our business, and we do not anticipate paying any cash dividends on our common stock in the foreseeable future. Any future determination to pay dividends will be made at the discretion of our board of directors or any authorized committee thereof.

Unregistered Sales of Equity Securities

None

Issuer's Purchases of Equity Securities

None

Item 6. ***Selected Financial Data***

The information set forth below for the five years ended December 31, 2020 is not necessarily indicative of the results that may be expected in the future and interim results are not necessarily indicative of results to be expected for the full year. You should read the selected historical financial data below in conjunction with the section titled "Management's Discussion and Analysis of Financial Condition and Results of Operations" and the consolidated financial statements and related notes included elsewhere in this Annual Report.

	Year Ended December 31,				
	2020	2019	2018	2017	2016
	(in thousands, except share and per share amounts)				
Consolidated Statement of Operations Data:					
Revenues:					
Collaboration and license	$ 219,315	$ 83,493	$ 41,693	$ 2,136	$ —
Product sales	38,720	20,221	9,802	476	133
Non-cash collaboration royalty revenue	12,995	—	—	—	—
Total revenues	271,030	103,714	51,495	2,612	133
Operating expenses:					
Cost of sales	6,129	9,008	1,146	1	—
Research and development	412,084	357,355	293,998	231,644	183,204
Selling, general and administrative	182,933	161,524	127,724	99,909	64,936
Total operating expenses	601,146	527,887	422,868	331,554	248,140
Loss from operations	(330,116)	(424,173)	(371,373)	(328,942)	(248,007)
Interest income	7,038	13,238	9,542	4,074	3,789
Gain from sale of priority review vouchers	—	—	170,322	—	—
Change in fair value of equity investments	170,403	13,413	—	—	—
Non-cash interest expense on liability related to the sale of future royalties	(33,291)	(1,135)	—	—	—
Other income (expense)	607	(787)	(5,588)	6,530	(1,621)
Loss before income taxes	(185,359)	(399,444)	(197,097)	(318,338)	(245,839)
Provision for income taxes	(1,207)	(3,283)	(514)	16,199	(35)
Net loss	$ (186,566)	$ (402,727)	$ (197,611)	$ (302,139)	$ (245,874)
Net loss per share, basic and diluted(1)	$ (3.07)	$ (7.12)	$ (3.97)	$ (7.12)	$ (6.21)
Shares used to compute net loss per share, basic and diluted(1)	60,845,550	56,576,885	49,775,223	42,453,135	39,586,908

(1) See Notes 2 and 16 to our audited consolidated financial statements of this Annual Report for an explanation of the calculations of basic and diluted net loss per share attributable to common stockholders.

	As of December 31,				
	2020	2019	2018	2017	2016
	(in thousands)				
Consolidated Balance Sheet Data:					
Cash, cash equivalents and marketable debt securities	$ 1,212,039	$ 760,404	$ 459,706	$ 244,468	$ 498,111
Working capital	1,105,695	747,717	447,644	198,569	341,436
Total assets	1,759,555	1,135,496	719,558	490,753	540,626
Liability related to the sale of future royalties	335,665	315,369	—	—	—
Total stockholders' equity	1,154,375	653,764	608,908	383,454	473,974

Item 7. ***Management's Discussion and Analysis of Financial Condition and Results of Operations***

MANAGEMENT'S DISCUSSION AND ANALYSIS OF FINANCIAL CONDITION AND RESULTS OF OPERATIONS

You should read the following discussion and analysis of our financial condition and results of operations together with the section of this Annual Report entitled "Selected Financial Data" and our consolidated financial statements and related notes included elsewhere in this Annual Report.

This discussion and analysis generally covers our financial condition and results of operations for the year ended December 31, 2020, including year-over-year comparisons versus the year ended December 31, 2019. Our Annual Report on Form 10-K for the year ended December 31, 2019 includes a discussion and analysis of our financial condition and results of operations for the year ended December 31, 2018 in Item 7 of Part II, "Management's Discussion and Analysis of Financial Condition and Results of Operations."

Overview

Ultragenyx Pharmaceutical Inc. (we or the Company) is 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 typically no approved therapies treating the underlying disease. Our strategy, which is predicated upon time- and cost-efficient drug development, allows us to pursue multiple programs in parallel with the goal of delivering safe and effective therapies to patients with the utmost urgency.

Impact of COVID-19 Pandemic

Our business operations have been and continue to be affected by the COVID-19 pandemic. In addition to some impact on our preclinical manufacturing activities and certain regulatory interactions, we have experienced interruptions to our clinical trial activities, primarily due to delays or disruptions to patient enrollment and dosing as a result of shelter-in-place orders or quarantines, and certain data from our gene therapy product candidates was delayed as a result of the COVID-19 pandemic. The FDA has also delayed certain key meetings or discussions with us related to one of our product candidates, which may adversely impact the progression of our clinical study for such product candidate. The continuing outbreak has caused delays in delivery of ancillary clinical trial materials as certain of our third-party manufacturers or suppliers have prioritized and allocated more resources and capacity to supply drug product or raw materials to other companies engaged in the study of potential treatments or vaccinations for COVID-19. Social distancing measures and travel limitations in response to the pandemic have also made it difficult for us to identify new patients for our commercialized products, which may result in loss of revenue. We have also restricted access to our facilities to personnel and third parties who perform critical activities that must be performed on-site and as a result, most of our personnel currently work remotely. Such remote working policies may negatively impact productivity and disrupt our business operations.

As the COVID-19 global pandemic continues, we may experience lower revenue and increased expenses as a result of disruptions to our clinical trial, commercialization and regulatory activities, in addition to delays or shortages of drug product and raw materials. The magnitude and extent to which the pandemic may impact our business operations and operating results will continue to remain highly dependent on future developments, which are very uncertain and cannot be predicted with confidence. As a result, we cannot reliably estimate the extent to which the COVID-19 pandemic will impact our financial statements in 2021 and beyond. See Item 1A: "Risk Factors" for additional details.

Approved Therapies and Clinical Product Candidates

Our current approved therapies and clinical-stage pipeline consist of four product categories: biologics, small molecules, gene therapy, and nucleic acid product candidates. We have three commercially approved products, Crysvita® (burosumab) for the treatment of XLH and TIO, Mepsevii® (vestronidase alfa) for the treatment of MPSVII or Sly Syndrome, and Dojolvi® (triheptanoin) for the treatment of LC-FAOD, and we anticipate having six product candidates in the clinical pipeline in 2021. Please see "Part I. Item 1. Business" above for a description of our approved products and our clinical stage pipeline products.

Financial Operations Overview

We are a biopharmaceutical company with a limited operating history. To date, we have invested substantially all of our efforts and financial resources in identifying, acquiring, and developing our products and product candidates, including conducting clinical studies and providing selling, general and administrative support for these operations. To date, we have funded our operations primarily from the sale of our equity securities, the sale of certain future royalties, and strategic collaboration arrangements.

We have incurred net losses in each year since inception. Our net losses were $186.6 million and $402.7 million for the years ended December 31, 2020 and 2019. Net loss for the years ended December 31, 2020 and 2019 included a $170.4 million and $13.4 million gain, respectively, resulting from changes in fair value of our investments in Arcturus Therapeutics Holdings Inc. (Arcturus)

and Solid Biosciences Inc. (Solid) equity securities. Substantially all of our net losses have resulted from costs incurred in connection with our research and development programs and from selling, general and administrative costs associated with our operations.

For the year ended December 31, 2020, our total revenues increased to $271.0 million, compared to $103.7 million for the same period in 2019. Revenue for the year ended December 31, 2020 included $89.2 million in revenue from our collaboration and license agreement with Daiichi Sankyo Co., Ltd. (Daiichi Sankyo) which we executed in March 2020. The remainder of the increase was driven by higher revenue from Crysvita collaboration revenue in the profit-share territory, increase in revenue for our approved products and an increase in collaboration royalty revenue.

As of December 31, 2020, we had $1,212.0 million in available cash, cash equivalents and marketable debt securities.

Critical Accounting Policies and Significant Judgments and Estimates

Our management's discussion and analysis of our financial condition and results of operations is based on our consolidated financial statements, which have been prepared in accordance with U.S. generally accepted accounting principles, or GAAP. The preparation of these consolidated financial statements requires us to make estimates and assumptions that affect the reported amounts of assets and liabilities and the disclosure of contingent assets and liabilities at the date of the financial statements, as well as the reported expenses incurred during the reporting periods. Our estimates are based on our historical experience and on various other factors that we believe are reasonable under the circumstances, the results of which form the basis for making judgments about the carrying value of assets and liabilities that are not readily apparent from other sources. Actual results may differ from these estimates under different assumptions or conditions. We periodically review our estimates as a result of changes in circumstances, facts and experience. The effects of material revisions in estimates are reflected in the financial statements prospectively from the date of the change in estimate. Our significant accounting policies are more fully described in Note 2 to our financial statements included elsewhere in this Annual Report.

We define our critical accounting policies as those GAAP accounting principles that require us to make subjective estimates and judgments about matters that are uncertain and are likely to have a material impact on our financial condition and results of operations as well as the specific manner in which we apply those principles. We believe the critical accounting policies used in the preparation of our financial statements that require significant estimates and judgments are as follows:

Valuation of Acquired Intangible Assets

We have recorded acquired intangible assets related to our acquisition of Dimension Therapeutics, Inc., or Dimension, in November 2017. Intangible assets with definite useful lives are amortized over their estimated useful lives or other systematic basis and reviewed for impairment if certain events occur.

Intangible assets related to IPR&D projects are considered to be indefinite-lived until the completion or abandonment of the associated research and development efforts. During the period the assets are considered indefinite-lived, they will not be amortized but will be tested for impairment. Impairment testing is performed at least annually in the fourth quarter or when a triggering event occurs that could indicate a potential impairment. If the carrying value of the assets is not expected to be recovered, the assets are written down to their estimated fair values with the related impairment charge recognized in our consolidated statements of operations in the period in which the impairment occurs. If and when development is complete, which generally occurs when regulatory approval to market a product is obtained, the associated assets are deemed finite-lived and are amortized over a period that best reflects the economic benefits provided by these assets.

If projects are not successfully developed, our sales and profitability may be adversely affected in future periods. Additionally, the value of the acquired intangible assets, including IPR&D, may become impaired if the underlying projects do not progress as we initially estimated. We believe that the assumptions used in developing our estimates of intangible asset values were reasonable at the time of the acquisition. However, the underlying assumptions used to estimate expected project sales, development costs, profitability, or the events associated with such projects, such as clinical results, may not occur as we estimated at the acquisition date.

Accrued Research and Development, and Research and Development Expenses

As part of the process of preparing consolidated financial statements, we are required to estimate and accrue expenses, the largest of which is related to accrued research and development expenses. This process involves reviewing contracts and purchase orders, identifying services that have been performed on our behalf, and estimating the level of service performed and the associated cost incurred for the service when we have not yet been invoiced or otherwise notified of the actual costs.

We record accruals for estimated costs of research, preclinical and clinical studies, and manufacturing development. These costs are a significant component of our research and development expenses. A substantial portion of our ongoing research and development activities is conducted by third-party service providers. We accrue the costs incurred under our agreements with these third parties based on actual work completed in accordance with agreements established with these third parties. We determine the actual costs through discussions with internal personnel and external service providers as to the progress or stage of completion of the services and the agreed-upon fee to be paid for such services. We make significant judgments and estimates in determining the accrual balance in each reporting period. As actual costs become known, we adjust our accruals. Although we do not expect our estimates to be materially different from amounts actually incurred, our understanding of the status and timing of services performed relative to the actual status and timing of services performed may vary and could result in us reporting amounts that are too high or too low in any particular period. Our accrual is dependent, in part, upon the receipt of timely and accurate reporting from clinical research organizations and other third-party vendors.

Research and development costs are expensed as incurred and consist of salaries and benefits, stock-based compensation, lab supplies, materials and facility costs, as well as fees paid to other nonemployees and entities that conduct certain research and development activities on our behalf. Amounts incurred in connection with collaboration and license agreements are also included in research and development expense. Payments made prior to the receipt of goods or services to be used in research and development are capitalized until the goods or services are received.

To date, there have been no material differences from our accrued estimated expenses to the actual clinical trial expenses; however, due to the nature of estimates, we cannot assure you that we will not make changes to our estimates in the future as we become aware of additional information about the status or conduct of our clinical studies and other research activities.

Revenue Recognition

Collaboration and License Revenue

We have certain license and collaboration agreements that are within the scope of Accounting Standards Codification (ASC) 808, *Collaborative Agreements*, which provides guidance on the presentation and disclosure of collaborative arrangements. Generally, the classification of the transactions under the collaborative arrangements is determined based on the nature of contractual terms of the arrangement, along with the nature of the operations of the participants. We record our share of collaboration revenue, net of transfer pricing related to net sales in the period in which such sales occur, if we are considered as an agent in the arrangement. We are considered an agent when the collaboration partner controls the product before transfer to the customers and has the ability to direct the use of and obtain substantially all of the remaining benefits from the product. Funding received related to research and development services and commercialization costs is generally classified as a reduction of research and development expenses and selling, general and administrative expenses, respectively, in the consolidated statement of operations, because the provision of such services for collaborative partners are not considered to be part of our ongoing major or central operations.

We also record royalty revenues under certain of our license or collaboration agreements in exchange for license of intellectual property. If we do not have any future performance obligations for these license or collaboration agreements, royalty revenue is recorded as the underlying sales occur.

In order to record collaboration revenue, we utilize certain information from our collaboration partners, including revenue from the sale of the product, associated reserves on revenue, and costs incurred for development and sales activities. For the periods covered in the financial statements presented, there have been no material changes to prior period estimates of revenues and expenses.

The terms of our collaboration and license agreements may contain multiple performance obligations, which may include licenses and research and development activities. We evaluate these agreements under ASC 606, *Revenue from Contracts with Customers* (ASC 606), to determine the distinct performance obligations. We analogize to ASC 606 for the accounting for distinct performance obligations for which there is a customer relationship. Prior to recognizing revenue, we make estimates of the transaction price, including variable consideration that is subject to a constraint. Amounts of variable consideration are included in the transaction price to the extent that it is probable that a significant reversal in the amount of cumulative revenue recognized will not occur and when the uncertainty associated with the variable consideration is subsequently resolved. Total consideration may include nonrefundable upfront license fees, payments for research and development activities, reimbursement of certain third-party costs, payments based upon the achievement of specified milestones, and royalty payments based on product sales derived from the collaboration.

If there are multiple distinct performance obligations, we allocate the transaction price to each distinct performance obligation based on our relative standalone selling price. The standalone selling price is generally determined based on the prices charged to customers or using expected cost-plus margin. We estimate the efforts needed to complete the performance obligations and recognizes revenue by measuring the progress towards complete satisfaction of the performance obligations using input measures.

Product sales

We sell our approved products through a limited number of distributors. Under ASC 606, revenue from product sales is recognized at the point in time when the delivery is made and when title and risk of loss transfers to these distributors. We also

recognize revenue from sales of certain products on a "named patient" basis, which are allowed in certain countries prior to the commercial approval of the product. Prior to recognizing revenue, we make estimates of the transaction price, including any variable consideration that is subject to a constraint. Amounts of variable consideration are included in the transaction price to the extent that it is probable that a significant reversal in the amount of cumulative revenue recognized will not occur and when the uncertainty associated with the variable consideration is subsequently resolved. Product sales are recorded net of estimated government-mandated rebates and chargebacks, estimated product returns, and other deductions.

Provisions for returns and other adjustments are provided for in the period the related revenue is recorded, as estimated by management. These reserves are based on estimates of the amounts earned or to be claimed on the related sales and are reviewed periodically and adjusted as necessary. Our estimates of government mandated rebates, chargebacks, estimated product returns, and other deductions depends on the identification of key customer contract terms and conditions, as well as estimates of sales volumes to different classes of payors. If actual results vary, we may need to adjust these estimates, which could have an effect on earnings in the period of the adjustment.

Non-cash collaboration royalty revenue

Effective January 1, 2020, we sold the right to receive certain royalty payments from net sales of Crysvita in the European territories to RPI Finance Trust (RPI), an affiliate of Royalty Pharma. We record the royalty revenue from the net sales of Crysvita in the applicable European territories on a prospective basis as non-cash royalty revenue in the Consolidated Statements of Operations over the term of the arrangement.

Inventory

We expense costs associated with the manufacture of our products prior to regulatory approval. Typically, capitalization of such costs begin when we have received the regulatory approval of the product. Prior to the FDA approval of Mepsevii in November 2017, Crysvita in April 2018, and Dojolvi in June 2020, manufacturing and related costs were expensed; accordingly, these costs were not capitalized and as a result are not reflected in the costs of sales after the regulatory approval date. We expect inventory to increase as we produce products and capitalize the full costs of manufacturing the products. Similarly, we expect cost of sales to increase in relation to product revenues as we deplete the previously expensed inventories prior to receiving FDA approval.

Inventory that is manufactured after regulatory approval is valued at the lower of cost and net realizable value and cost is determined using the average-cost method.

We periodically review our inventories for excess amounts or obsolescence and write down obsolete or otherwise unmarketable inventory to the estimated net realizable value.

Liability Related to the Sale of Future Royalties

In December 2019, we entered into a Royalty Purchase Agreement with RPI Finance Trust (RPI), an affiliate of Royalty Pharma. Pursuant to the agreement, RPI paid us $320.0 million in consideration for the Company's right to receive royalty payments on the net sales of Crysvita in the European Union, the United Kingdom, and Switzerland effective January 1, 2020 under the terms of our Collaboration and License Agreement with KKC. The agreement with RPI will automatically terminate, and the payment of royalties to RPI will cease, in the event aggregate royalty payments received by RPI are equal to or greater than the capped amount of $608.0 million prior to December 31, 2030, or in the event aggregate royalty payments received by RPI are less than $608.0 million prior to December 31, 2030, when aggregate royalty payments received by RPI are equal to $800.0 million.

Proceeds from the transaction was recorded as a liability related to sale of future royalties on the balance sheet. We will amortize $320.0 million, net of transaction costs of $5.8 million using the effective interest method over the estimated life of the arrangement. In order to determine the amortization of the liability, we estimate the total amount of future royalty payments to be received by us and paid to RPI, subject to the capped amount, over the life of the arrangement. The aggregate future estimated royalty payments, less the $314.2 million of net proceeds, will be recorded as non-cash interest expense over the life of the arrangement. Consequently, we estimate an imputed interest on the unamortized portion of the liability and record interest expense relating to the transaction. We will continue to record the royalty revenue arising from the net sales of Crysvita in the applicable European territories as non-cash royalty revenue in our Consolidated Statements of Operations over the term of the arrangement.

We periodically assess the expected royalty payments using a combination of historical results, internal projections and forecasts from external sources. To the extent future expected royalty payments are greater or less than our initial estimates or the timing of such payments is materially different than its original estimates, we will prospectively adjust the amortization of the liability and the effective interest rate. For the three months ended December 31, 2020, our effective annual interest rate was approximately 9.8%.

There are a number of factors that could materially affect the amount and timing of royalty payments from KKC in the applicable European territories, most of which are not within our control. Such factors include, but are not limited to, the success of KKC's sales and promotion of Crysvita, changing standards of care, the introduction of competing products, pricing for reimbursement in various European territories, manufacturing or other delays, intellectual property matters, adverse events that result

in governmental health authority imposed restrictions on the use of Crysvita, significant changes in foreign exchange rates as the royalty payments are made in U.S. dollars (USD) while significant portions of the underlying European sales of Crysvita are made in currencies other than USD, and other events or circumstances that could result in reduced royalty payments from European sales of Crysvita, all of which would result in a reduction of non-cash royalty revenues and the non-cash interest expense over the life of the arrangement. Conversely, if sales of Crysvita in Europe are more than expected, the non-cash royalty revenues and the non-cash interest expense recorded by us would be greater over the term of the arrangement.

Stock-Based Compensation

Stock-based compensation costs related to equity awards granted to employees are measured at the date of grant based on the estimated fair value of the award, net of estimated forfeitures. We estimate the grant date fair value of options, and the resulting stock-based compensation expense, using the Black-Scholes option-pricing model. The grant date fair value of the stock-based awards is recognized on a straight-line basis over the requisite service period, which is generally the vesting period of the respective awards. We expect to continue to grant stock options in the future, and to the extent that we do, our actual stock-based compensation expense will likely increase. The Black-Scholes option-pricing model requires the use of certain subjective assumptions which determine the estimated fair value of stock-based awards.

- *Expected Term* — The expected term represents the period that the stock-based awards are expected to be outstanding and is determined using the simplified method (based on the midpoint between the vesting date and the end of the contractual term).
- *Expected Volatility*— The expected volatility is based on historical volatility over the look-back period corresponding to the expected term.

In addition to the assumptions used in the Black-Scholes option-pricing model, we also estimate a forfeiture rate to calculate the stock-based compensation for our awards. We will continue to use judgment in evaluating the expected volatility, expected terms, and forfeiture rates utilized for our stock-based compensation calculations on a prospective basis and will revise in subsequent periods, if actual forfeitures differ from those estimates.

For restricted stock units (RSUs) and performance stock units (PSUs), the fair value is based on the market value of our common stock on the date of grant. Stock-based compensation expense for RSUs is recognized on a straight-line basis over the requisite service period. PSUs are subject to vest only if certain specified criteria are achieved and the employees' continued service with the Company after achievement of the specified criteria. For certain PSUs, the number of PSUs that may vest are also subject to the achievement of certain specified criteria. Compensation expense for PSUs is recognized only after the achievement of the specified criteria is considered probable and recognized on a straight-line basis between the grant date and the expected vest date, with a catch-up for previously unrecognized expense, if any, recognized in the period the achievement criteria is deemed probable.

For the years ended December 31, 2020, 2019, and 2018 stock-based compensation expense was $85.7 million, $82.0 million and $80.1 million, respectively. As of December 31, 2020, we had $155.6 million of total unrecognized stock-based compensation costs, net of estimated forfeitures, which we expect to recognize over a weighted-average period of 2.48 years.

Income Taxes

We use the liability method of accounting for income taxes. Under this method, deferred tax assets and liabilities are determined based on the differences between the financial reporting and the tax bases of assets and liabilities and are measured using the enacted tax rates and laws that will be in effect when the differences are expected to reverse. We assess the likelihood that the resulting deferred tax assets will be realized. A valuation allowance is provided when it is more likely than not that some portion or all of a deferred tax asset will not be realized.

In conjunction with the Dimension acquisition in 2017, we recorded a deferred tax liability reflecting the tax impact of the difference between the book basis and tax basis of acquired IPR&D. Such deferred income tax liability was not used to offset deferred tax assets when analyzing our valuation allowance as the acquired IPR&D is considered to have an indefinite life until we complete or abandon development of the acquired IPR&D.

We recognize benefits of uncertain tax positions if it is more likely than not that such positions will be sustained upon examination based solely on their technical merits, as the largest amount of benefit that is more likely than not to be realized upon the ultimate settlement. Our policy is to recognize interest and penalties related to the underpayment of income taxes as a component of income tax expense or benefit. To date, there have been no interest or penalties charged in relation to the unrecognized tax benefits.

As of December 31, 2020, our total deferred tax assets were $561.1 million, excluding the deferred tax liability generated from the Dimension acquisition. Due to our lack of earnings history and uncertainties surrounding our ability to generate future taxable income, the net deferred tax assets have been fully offset by a valuation allowance. The deferred tax assets were primarily comprised of federal and state tax net operating losses and tax credit carryforwards. Utilization of the net operating loss and tax credit carryforwards may be subject to an annual limitation due to historical or future ownership percentage change rules provided by the Internal Revenue Code of 1986, and similar state provisions. The annual limitation may result in the expiration of certain net operating loss and tax credit carryforwards before their utilization.

Results of Operations

Comparison of Years Ended December 31, 2020 and 2019

Revenues (dollars in thousands)

	Year Ended December 31,		Dollar	%
	2020	2019	Change	Change
Collaboration and license revenue:				
Crysvita collaboration revenue in profit-share territory	$ 128,597	$ 74,869	$ 53,728	72%
Crysvita royalty revenue in European territory	1,498	8,120	(6,622)	(82%)
Daiichi Sankyo	89,220	—	89,220	*
Bayer	—	504	(504)	(100%)
Total collaboration and license revenue	219,315	83,493	135,822	163%
Product sales:				
Crysvita	10,350	4,286	6,064	141%
Mepsevii	15,342	12,634	2,708	21%
Dojolvi	13,028	3,301	9,727	295%
Total product sales	38,720	20,221	18,499	91%
Crysvita non-cash collaboration royalty revenue	12,995	—	12,995	*
Total revenues	$ 271,030	$ 103,714	$ 167,316	161%

* not meaningful

For the year ended December 31, 2020, the Company's share of Crysvita collaboration revenue in the profit-share territory increased by $53.7 million, as compared to the same period in 2019. The increase primarily reflects the continuing increase in demand for Crysvita due to an increase in the number of patients on therapy.

In December 2019, we sold the rights to the Crysvita royalty payments in the European territory, including the United Kingdom and Switzerland, to Royalty Pharma. Beginning in 2020, we recorded the royalty revenue as non-cash royalty revenues. During the year ended December 31, 2020, there was a change in estimate of the revenue reserves related to sales made prior to January 1, 2020. As a result, we recorded an additional $1.5 million as royalty revenue in the European territory.

In March 2020, we executed a license agreement with Daiichi Sankyo, pursuant to which we granted Daiichi Sankyo a non-exclusive license to intellectual property, including know-how and patent applications, with respect to our HeLa PCL and HEK293 transient transfection manufacturing technology platforms for AAV-based gene therapy products. We will also provide certain technical assistance and technology transfer services during the technology transfer period of three years to enable Daiichi Sankyo to use the technologies for its internal gene therapy programs. For the year ended December 31, 2020, we recognized $89.2 million as collaboration and license revenue from this arrangement. As of December 31, 2020, we expect to recognize a substantial majority of the remaining contract liabilities balance of $66.6 million as revenue over the technology transfer service period, which is currently estimated to be complete by the end of 2021.

The decrease in collaboration and license revenue from our research arrangement with Bayer was due to the transition of the clinical development to Bayer as part of the research arrangement.

The increase in product sales of $18.5 million for the year ended December 31, 2020 compared to the same period in 2019 was primarily due to the launch of Dojolvi in the United States in the third quarter of 2020, continuing increase in demand for Crysvita and Mepsevii, and an increase in sales of Dojolvi under our named patient program in certain countries.

Cost of Sales (dollars in thousands)

	Year Ended December 31,		Dollar	%
	2020	2019	Change	Change
Cost of sales	$ 6,129	$ 9,008	$ (2,879)	(32%)

Cost of sales related to our approved products decreased by $2.9 million for the year ended December 31, 2020, compared to the same period in 2019. The cost of sales for the year ended December 31, 2020 included a credit for the manufacturing of future inventory batches with an estimated value of $4.6 million and was agreed to during the period with one of our manufacturers due to certain inventory batches that did not meet specified quality standards. The Company previously recorded reserves of $5.7 million on these inventory batches during the year ended December 31, 2019. For the year ended December 31, 2020, we recorded an additional $3.0 million in reserves related to inventory in excess of our forecasted demand. The decrease in cost of sales for the year ended December 31, 2020 compared to the same period in 2019 was due to the reserve on inventory batches recorded in 2019 and related manufacturing credit recorded in 2020, partially offset by an increase in demand for our approved products, the launch of Dojolvi in the third quarter of 2020, and the increase in reserve for excess inventory.

Prior to the approval of our products, manufacturing and related costs were expensed; accordingly, these costs were not capitalized and as a result are not fully reflected in the costs of sales during the year ended December 31, 2020. If manufacturing and related costs were capitalized prior to the approval period and the credit of $4.6 million as noted above were excluded, we estimate that cost of sales for the years ended December 31, 2020 and 2019 would have been approximately $11.4 million and $9.7 million, respectively, for our commercial product sales. These estimates include the additional $3.0 million and $5.7 million of reserves on inventory for the year ended December 31, 2020 and 2019, respectively. We expect our gross margin percentage to decrease as we produce approved products that reflect the full costs of manufacturing and as we deplete inventories that we had expensed prior to receiving approval.

Research and Development Expenses (dollars in thousands)

	Year Ended December 31,		Dollar	%
	2020	2019	Change	Change
Crysvita	$ 29,270	$ 37,872	$ (8,602)	(23%)
Mepsevii	13,738	17,299	(3,561)	(21%)
Dojolvi	34,678	36,652	(1,974)	(5%)
DTX401	39,235	33,245	5,990	18%
DTX301	39,193	39,191	2	0%
GTX102	28,100	20,172	7,928	39%
Translational research	103,087	57,300	45,787	80%
Other research costs	124,783	115,624	9,159	8%
Total research and development expenses	$ 412,084	$ 357,355	$ 54,729	15%

Research and development expenses increased $54.7 million for the year ended December 31, 2020 compared to the same period in 2019. The increase in research and development expenses was primarily due to:

- for Crysvita, a decrease of $8.6 million primarily related to reduced clinical trial activity with the progressive completion of our extension studies and reduced allocation of employees and contractors to R&D support activities, net of KKC reimbursement;
- for Mepsevii, a decrease of $3.6 million primarily related to reduced clinical trial activity with the progressive completion of our extension studies and reduced allocation of employees and contractors to R&D support activities;
- for Dojolvi, a decrease of $2.0 million primarily related to the impact of inventory capitalization of commercial manufacturing costs post-approval by the FDA in June 2020 and NDA filing costs incurred in 2019;
- for DTX401, a net increase of $6.0 million, primarily related to close out costs for one of our manufacturing sites, as well as the timing of clinical drug substance manufacturing activities and drug product batch releases, including a credit for the manufacturing of future batches with an estimated value of $2.9 million that was agreed to in 2020 with one of our manufacturers due to certain batches that did not meet specified quality standards, in addition to increased internal and clinical vendor expenses in preparation for our Phase 3 trial;
- for DTX301, a nominal increase, primarily related to the timing of clinical drug substance manufacturing activities and drug product batch releases;
- for GTX102, an increase of $7.9 million, primarily due to the $25.0 million option extension payment to GeneTx that occurred in 2020, compared to the $20.0 million upfront payment to GeneTx that occurred in 2019;
- for translational research, an increase of $45.8 million primarily related to research, process development, and manufacturing activities, including the progression of our UX701, UX053, and UX068 programs toward IND filings; and in 2020, the $7.0 million payment to REGNEXBIO for exclusive, worldwide rights to NAV AAV8 and AAV9 vectors for the development and commercialization of gene therapy treatments for a rare metabolic disorder; and
- an increase of $9.2 million in other research and development costs primarily related to the one-time in-process R&D expense of $13.2 million related to the Solid Collaboration and License Agreement incurred in October 2020 and increases in general operating, facilities, IT, and other overhead expenses in support of our clinical and research program pipeline, partially offset by reduced clinical trial expense for the wind-down of the UX007 Glut 1 program.

We expect our annual research and development expenses to continue to increase in the future as we advance our product candidates such as UX143 through clinical development. The timing and amount of expenses incurred will depend largely upon the outcomes of current or future clinical studies for our product candidates as well as the related regulatory requirements, manufacturing costs, and any costs associated with the advancement of our preclinical programs.

Selling, General and Administrative Expenses (dollars in thousands)

	Year Ended December 31,		Dollar	%
	2020	2019	Change	Change
Selling, general and administrative	$ 182,933	$ 161,524	$ 21,409	13%

Selling, general and administrative expenses increased $21.4 million for the year ended December 31, 2020 compared to the same period in 2019. The increases in selling, general and administrative expenses were primarily due to increases in personnel costs resulting from an increase in the number of employees in support of our commercial activities, commercialization costs, and professional services costs, partially offset by lower travel and related expenses due to travel restrictions in connection with the COVID-19 pandemic.

We expect selling, general and administrative expenses to continue to increase in the future to support our organizational growth and for our expected staged build out of our commercial organization over the next several years related to our approved products and multiple clinical-stage product candidates.

Interest Income (dollars in thousands)

	Year Ended December 31,		Dollar	%
	2020	2019	Change	Change
Interest income	$ 7,038	$ 13,238	$ (6,200)	(47%)

Interest income decreased $6.2 million for the year ended December 31, 2020 compared to the same period in 2019, primarily due to lower portfolio yields as a result of lower interest rates during the year ended December 31, 2020.

Change in Fair Value of Equity Investments (dollars in thousands)

	Year Ended December 31,		Dollar	%
	2020	2019	Change	Change
Change in fair value of equity investments	$ 170,403	$ 13,413	$ 156,990	1170%

The increase in the fair value of our equity investments of $157.0 million for the year ended December 31, 2020 was due to the increase in our unrealized gains from the remeasurement of the Arcturus common stock, and the realized gains from the sale of a portion of the Company's Arcturus common stock holdings, resulting in an increase in net change of $124.5 million, and the unrealized gains on our investment in Solid common stock of $32.5 million. Given the historic volatility of the publicly traded stock price of Arcturus and Solid, the fair value adjustments of our equity investments may be subject to wide fluctuations which may have a significant impact on our earnings in future periods.

Non-cash Interest Expense on Liability Related to the Sale of Future Royalties (dollars in thousands)

	Year Ended December 31,		Dollar	%
	2020	2019	Change	Change
Non-cash interest expense on liability related to the sale of future royalties	$ 33,291	$ 1,135	$ 32,156	2833%

The increase in the non-cash interest expense on liability related to the sale of future royalties of $32.2 million for the year ended December 31, 2020 was due to the interest accreted on the liability related to the sale of future royalties for net sales of Crysvita in the European territory pursuant to the Royalty Purchase Agreement entered into with RPI in December 2019. To the extent the royalty payments are greater or less than our initial estimates or the timing of such payments is materially different than our original estimates, we will prospectively adjust the effective interest rate.

Other Income (Expense) (dollars in thousands)

	Year Ended December 31,		Dollar	%
	2020	2019	Change	Change
Other income (expense)	$ 607	$ (787)	$ 1,394	(177%)

Other income (expense) increased $1.4 million for the year ended December 31, 2020 compared to the same period in 2019. The fluctuations were primarily due to fluctuations in foreign exchange rates.

Provision for income taxes

	Year Ended December 31,		Dollar	%
	2020	2019	Change	Change
Provision for income taxes	$ (1,207)	$ (3,283)	$ 2,076	(63%)

The provision for incomes taxes decreased by $2.1 million for the year ended December 31, 2020 compared to the same period in 2019. The decrease was primarily due to changes in state tax apportionment which resulted in an increase in the deferred tax liability from the acquisition of Dimension that was recorded in 2019.

Liquidity and Capital Resources

To date, we have funded our operations primarily from the sale of our equity securities, the sale of certain future royalties, and strategic collaboration arrangements.

As of December 31, 2020, we had $1,212.0 million in available cash, cash equivalents, and marketable debt securities. We believe that our existing capital resources will be sufficient to fund our projected operating requirements for at least the next twelve months. Our cash, cash equivalents, and marketable debt securities are held in a variety of deposit accounts, interest-bearing accounts, corporate bond securities, U.S government securities, asset-backed securities, and money market funds. Cash in excess of immediate requirements is invested with a view toward liquidity and capital preservation, and we seek to minimize the potential effects of concentration and credit risk.

In December 2019, we received net proceeds of $314.2 million from the sale of future royalties to RPI. In March 2020, we received $75.0 million in cash from the sale of 1,243,913 shares of our common stock to Daiichi Sankyo and in April 2020, we received $125.0 million in an upfront payment related to the Daiichi Sankyo License Agreement. In November 2020, we completed an underwritten public offering in which we sold 5,111,110 shares of common stock and received net proceeds of $435.6 million. In December 2020, we sold 800,000 shares of Arcturus common stock and received net proceeds of $79.8 million. During the year ended December 31, 2020, the proceeds from our at-the-market, or ATM, offering was $20.4 million, after commissions and other offering costs. As of December 31, 2020, we had completed the sale of all available amounts under our ATM facility.

The following table summarizes our cash flows for the periods indicated (in thousands):

	Year Ended December 31,		
	2020	2019	2018
Cash used in operating activities	$ (132,220)	$ (345,383)	$ (290,566)
Cash used in investing activities	(179,121)	(13,039)	(33,331)
Cash provided by financing activities	600,272	679,306	336,853
Effect of exchange rate changes on cash	1,119	(165)	(472)
Net increase in cash, cash equivalents, and restricted cash	$ 290,050	$ 320,719	$ 12,484

Cash Used in Operating Activities

Our primary use of cash is to fund operating expenses, which consist primarily of research and development and commercial expenditures. Due to our significant research and development expenditures, we have generated significant operating losses since our inception. Cash used to fund operating expenses is affected by the timing of when we pay these expenses, as reflected in the change in our outstanding accounts payable and accrued expenses.

Cash used in operating activities for the year ended December 31, 2020 was $132.2 million and reflected a net loss of $186.6 million, $170.4 million for a change in fair value of equity investments from Arcturus and Solid and $13.0 million for non-cash collaboration royalty revenues related to the sale of future royalties to RPI, offset by non-cash charges of $85.7 million for stock-based compensation, $12.3 million for depreciation, $0.8 million for the amortization of the premium paid on purchased investments, and $33.3 million for non-cash interest incurred on the liability related to the sale of future royalties to RPI. Cash used in operating activities also reflected a $1.3 million decrease due to an increase in inventory for Mepsevii and Dojolvi. These decreases were offset by a $9.8 million increase due to a decrease in accounts receivable primarily related to change in the timing of billing to a collaboration partner, a $2.7 million increase due to decrease in prepaid expenses and other assets primarily related to a change in the timing of billing to a collaboration partner, a $26.9 million increase in accounts payable, accrued, and other liabilities primarily due to an increase in annual accrued bonus due to higher employee headcount and attainment of company goals, and an increase of $66.6 million in contract liabilities, net, related to the license agreements with Daiichi Sankyo.

Cash used in operating activities for the year ended December 31, 2019 was $345.4 million and reflected a net loss of $402.7 million, $6.2 million for the amortization of the discount paid on purchased investments, and $13.4 million for an unrealized gain in the Arcturus equity investment, offset by non-cash charges of $82.0 million for stock-based compensation, $8.5 million for depreciation and amortization, $0.7 million non-cash foreign currency remeasurement losses in connection with fluctuations of exchange rates related to intercompany transactions with foreign subsidiaries that are denominated in our reporting currency, and $1.1 million for non-cash interest incurred on the liability related to the sale of future royalties to RPI. Cash used in operating activities also reflected a $20.1 million decrease due to an increase in accounts receivable from the commercialization of Mepsevii and Crysvita, a $4.5 million decrease due to an increase in inventory as we build out our commercial inventory supplies as we commercialize Mepsevii, and a $8.2 million decrease due to an increase in prepaid expenses and other assets primarily due to an increase in general receivables, amounts due from a collaboration partner, and amounts owed for a tenant improvement allowance. These decreases were offset by a $13.3 million increase in accounts payable, accrued, and other liabilities primarily due to increased commercial and research activities and the timing of payments and receipt of invoices offset by the derecognition of deferred rent obligations for the new lease accounting guidance and a $2.1 million increase in deferred tax liabilities due to adjustments made related to the Dimension acquisition.

Cash Used in Investing Activities

Cash used in investing activities for the year ended December 31, 2020 was $179.1 million and related to purchases of property, plant, and equipment of $43.9 million, which includes $21.1 million paid for the acquisition of the land and ongoing construction costs for the gene therapy manufacturing plant in Bedford, Massachusetts, purchases of marketable debt securities of $813.2 million, purchases of equity investments of $37.1 million primarily related to $26.8 million for the purchase of Solid shares and $9.6 million for the exercise of the option to purchase additional Arcturus shares, and other activities of $5.6 million that included $3.3 million for the purchase of a convertible notes receivable and the milestone payments of $2.3 million recorded as an intangible asset resulting from the FDA approval of Dojolvi, offset by proceeds from maturities of marketable debt securities of $589.8 million, the sale of Arcturus common stock of $79.8 million, and the sale of marketable debt securities of $51.0 million.

Cash used in investing activities for the year ended December 31, 2019 was $13.0 million and related to purchases of property, plant, and equipment of $24.8 million, purchases of marketable debt securities of $692.8 million, and the purchase of the Arcturus equity investment of $14.3 million, offset by proceeds from maturities of marketable debt securities of $676.2 million and the sale of marketable debt securities of $42.7 million.

Cash Flows Provided by Financing Activities

Cash provided by financing activities for the year ended December 31, 2020 was $600.3 million and was comprised of $435.6 million in net proceeds from the issuance of sale of common stock in our underwritten public offering, $55.3 million in net proceeds from the issuance of common stock in connection with the license agreement with Daiichi Sankyo in March 2020, $20.4 million in net proceeds from the issuance of common stock from our ATM offering, and $89.3 million in net proceeds from the issuance of common stock upon the exercise of warrants and stock options, net of taxes withheld from the vesting of restricted stock units, offset by other activities of $0.2 million in principal repayments of finance leases.

Cash provided by financing activities for the year ended December 31, 2019 was $679.3 million and was comprised of $314.2 million related to net proceeds from the sale of future royalties to Royalty Pharma, $330.4 million in net proceeds from the issuance of common stock in our underwritten public offering, $24.8 million in net proceeds from the issuance of common stock from our ATM offering, and $9.8 million in net proceeds from the issuance of common stock upon the exercise of stock options, offset by taxes withheld from the vesting of restricted stock units.

Funding Requirements

We anticipate that, excluding non-recurring items, we will continue to generate annual losses for the foreseeable future as we continue the development of, and seek regulatory approvals for, our product candidates, and continue with commercialization of approved products. We will likely require additional capital to fund our operations, to complete our ongoing and planned clinical studies, to commercialize our products, to continue investing in early-stage research capabilities to promote our pipeline growth, to continue to acquire or invest in businesses or products that complement or expand our business, and to further develop our general infrastructure, including construction of our GMP gene therapy manufacturing facility, and such funding may not be available to us on acceptable terms or at all.

If we are unable to raise additional capital in sufficient amounts or on terms acceptable to us, we may be required to delay, limit, reduce the scope of, or terminate one or more of our clinical studies, research and development programs, future commercialization efforts, or grant rights to develop and market product candidates that we would otherwise prefer to develop and market ourselves.

Our future funding requirements will depend on many factors, including the following:

- the scope, rate of progress, results and cost of our clinical studies, nonclinical testing, and other related activities;
- the cost of manufacturing clinical supplies, and establishing commercial supplies, of our product candidates, products that we have begun to commercialize, and any products that we may develop in the future, including the potential development of our own GMP gene therapy manufacturing plant;
- the number and characteristics of product candidates that we pursue;
- the cost, timing, and outcomes of regulatory approvals;
- the cost and timing of establishing our commercial infrastructure, and distribution capabilities;
- the magnitude and extent to which the COVID-19 pandemic impacts our business operations and operating results, as described in "Management's Discussion and Analysis of Financial Condition and Results of Operations" and "Risk Factors – Risks Related to Our Business Operations"; and
- the terms and timing of any collaborative, licensing, marketing, distribution, acquisition (including whether we exercise our option to acquire GeneTx pursuant to the terms of our Unitholder Option Agreement with them) and other arrangements that we may establish, including any required upfront milestone, royalty, reimbursements or other payments thereunder.

We expect to satisfy future cash needs through existing capital balances and through some combination of public or private equity offerings, debt financings, collaborations, strategic alliances, licensing arrangements, and other marketing and distribution arrangements. Please see "Risk Factors—Risks Related to Our Financial Condition and Capital Requirements."

Contractual Obligations

We have contractual obligations from our operating and finance leases, manufacturing and service contracts, licenses, royalties, development and collaboration arrangements, and other research and development activities. The following table summarizes our significant binding contractual obligations at December 31, 2020 (in thousands):

	Payments due by period				
	Less than 1 year	1 to 3 years	3 to 5 years	More than 5 years	Total
Operating and finance leases	$ 11,931	$ 24,784	$ 16,566	$ 3,456	$ 56,737
Manufacturing and service contracts	4,330	472	—	—	4,802
Land and building construction agreement	26,078	382	—	—	26,460
License and collaboration agreement*	50,000	—	—	—	50,000
Total	$ 92,339	$ 25,638	$ 16,566	$ 3,456	$ 137,999

* Includes a $50.0 million purchase commitment with Mereo BioPharma Group plc under the license and collaboration agreement which was subsequently paid in January 2021 upon the closing of the transaction

The terms of certain of our licenses, royalties, development and collaboration agreements, as well as other research and development activities, require us to pay potential future milestone payments based on product development success. The above table excludes such obligations as the amount and timing of such obligations are unknown or uncertain, which potential obligations are further described in Notes 9 and 15 to the accompanying Consolidated Financial Statements.

Recent Accounting Pronouncements

None

Off-Balance Sheet Arrangements

Since our inception in April 2010, we have not engaged in any off-balance sheet arrangements, as defined in the rules and regulations of the SEC.

Item 7A. ***Quantitative and Qualitative Disclosures About Market Risk***

Equity Risk

We have exposure to equity risk with respect to the equity investments that we hold in Arcturus and Solid. The carrying value of our equity investment held in Arcturus was $95.4 million and $27.8 million as of December 31, 2020 and 2019, respectively, and the carrying value of our equity investment held in Solid was $59.3 million as of December 31, 2020. If the Arcturus or Solid stock price had been lower at December 31, 2020 compared to December 31, 2019, we would have reported an even greater net loss for the year ended December 31, 2020. A hypothetical 10 percent decrease in the market price for our equity investments as of December 31, 2020 and 2019 would decrease the fair value by $15.5 million and $2.7 million, respectively. Given the historic volatility of the publicly traded stock price of Arcturus and Solid, the fair value of our investments in Arcturus and Solid is subject to wide fluctuations which may have a significant impact on our net income (loss) in future periods.

Interest Rate Risk

Our exposure to market risk for changes in interest rates relates primarily to interest earned on our cash equivalents and marketable debt securities. The primary objective of our investment activities is to preserve our capital to fund operations. A secondary objective is to maximize income from our investments without assuming significant risk. Our investment policy provides for investments in low-risk, investment-grade debt instruments. As of December 31, 2020 and 2019, we had cash, cash equivalents, and marketable debt securities totaling $1,212.0 million and $760.4 million, respectively, which include bank deposits, money market funds, U.S. government treasury and agency securities, and investment-grade corporate bond securities which are subject to default, changes in credit rating, and changes in market value. The securities in our investment portfolio are classified as available for sale and are subject to interest rate risk and will decrease in value if market interest rates increase. Due to the COVID-19 pandemic and the reduction of rates by the U.S. Federal Reserve, we expect that the interest yield on our investments may continue to decrease. A hypothetical 100 basis point change in interest rates during any of the periods presented would not have had a material impact on the fair market value of our cash equivalents and marketable debt securities as of December 31, 2020 and 2019. To date, we have not experienced a loss of principal on any of our investments and as of December 31, 2020, we did not record any allowance for credit loss from our investments.

Foreign Currency Risk

We face foreign exchange risk as a result of entering into transactions denominated in currencies other than U.S. dollars. Due to the uncertain timing of expected payments in foreign currencies, we do not utilize any forward exchange contracts. All foreign transactions settle on the applicable spot exchange basis at the time such payments are made. Volatile market conditions arising from the COVID-19 pandemic may result in significant changes in exchange rates, and in particular a weakening of foreign currencies relative to the U.S. dollar may negatively affect our revenue and operating income as expressed in U.S. dollars. An adverse movement in foreign exchange rates could have a material effect on payments made to foreign suppliers and for license agreements. For the year ended December 31, 2020, a majority of our revenue and expense activities and capital expenditures were denominated in U.S. dollars. A hypothetical 10% change in foreign exchange rates during any of the periods presented would not have had a material impact on our consolidated financial statements.

Item 8. ***Financial Statements and Supplementary Data***

Our financial statements are annexed to this Annual Report beginning on page F-1 and are incorporated by reference into this Item 8.

Item 9. ***Changes in and Disagreements with Accountants on Accounting and Financial Disclosure***

None.

Item 9A. ***Controls and Procedures***

Evaluation of Disclosure Controls and Procedures

We carried out an evaluation, under the supervision and with the participation of our management, including our Chief Executive Officer and our Chief Financial Officer, of the effectiveness of our "disclosure controls and procedures" as of the end of the period covered by this Annual Report, pursuant to Rules 13a-15(b) and 15d-15(b) under the Exchange Act. In connection with that evaluation, our Chief Executive Officer and our Chief Financial Officer concluded that our disclosure controls and procedures were effective and designed to provide reasonable assurance that the information required to be disclosed is recorded, processed, summarized and reported within the time periods specified in the SEC rules and forms as of December 31, 2020. For the purpose of this review, disclosure controls and procedures means controls and procedures designed to ensure that information required to be disclosed by us in the reports that we file or submit is recorded, processed, summarized and reported within the time periods specified in the SEC's rules and forms. These disclosure controls and procedures include, without limitation, controls and procedures designed to ensure that information required to be disclosed by us in the reports that we file or submit is accumulated and communicated to management, including our principal executive officer and principal financial officer, as appropriate to allow timely decisions regarding required disclosure. In designing and evaluating the disclosure controls and procedures, our management recognized that any controls and procedures, no matter how well designed and operated, can provide only reasonable assurance of achieving the desired control objectives, and our management necessarily was required to apply its judgment in evaluating the cost-benefit relationship of possible controls and procedures.

Management's Annual Report on Internal Control Over Financial Reporting

Management is responsible for establishing and maintaining adequate internal control over financial reporting as defined in Rules 13a-15(f) and 15d-15(f) of the Exchange Act. Our management used the Committee of Sponsoring Organizations of the Treadway Commission Internal Control - *Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission* (2013 framework), or the COSO framework, to evaluate the effectiveness of internal control over financial reporting. Management believes that the COSO framework is a suitable framework for its evaluation of financial reporting because it is free from bias, permits reasonably consistent qualitative and quantitative measurements of our internal control over financial reporting, is sufficiently complete so that those relevant factors that would alter a conclusion about the effectiveness of our internal control over financial reporting are not omitted and is relevant to an evaluation of internal control over financial reporting.

Management has assessed the effectiveness of our internal control over financial reporting as of December 31, 2020 and has concluded that such internal control over financial reporting is effective.

Our independent registered public accounting firm, Ernst & Young LLP, has audited the financial statements included in this Annual Report and has issued a report on the effectiveness of our internal control over financial reporting. The report of Ernst & Young LLP is included below.

Changes in Internal Control over Financial Reporting

There have been no changes in our internal control over financial reporting (as defined in Rules 13a-15(f) and 15d-15(f) under the Exchange Act) during our fourth quarter ended December 31, 2020, that have materially affected, or are reasonably likely to materially affect our internal control over financial reporting.

Report of Independent Registered Public Accounting Firm

To the Stockholders and the Board of Directors of Ultragenyx Pharmaceutical Inc.:

Opinion on Internal Control over Financial Reporting

We have audited Ultragenyx Pharmaceutical Inc.'s internal control over financial reporting as of December 31, 2020, based on criteria established in *Internal Control—Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission* (2013 framework) (the COSO criteria). In our opinion, Ultragenyx Pharmaceutical Inc (the Company) maintained, in all material respects, effective internal control over financial reporting as of December 31, 2020, based on the COSO criteria.

We also have audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States) (PCAOB), the consolidated balance sheets of Ultragenyx Pharmaceutical Inc. (the Company) as of December 31, 2020 and 2019, the related consolidated statements of operations, comprehensive loss, stockholders' equity and cash flows for each of the three years in the period ended December 31, 2020, and our report dated February 11, 2021 expressed an unqualified opinion thereon.

Basis for Opinion

The Company's management is responsible for maintaining effective internal control over financial reporting and for its assessment of the effectiveness of internal control over financial reporting included in the accompanying Management's Annual Report on Internal Control over Financial Reporting. Our responsibility is to express an opinion on the Company's internal control

over financial reporting based on our audit. We are a public accounting firm registered with the PCAOB and are required to be independent with respect to the Company in accordance with the U.S. federal securities laws and the applicable rules and regulations of the Securities and Exchange Commission and the PCAOB.

We conducted our audit in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether effective internal control over financial reporting was maintained in all material respects. Our audit included obtaining an understanding of internal control over financial reporting, assessing the risk that a material weakness exists, testing and evaluating the design and operating effectiveness of internal control based on the assessed risk, and performing such other procedures as we considered necessary in the circumstances. We believe that our audit provides a reasonable basis for our opinion.

Definition and Limitations of Internal Control Over Financial Reporting

A company's internal control over financial reporting is a process designed to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles. A company's internal control over financial reporting includes those policies and procedures that (1) pertain to the maintenance of records that, in reasonable detail, accurately and fairly reflect the transactions and dispositions of the assets of the company; (2) provide reasonable assurance that transactions are recorded as necessary to permit preparation of financial statements in accordance with generally accepted accounting principles, and that receipts and expenditures of the company are being made only in accordance with authorizations of management and directors of the company; and (3) provide reasonable assurance regarding prevention or timely detection of unauthorized acquisition, use, or disposition of the company's assets that could have a material effect on the financial statements.

Because of its inherent limitations, internal control over financial reporting may not prevent or detect misstatements. Also, projections of any evaluation of effectiveness to future periods are subject to the risk that controls may become inadequate because of changes in conditions, or that the degree of compliance with the policies or procedures may deteriorate.

/s/ Ernst & Young LLP

San Jose, California
February 11, 2021

Item 9B. Other Information

None.

PART III

Item 10. ***Directors, Executive Officers and Corporate Governance***

The information required by this Item is incorporated herein by reference to information in the proxy statement for our 2021 Annual Meeting of Stockholders, which we will file with the SEC within 120 days of the end of the fiscal year to which this Annual Report relates (the "2021 Proxy Statement"), including under the headings "Proposal No. 1—Election of Class II Directors," "Information About Our Executive Officers," "Corporate Governance—Global Code of Conduct," "Proposal No. 1—Election of Class II Directors—Nomination of Directors," "Board of Directors and Committees," and, as applicable, "Delinquent Section 16(a) Reports." We have adopted a code of ethics that applies to all of our directors, officers and employees, including our principal executive, principal financial and principal accounting officers, or persons performing similar functions, or Code of Ethics. Our Code of Ethics is posted on our corporate governance website located at *www.ultragenyx.com*. We intend to disclose future amendments to certain provisions of the Code of Ethics, and waivers of the Code of Ethics granted to executive officers and directors, on the website within four business days following the date of the amendment or waiver.

Item 11. ***Executive Compensation***

The information required by this Item is incorporated herein by reference to information in the 2021 Proxy Statement, including under the headings "Executive Compensation," "Director Compensation," "Board of Directors and Committees—Compensation Committee Interlocks and Insider Participation," "Executive Compensation—Risk Management and Mitigation," and "Executive Compensation—Compensation Committee Report."

Item 12. ***Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters***

The information required by this Item is incorporated herein by reference to information in the 2021 Proxy Statement, including under the headings "Security Ownership of Certain Beneficial Owners and Management" and "Equity Compensation Plan Information."

Item 13. ***Certain Relationships and Related Transactions, and Director Independence***

The information required by this Item is incorporated herein by reference to information in the 2021 Proxy Statement, including under the headings "Certain Relationships and Related-Person Transactions," "Corporate Governance," and "Board of Directors and Committees."

Item 14. ***Principal Accountant Fees and Services***

The information required by this Item is incorporated herein by reference to information in the 2021 Proxy Statement, including under the heading "Proposal No. 2—Ratification of the Selection of Independent Registered Public Accounting Firm."

PART IV

Item 15. ***Exhibits and Financial Statement Schedules***

(a) The following documents are filed as part of this Annual Report.

(1) Consolidated Financial Statements

Consolidated Financial Statements—See Index to Consolidated Financial Statements at page F-1 of this Annual Report.

(2) Consolidated Financial Statement Schedules

Consolidated Financial statement schedules have been omitted in this Annual Report because they are not applicable, not required under the instructions, or the information requested is set forth in the consolidated financial statements or related notes thereto.

(b) Exhibits

Exhibit Number	Exhibit Description	Incorporated by Reference			Filed Herewith
		Form	Date	Number	
3.1	Amended and Restated Certificate of Incorporation	8-K	2/5/2014	3.1	
3.2	Amended and Restated Bylaws	8-K	2/5/2014	3.2	
4.1	Reference is made to Exhibits 3.1 and 3.2				
4.2	Form of Common Stock Certificate	S-1	11/8/2013	4.2	
4.3	Description of Common Stock	10-K	2/14/2020	4.3	
10.1†	Collaboration and License Agreement, effective as of August 29, 2013, between Ultragenyx Pharmaceutical Inc. and Kyowa Hakko Kirin Co., Ltd.	S-1/A	12/23/2013	10.1	
10.2	Amendment No. 1 to Collaboration and License Agreement, effective as of August 24, 2015, between Ultragenyx Pharmaceutical Inc. and Kyowa Hakko Kirin Co., Ltd.	10-Q	11/10/2015	10.2	
10.3	Amendment No. 2 to Collaboration and License Agreement, effective as of November 28, 2016, between Ultragenyx Pharmaceutical Inc. and Kyowa Hakko Kirin Co., Ltd.	10-K	2/21/2018	10.3	
10.4†	Amendment No. 3 to Collaboration and License Agreement, effective September 29, 2017, between Ultragenyx Pharmaceutical Inc. and Kyowa Hakko Kirin Co., Ltd.	10-K	2/21/2018	10.4	
10.5†	Amendment No. 4 to Collaboration and License Agreement, effective as of January 29, 2018, between Ultragenyx Pharmaceutical Inc. and Kyowa Hakko Kirin Co., Ltd.	10-K	2/21/2018	10.5	
10.6†	Amendment No. 5 to Collaboration and License Agreement, effective as of April 30, 2018, between Ultragenyx Pharmaceutical Inc. and Kyowa Hakko Kirin Co., Ltd.	10-Q	8/3/2018	10.1	
10.7*	Amendment No. 6 to Collaboration and License Agreement, effective as of February 1, 2019, between Ultragenyx Pharmaceutical Inc. and Kyowa Hakko Kirin Co., Ltd.	10-Q	5/7/2019	10.2	
10.8*	Amendment No. 7 to Collaboration and License Agreement, effective as of December 5, 2018, between Ultragenyx Pharmaceutical Inc. and Kyowa Hakko Kirin Co., Ltd.	10-Q	5/7/2019	10.3	
10.9*	Amendment No. 8 to Collaboration and License Agreement, effective as of July 4, 2019, between Ultragenyx Pharmaceutical Inc. and Kyowa Kirin Co., Ltd. (formerly, Kyowa Hakko Kirin Co., Ltd.)	10-Q	8/2/2019	10.1	

Exhibit Number	Exhibit Description	Incorporated by Reference			Filed Herewith
		Form	Date	Number	
10.10*	Amendment No. 9 to Collaboration and License Agreement, effective December 23, 2019, between Ultragenyx Pharmaceutical Inc. and Kyowa Kirin Co., Ltd.	10-K	2/14/2020	10.10	
10.11*	Amendment No. 10 to Collaboration and License Agreement, effective as of April 1, 2020, between Ultragenyx Pharmaceutical Inc. and Kyowa Kirin Co., Ltd.	10-Q	5/7/2020	10.2	
10.12*	License Agreement, dated as of September 20, 2012, between Ultragenyx Pharmaceutical Inc. and Baylor Research Institute				X
10.13*	Amendment to the License Agreement, dated as of March 22, 2013, between Ultragenyx Pharmaceutical Inc. and Baylor Research Institute				X
10.14†	Exclusive License Agreement, dated as of November 22, 2010, between Ultragenyx Pharmaceutical Inc. and Saint Louis University	S-1/A	12/23/2013	10.8	
10.15†	License Agreement, dated October 30, 2013, by and between Dimension Therapeutics, Inc. and REGENXBIO Inc. (f/k/a ReGenX Biosciences, LLC), as amended	10-K	2/21/2018	10.13	
10.16†	Option and License Agreement, dated March 10, 2015, by and between Dimension Therapeutics, Inc. and REGENXBIO Inc.	10-K	2/21/2018	10.14	
10.17*	First Amendment to Option and License Agreement, dated March 18, 2019, by and between REGENXBIO, Inc. and Ultragenyx Pharmaceutical Inc. (as assignee of Dimension Therapeutics, Inc.)	10-Q	5/7/2019	10.1	
10.18*	Amended and Restated Collaboration Agreement and License Agreement, dated June 3, 2019, between Ultragenyx Pharmaceutical Inc. and Bayer Healthcare LLC	10-Q	8/2/2019	10.2	
10.19†	Research, Collaboration and License Agreement, dated as of May 5, 2016, by and between Dimension Therapeutics, Inc. and The Trustees of the University of Pennsylvania, as amended	10-K	2/21/2018	10.16	
10.20†	3rd Amendment to Research, Collaboration and License Agreement, entered into as of October 30, 2017, by and between Dimension Therapeutics, Inc. and The Trustees of the University of Pennsylvania	10-K	2/21/2018	10.17	
10.21†	Commercial Supply and Services Agreement – Drug Substance, effective December 7, 2017, between Ultragenyx Europe GmbH and Rentschler Biopharma SE	10-K	2/21/2018	10.18	
10.22†	Commercial Supply and Services Agreement – Drug Product, effective January 31, 2018, between Ultragenyx Europe GmbH and Rentschler Biopharma SE	10-K	2/21/2018	10.19	
10.23	Supply Agreement, dated as of November 19, 2012, between Ultragenyx Pharmaceutical Inc. and CREMER OLEO GmbH & Co KG	10-K	2/21/2018	10.11	

Exhibit Number	Exhibit Description	Incorporated by Reference			Filed Herewith
		Form	Date	Number	
10.24*	Master Services Agreement, dated April 8, 2019, between Ultragenyx Pharmaceutical Inc. and Aenova Haupt Pharma Wolfratshausen GmbH				X
10.25*	Royalty Purchase Agreement, dated as of December 17, 2019, between Ultragenyx Pharmaceutical Inc. and RPI Finance Trust	10-K	2/14/2020	10.25	
10.26	Equity Purchase Agreement, dated as of June 18, 2019 by and among Ultragenyx Pharmaceutical Inc. and Arcturus Therapeutics Ltd.	10-Q	7/30/2020	10.1	
10.27#	2011 Equity Incentive Plan (including forms of Stock Option Grant Notice and Stock Option Agreement thereunder)	S-1	11/8/2013	10.11	
10.28#	Amendment to the 2011 Equity Incentive Plan	S-1	11/8/2013	10.12	
10.29#	2014 Incentive Plan (as amended)	10-K	2/17/2017	10.20	
10.30#	Form of Incentive Stock Option Agreement	S-1/A	1/17/2014	10.14	
10.31#	Form of Non Statutory Stock Option Agreement (Employees)	S-1/A	1/17/2014	10.15	
10.32#	Form of Non Statutory Stock Option Agreement (Employees)(ex-U.S.)	10-Q	5/10/2016	10.3	
10.33#	Form of Non-Statutory Stock Option Agreement (Directors)	S-1/A	1/17/2014	10.16	
10.34#	Form of Restricted Stock Unit Agreement (Employees)	10-Q	5/10/2016	10.1	
10.35#	Form of Restricted Stock Unit Agreement (Employees)(ex-U.S.)	10-Q	5/10/2016	10.2	
10.36#	Form of Restricted Stock Unit Agreement (Directors)	S-1/A	1/17/2014	10.18	
10.37#	Form of Performance Stock Unit Agreement (Current Employees)	10-K	2/21/2018	10.31	
10.38#	Form of Performance Stock Unit Agreement (New Employees)	10-K	2/21/2018	10.32	
10.39#	Form of Performance Stock Unit Agreement (2019)	10-Q	5/7/2019	10.4	
10.40#	Form of Performance Stock Unit Agreement (2020)	10-Q	5/7/2020	10.3	
10.41#	2014 Employee Stock Purchase Plan (as amended)	10-K	2/17/2017	10.28	
10.42#	Corporate Bonus Plan	S-1/A	1/17/2014	10.27	
10.43#	Employment Inducement Plan				X
10.44#	Form of Non Statutory Stock Option Agreement (Inducement Plan)				X
10.45#	Form of Non Statutory Stock Option Agreement (Inducement Plan) (ex-US)				X
10.46#	Form of Restricted Stock Unit Agreement (Inducement Plan)				X
10.47#	Form of Restricted Stock Unit Agreement (Inducement Plan)(ex-US)				X
10.48#	Executive Employment Agreement, dated as of June 15, 2011, between Ultragenyx Pharmaceutical Inc. and Emil D. Kakkis, M.D., Ph.D.	S-1	11/8/2013	10.18	
10.49#	Amendment No. 1 to Executive Employment Agreement, dated August 8, 2014, by and between Ultragenyx Pharmaceutical Inc. and Emil D. Kakkis, M.D., Ph.D.	10-Q	8/11/2014	10.2	

Exhibit Number	Exhibit Description	Incorporated by Reference			Filed Herewith
		Form	Date	Number	
10.50#	Offer Letter, dated as of October 31, 2011, between Ultragenyx Pharmaceutical Inc. and Thomas Kassberg	S-1	11/8/2013	10.19	
10.51#	Amendment No. 1 to Offer of Employment, dated as of August 8, 2014, by and between Ultragenyx Pharmaceutical Inc. and Thomas Kassberg	10-Q	8/11/2014	10.3	
10.52#	Transition Letter Agreement, dated as of March 5, 2020, between Ultragenyx Pharmaceutical Inc. and Shalini Sharp	8-K	3/6/2020	10.1	
10.53#	Amendment, dated as of August 28, 2020 to Transition Letter Agreement between Ultragenyx Pharmaceutical Inc. and Shalini Sharp dated as of March 5, 2020	8-K	9/2/2020	10.2	
10.54#	Amendment No. 2, dated as of October 8, 2020, to Transition Letter Agreement between Ultragenyx Pharmaceutical Inc. and Shalini Sharp dated as of March 5, 2020, as amended on August 28, 2020	8-K	10/13/2020	10.2	
10.55#	Offer Letter, dated as of August 28, 2020 between Ultragenyx Pharmaceutical Inc. and Mardi C. Dier.	8-K	9/2/2020	10.1	
10.56#	Amendment, dated as of, October 9, 2020 to the Offer Letter between Ultragenyx Pharmaceutical Inc. and Mardi C. Dier dated August 28, 2020	8-K	10/13/2020	10.1	
10.57#	Offer Letter, dated as of April 26, 2016, between Ultragenyx Pharmaceutical Inc. and Karah Parschauer	10-Q	8/9/2016	10.3	
10.58#	Offer Letter, dated as of February 20, 2015, between Ultragenyx Pharmaceutical Inc. and Dennis Huang	10-K	2/17/2017	10.36	
10.59#	Offer Letter, dated as of June 11, 2015, between Ultragenyx Pharmaceutical Inc. and John R. Pinion II	10-K	2/17/2017	10.37	
10.60#	Offer Letter, dated as of January 15, 2018, between Ultragenyx Pharmaceutical Inc. and Camille Bedrosian, M.D.	10-K	2/21/2018	10.46	
10.61#	Offer Letter, dated May 16, 2017, by and between Ultragenyx Pharmaceutical Inc. and Erik Harris	10-Q	8/2/2019	10.4	
10.62#	Addendum #1, dated August 8, 2017, to Offer Letter dated May 16, 2017 between Ultragenyx Pharmaceutical Inc. and Erik Harris	10-Q	8/2/2019	10.5	
10.63#	Addendum #2, dated June 19, 2019, to Offer Letter dated May 16, 2017 between Ultragenyx Pharmaceutical Inc. and Erik Harris	10-Q	8/2/2019	10.6	
10.64#	Form of Indemnification Agreement	10-K	3/24/2014	10.23	
10.65	Standard Lease, dated as of July 5, 2011, between Ultragenyx Pharmaceutical Inc. and Condiotti Enterprises, Inc.	S-1	11/8/2013	10.22	
10.66	Addendum One to Standard Lease, dated as of July 5, 2011, between Ultragenyx Pharmaceutical Inc. and Condiotti Enterprises, Inc.	10-K	2/26/2016	10.34	

Exhibit Number	Exhibit Description	Incorporated by Reference			Filed Herewith
		Form	Date	Number	
10.67	Addendum Two to Standard Lease, dated as of March 7, 2012, between Ultragenyx Pharmaceutical Inc. and Condiotti Enterprises, Inc.	10-K	2/26/2016	10.35	
10.68	Addendum #3 to Standard Lease, effective as of February 12, 2014, by and between Ultragenyx Pharmaceutical Inc. and Condiotti Enterprises, Inc.	8-K	2/25/2014	10.1	
10.69	Addendum #4 to Standard Lease, effective as of March 9, 2015, by and between Ultragenyx Pharmaceutical Inc. and Condiotti Enterprises, Inc.	8-K	3/13/2015	10.1	
10.70	Addendum #5 to Standard Lease, effective as of April 7, 2015, by and between Ultragenyx Pharmaceutical Inc. and Condiotti Enterprises, Inc.	10-K	2/26/2016	10.38	
10.71	Addendum #6 to Standard Lease, effective as of April 29, 2019, by and between Ultragenyx Pharmaceutical Inc. and Condiotti Enterprises, Inc.	10-Q	8/2/2019	10.3	
10.72	Lease Agreement between Marina Boulevard Property, LLC and Ultragenyx Pharmaceutical Inc., dated as of December 8, 2015	10-K	2/26/2016	10.43	
10.73	Indenture of Lease between Dimension Therapeutics, Inc. and Rivertech Associates II, LLC, dated March 11, 2014, as amended	10-K	2/21/2018	10.64	
10.74	Second Lease Amendment to the Lease between Dimension Therapeutics, Inc. and Rivertech Associates II, LLC, dated April 28, 2017	10-K	2/21/2018	10.65	
10.75	Third Lease Amendment to the Lease between Ultragenyx Pharmaceutical Inc. and Rivertech Associates II, LLC, effective December 31, 2018	10-K	2/20/2019	10.66	
10.76	Lease Agreement, by and between Dimension Therapeutics, Inc. and ARE-MA Region No. 20, LLC, dated November 2, 2015, and Consent to Assignment to Ultragenyx Pharmaceutical Inc.	10-K	2/21/2018	10.66	
10.77	First Amendment to Lease Agreement, dated March 20, 2018, between Ultragenyx Pharmaceutical Inc. and ARE-MA Region No. 20, LLC	10-Q	5/8/2018	10.6	
10.78	Second Amendment to Lease Agreement, made July 1, 2018, between Ultragenyx Pharmaceutical Inc. and ARE-MA Region No. 20, LLC	10-Q	8/3/2018	10.3	
10.79	Third Amendment, dated July 29, 2019, to the Lease Agreement dated October 30, 2015 by and between Ultragenyx Pharmaceutical Inc. and ARE-MA Region No., LLC.	10-Q	7/30/2020	10.2	
10.80	Amended and Restated Fourth Amendment, dated August 4, 2020, to the Lease Agreement dated October 30, 2015 by and between Ultragenyx Pharmaceutical Inc. and ARE-MA Region No., LLC.	10-Q	10/27/2020	10.5	

Exhibit Number	Exhibit Description	Incorporated by Reference			Filed Herewith
		Form	Date	Number	
10.81	Lease Agreement, dated December 15, 2019, between Ultragenyx Pharmaceutical Inc. and ARE-San Francisco No. 17, LLC.				X
10.82	First Amendment, dated September 20, 2020, to the Lease Agreement dated December 15, 2019 between Ultragenyx Pharmaceutical Inc. and ARE-San Francisco No. 17, LLC.				X
10.83	Second Amendment, dated October 21, 2020, to the Lease Agreement dated December 15, 2019 between Ultragenyx Pharmaceutical Inc. and ARE-San Francisco No. 17, LLC.				X
10.84	Office Lease, dated April 19, 2019, between Ultragenyx Pharmaceutical Inc. and Woburn MCB II, LLC	10-K	2/14/2020	10.70	
10.85	Commercial Lease, dated July 2, 2018, between Ultragenyx Pharmaceutical Inc. and 32 Leveroni LLC	10-K	2/14/2020	10.71	
21.1	Subsidiaries of Ultragenyx Pharmaceutical Inc.				X
23.1	Consent of Independent Registered Public Accounting Firm				X
24.1	Power of Attorney (included on the signature page of this report)				
31.1	Certification of Chief Executive Officer of Ultragenyx Pharmaceutical Inc., as required by Rule 13a-14(a) or Rule 15d-14(a) of the Exchange Act as adopted pursuant to Section 302 of the Sarbanes-Oxley Act of 2002				X
31.2	Certification of Chief Financial Officer of Ultragenyx Pharmaceutical Inc., as required by Rule 13a-14(a) or Rule 15d-14(a) of the Exchange Act as adopted pursuant to Section 302 of the Sarbanes-Oxley Act of 2002				X
32.1§	Certification by the Chief Executive Officer and Chief Financial Officer, as required by Rule 13a-14(b) or Rule 15d-14(b) and Section 1350 of Chapter 36 of Title 18 of the United States Code (18 U.S.C. §1350)				X
101.INS	XBRL Instance Document, formatted in Inline XBRL				X
101.SCH	Inline XBRL Taxonomy Extension Schema Document				X
101.CAL	Inline XBRL Taxonomy Extension Calculation Linkbase Document				X
101.DEF	Inline XBRL Taxonomy Extension Definition Linkbase Document				X
101.LAB	Inline XBRL Taxonomy Extension Labels Linkbase Document				X
101.PRE	Inline XBRL Taxonomy Extension Presentation Linkbase Document				X
104	The cover page from this Annual Report on Form 10-K, formatted in Inline XBRL				

† Confidential treatment has been granted with respect to certain portions (indicated by asterisks) of this exhibit. Omitted portions have been filed separately with the SEC.

* Certain confidential portions of this exhibit were omitted by means of marking such portions with asterisks because the identified confidential portions (i) are not material and (ii) would be competitively harmful if publicly disclosed.

\# Indicates management contract or compensatory plan.

§ The certification attached as Exhibit 32.1 that accompanies this Annual Report is not deemed filed with the SEC and is not to be incorporated by reference into any filing of Ultragenyx Pharmaceutical Inc. under the Securities Act or the Exchange Act, whether made before or after the date of this Annual Report, irrespective of any general incorporation language contained in such filing.

Item 16. ***Form 10-K Summary***

None.

SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized.

ULTRAGENYX PHARMACEUTICAL INC.

By: /s/ Emil D. Kakkis
Emil D. Kakkis, M.D., Ph.D.
President and Chief Executive Officer

Date: February 11, 2021

POWER OF ATTORNEY

KNOW ALL PERSONS BY THESE PRESENTS, that each person whose signature appears below constitutes and appoints Emil D. Kakkis, M.D., Ph.D. and Mardi C. Dier, and each of them, as his or her true and lawful attorneys-in-fact and agents, with full power of substitution for him or her, and in his or her name in any and all capacities, to sign any and all amendments to this Annual Report, and to file the same, with exhibits thereto and other documents in connection therewith, with the Securities and Exchange Commission, granting unto said attorneys-in-fact and agents, and each of them, full power and authority to do and perform each and every act and thing requisite and necessary to be done therewith, as fully to all intents and purposes as he or she might or could do in person, hereby ratifying and confirming all that said attorneys-in-fact and agents, and any of them, his or her substitute or substitutes, may lawfully do or cause to be done by virtue hereof.

Pursuant to the requirements of the Securities Exchange Act of 1934, this report has been signed below by the following persons on behalf of the registrant and in the capacities and on the dates indicated.

Signature	Title	Date
/s/ Emil D. Kakkis Emil D. Kakkis, M.D., Ph.D.	President and Chief Executive Officer and Director (Principal Executive Officer)	February 11, 2021
/s/ Mardi C. Dier Mardi C. Dier	Executive Vice President and Chief Financial Officer (Principal Financial Officer)	February 11, 2021
/s/ Theodore A. Huizenga Theodore A. Huizenga	Senior Vice President, Corporate Controller (Principal Accounting Officer)	February 11, 2021
/s/ Daniel G. Welch Daniel G. Welch	Chairman of the Board	February 11, 2021
/s/ William Aliski William Aliski	Director	February 11, 2021
/s/ Deborah Dunsire Deborah Dunsire, M.D.	Director	February 11, 2021
/s/ Lars Ekman Lars Ekman, M.D., Ph.D.	Director	February 11, 2021
/s/ Matthew K. Fust Matthew K. Fust	Director	February 11, 2021
/s/ Michael Narachi Michael Narachi	Director	February 11, 2021
/s/ Clay B. Siegall Clay B. Siegall, Ph.D.	Director	February 11, 2021
/s/ Shehnaaz Suliman Shehnaaz Suliman, M.D.	Director	February 11, 2021

Ultragenyx Pharmaceutical Inc.

INDEX TO FINANCIAL STATEMENTS

Report of Independent Registered Public Accounting Firm

To the Stockholders and the Board of Directors of Ultragenyx Pharmaceutical Inc.:

Opinion on the Financial Statements

We have audited the accompanying consolidated balance sheets of Ultragenyx Pharmaceutical Inc. (the Company) as of December 31, 2020 and 2019, the related consolidated statements of operations, comprehensive loss, stockholders' equity and cash flows for each of the three years in the period ended December 31, 2020, and the related notes (collectively referred to as the "consolidated financial statements"). In our opinion, the consolidated financial statements present fairly, in all material respects, the financial position of the Company at December 31, 2020 and 2019, and the results of its operations and its cash flows for each of the three years in the period ended December 31, 2020, in conformity with U.S. generally accepted accounting principles.

We also have audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States) (PCAOB), the Company's internal control over financial reporting as of December 31, 2020, based on criteria established in *Internal Control-Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission* (2013 framework) and our report dated February 11, 2021 expressed an unqualified opinion thereon.

Basis for Opinion

These financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on the Company's financial statements based on our audits. We are a public accounting firm registered with the PCAOB and are required to be independent with respect to the Company in accordance with the U.S. federal securities laws and the applicable rules and regulations of the Securities and Exchange Commission and the PCAOB.

We conducted our audits in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement, whether due to error or fraud. Our audits included performing procedures to assess the risks of material misstatement of the financial statements, whether due to error or fraud, and performing procedures that respond to those risks. Such procedures included examining, on a test basis, evidence regarding the amounts and disclosures in the financial statements. Our audits also included evaluating the accounting principles used and significant estimates made by management, as well as evaluating the overall presentation of the financial statements. We believe that our audits provide a reasonable basis for our opinion.

Critical Audit Matters

The critical audit matters communicated below are matters arising from the current period audit of the financial statements that were communicated or required to be communicated to the audit committee and that: (1) relate to accounts or disclosures that are material to the financial statements and (2) involved our especially challenging, subjective or complex judgments. The communication of critical audit matters does not alter in any way our opinion on the consolidated financial statements, taken as a whole, and we are not, by communicating the critical audit matters below, providing separate opinions on the critical audit matters or on the accounts or disclosures to which they relate.

Net product sales

Description of the Matter	The Company sells approved products through a limited number of distributors. As discussed in Note 2, when recognizing revenue, the Company makes an estimate of the transaction price, including an assessment of whether to constrain any variable consideration. Product sales are recorded net of estimated government-mandated rebates and chargebacks, estimated product returns, and other deductions at the time revenue is recorded. Limited historical data is available for use in developing such estimates which are periodically reviewed and adjusted as necessary. Auditing the Company's net product sales was complex due to the Company's limited history of product sales and the growth of sales in international markets. The Company's estimates of government mandated rebates, chargebacks and estimated product returns depend on the identification of key customer contract terms and conditions, as well as estimates of sales volumes to different classes of payors. The revenue recognition process can be complex and involves significant judgment to identify and assess the terms and conditions of customer agreements and related government regulations that could affect revenue recognition, as the Company's revenue expands with new customers and new markets.
How We Addressed the Matter in Our Audit	We obtained an understanding, evaluated the design and tested the operating effectiveness of controls over the Company's process of recording product sales and related rebates, chargebacks and returns. We also tested management's controls related to the identification and assessment of the terms and conditions of customer agreements and the completeness and accuracy of data utilized in the controls, and the calculations supporting management's estimates. To test net product sales, our audit procedures included, among others, tracing a sample of revenue transactions recognized during the year to source documentation. We also confirmed a sample of outstanding receivable balances directly with the Company's customers. To test management's estimates of rebates, chargebacks and returns, we obtained management's calculations for the respective estimates and performed one or more of the following procedures: tested management's estimation process to assess whether the recorded reserve balances are within a reasonable range of estimate, performed retrospective reviews, assessed subsequent events, and tested a sample of credits issued throughout the year.

Liability related to the sale of future royalties

Description of the Matter	As discussed in Note 10, the Company entered into a royalty purchase agreement in 2019, in which the Company sold its right to receive royalty payments arising from the net sales of Crysvita in the European market in exchange for $320 million. The proceeds from the transaction were recorded as a liability that is being amortized using the effective interest method over the estimated life of the arrangement. In order to determine the amortization of the liability, the Company is required to estimate the total amount of future royalty payments to be paid to the counterparty, subject to the capped amount, over the life of the arrangement. The Company estimates an imputed interest on the unamortized portion of the liability and records interest expense relating to the transaction. Auditing the Company's liability related to the sale of future royalties was complex due to the subjective judgments required to forecast the expected royalty payments subject to the agreement. Specifically, the forecasted revenues of Crysvita in the European market involved significant estimation uncertainty.
How We Addressed the Matter in Our Audit	We obtained an understanding, evaluated the design and tested the operating effectiveness of controls over the Company's process of accounting for the liability related to the sale of future royalties, including controls over the Company's estimates of projected sales of Crysvita in the European market. To test management's estimates of the future royalties and the imputed effective interest rate, we performed audit procedures that included, among others, evaluating the reasonableness of management's assumptions related to the treatable patient population, estimated pricing and reimbursement, and the rate of adoption. We compared the significant assumptions with historical trends of actual sales, analyst expectations and performed sensitivity analyses of estimated future royalties to evaluate the impact of the changes in the future royalties on the implied effective interest rate.

/s/ Ernst & Young LLP

We have served as the Company's auditor since 2010.

San Jose, California
February 11, 2021

ULTRAGENYX PHARMACEUTICAL INC.

CONSOLIDATED BALANCE SHEETS

(In thousands, except share and per share amounts)

	December 31,	
	2020	**2019**
ASSETS		
Current assets:		
Cash and cash equivalents	$ 713,526	$ 433,584
Marketable debt securities	488,007	321,646
Accounts receivable, net	23,093	32,844
Inventory	13,048	11,546
Prepaid expenses and other current assets	57,630	51,397
Total current assets	1,295,304	851,017
Property, plant, and equipment, net	73,515	44,348
Equity investments	155,375	27,752
Marketable debt securities	10,506	5,174
Right-of-use assets	40,524	30,328
Intangible assets, net	131,113	129,000
Goodwill	44,406	44,406
Other assets	8,812	3,471
Total assets	$ 1,759,555	$ 1,135,496
LIABILITIES AND STOCKHOLDERS' EQUITY		
Current liabilities:		
Accounts payable	$ 12,923	$ 12,871
Accrued liabilities	108,491	83,194
Contract liabilities	59,219	—
Lease liabilities	8,976	7,235
Total current liabilities	189,609	103,300
Contract liabilities	7,349	—
Lease liabilities	39,251	29,757
Deferred tax liabilities	33,306	33,306
Liability related to the sale of future royalties	335,665	315,369
Total liabilities	605,180	481,732
Commitments and contingencies (Notes 8 and 15)		
Stockholders' equity:		
Preferred stock, par value of $0.001 per share—25,000,000 shares authorized; nil outstanding as of December 31, 2020 and 2019	—	—
Common stock, par value of $0.001 per share—250,000,000 shares authorized; 66,818,520 and 57,838,220 shares issued and outstanding as of December 31, 2020 and 2019, respectively	67	58
Additional paid-in capital	2,773,195	2,086,863
Accumulated other comprehensive income (loss)	689	(147)
Accumulated deficit	(1,619,576)	(1,433,010)
Total stockholders' equity	1,154,375	653,764
Total liabilities and stockholders' equity	$ 1,759,555	$ 1,135,496

See accompanying notes.

ULTRAGENYX PHARMACEUTICAL INC.

CONSOLIDATED STATEMENTS OF OPERATIONS

(In thousands, except share and per share amounts)

	Year Ended December 31,		
	2020	**2019**	**2018**
Revenues:			
Collaboration and license	$ 219,315	$ 83,493	$ 41,693
Product sales	38,720	20,221	9,802
Non-cash collaboration royalty revenue	12,995	—	—
Total revenues	271,030	103,714	51,495
Operating expenses:			
Cost of sales	6,129	9,008	1,146
Research and development	412,084	357,355	293,998
Selling, general and administrative	182,933	161,524	127,724
Total operating expenses	601,146	527,887	422,868
Loss from operations	(330,116)	(424,173)	(371,373)
Interest income	7,038	13,238	9,542
Gain from sale of priority review vouchers	—	—	170,322
Change in fair value of equity investments	170,403	13,413	—
Non-cash interest expense on liability related to the sale of future royalties	(33,291)	(1,135)	—
Other income (expense)	607	(787)	(5,588)
Loss before income taxes	(185,359)	(399,444)	(197,097)
Provision for income taxes	(1,207)	(3,283)	(514)
Net loss	$ (186,566)	$ (402,727)	$ (197,611)
Net loss per share, basic and diluted	$ (3.07)	$ (7.12)	$ (3.97)
Shares used in computing net loss per share, basic and diluted	60,845,550	56,576,885	49,775,223

See accompanying notes.

ULTRAGENYX PHARMACEUTICAL INC.

CONSOLIDATED STATEMENTS OF COMPREHENSIVE LOSS

(In thousands)

	Year Ended December 31,		
	2020	**2019**	**2018**
Net loss	$ (186,566)	$ (402,727)	$ (197,611)
Other comprehensive income:			
Foreign currency translation adjustments	735	23	(303)
Transfer of currency translation adjustments balance to other income related to the liquidation of foreign subsidiaries	—	—	5,272
Unrealized gain on available-for-sale securities	101	463	78
Other comprehensive income:	836	486	5,047
Total comprehensive loss	$ (185,730)	$ (402,241)	$ (192,564)

See accompanying notes.

ULTRAGENYX PHARMACEUTICAL INC.

CONSOLIDATED STATEMENTS OF STOCKHOLDERS' EQUITY

(In thousands, except share amounts)

	Common Stock		Additional Paid-In Capital	Accumulated Other Comprehensive Income (Loss)	Accumulated Deficit	Total Stockholders' Equity
	Shares	Amount				
Balance as of December 31, 2017	44,167,071	$ 44	$ 1,221,762	$ (5,680)	$ (832,672)	$ 383,454
Issuance of common stock in connection with underwritten public offering, net of issuance costs	5,043,860	5	270,964	—	—	270,969
Issuance of common stock in connection with at-the-market offering, net of issuance costs	640,257	1	38,055	—	—	38,056
Stock-based compensation expense	—	—	81,165	—	—	81,165
Issuance of common stock under equity plan awards, net of tax	1,009,400	1	27,827	—	—	27,828
Other comprehensive income	—	—	—	5,047	—	5,047
Net loss	—	—	—	—	(197,611)	(197,611)
Balance as of December 31, 2018	50,860,588	51	1,639,773	(633)	(1,030,283)	608,908
Issuance of common stock in connection with underwritten public offering, net of issuance costs	5,833,333	6	330,409	—	—	330,415
Issuance of common stock in connection with at-the-market offering, net of issuance costs	468,685	—	24,828	—	—	24,828
Stock-based compensation expense	—	—	82,025	—	—	82,025
Issuance of common stock under equity plan awards, net of tax	675,614	1	9,828	—	—	9,829
Other comprehensive income	—	—	—	486	—	486
Net loss	—	—	—	—	(402,727)	(402,727)
Balance as of December 31, 2019	57,838,220	58	2,086,863	(147)	(1,433,010)	653,764
Issuance of common stock in connection with underwritten public offering, net of issuance costs	5,111,110	5	435,551	—	—	435,556
Issuance of common stock in connection with license agreement, net of issuance costs	1,243,913	1	55,267	—	—	55,268
Issuance of common stock in connection with at-the-market offering, net of issuance costs	283,333	—	20,391	—	—	20,391
Stock-based compensation expense	—	—	85,833	—	—	85,833
Issuance of common stock upon exercise of warrants and under equity plan awards, net of tax	2,341,944	3	89,290	—	—	89,293
Other comprehensive income	—	—	—	836	—	836
Net loss	—	—	—	—	(186,566)	(186,566)
Balance as of December 31, 2020	66,818,520	$ 67	$ 2,773,195	$ 689	$ (1,619,576)	$ 1,154,375

See accompanying notes.

ULTRAGENYX PHARMACEUTICAL INC.

CONSOLIDATED STATEMENTS OF CASH FLOWS

(In thousands)

	Year Ended December 31,		
	2020	**2019**	**2018**
Operating activities:			
Net loss	$ (186,566)	$ (402,727)	$ (197,611)
Adjustments to reconcile net loss to net cash used in operating activities:			
Stock-based compensation	85,735	81,995	80,107
Amortization of premium (discount) on marketable debt securities, net	848	(6,214)	(2,641)
Depreciation and amortization	12,261	8,539	19,538
Foreign currency remeasurement (gain) loss	(221)	688	5,309
Change in fair value of equity investments	(170,403)	(13,413)	—
Non-cash collaboration royalty revenue	(12,995)	—	—
Non-cash interest expense on liability related to the sale of future royalties	33,291	1,135	—
Gain from sale of priority review vouchers	—	—	(170,322)
Other	1,167	1,933	(156)
Changes in operating assets and liabilities:			
Accounts receivable	9,840	(20,104)	(7,583)
Inventory	(1,346)	(4,451)	(5,283)
Prepaid expenses and other assets	2,748	(8,216)	(14,285)
Accounts payable, accrued, and other liabilities	26,853	13,312	2,361
Contract liabilities, net	66,568	—	—
Deferred tax liabilities	—	2,140	—
Net cash used in operating activities	(132,220)	(345,383)	(290,566)
Investing activities:			
Purchase of property, plant, and equipment	(43,905)	(24,832)	(4,076)
Purchase of marketable debt securities	(813,237)	(692,824)	(509,796)
Purchase of equity investments	(37,062)	(14,339)	—
Proceeds from sale of marketable debt securities	50,990	42,718	7,655
Proceeds from sale of equity investment	79,842	—	—
Proceeds from maturities of marketable debt securities	589,806	676,238	302,564
Proceeds from sale of priority review vouchers	—	—	170,322
Other	(5,555)	—	—
Net cash used in investing activities	(179,121)	(13,039)	(33,331)
Financing activities:			
Proceeds from the sale of future royalties, net	—	314,234	—
Proceeds from the issuance of common stock in connection with underwritten public offerings, net	435,556	330,415	270,969
Proceeds from the issuance of common stock in connection with the license agreement, net	55,268	—	—
Proceeds from the issuance of common stock in connection with at-the-market offering, net	20,391	24,828	38,056
Proceeds from the issuance of common stock from exercise of warrants and equity plan awards, net	89,293	9,829	27,828
Other	(236)	—	—
Net cash provided by financing activities	600,272	679,306	336,853
Effect of exchange rate changes on cash	1,119	(165)	(472)
Net increase in cash, cash equivalents, and restricted cash	290,050	320,719	12,484
Cash, cash equivalents, and restricted cash at beginning of year	436,244	115,525	103,041
Cash, cash equivalents, and restricted cash at end of year	$ 726,294	$ 436,244	$ 115,525

See accompanying notes.

ULTRAGENYX PHARMACEUTICAL INC.

CONSOLIDATED STATEMENTS OF CASH FLOWS

(In thousands)

	Year Ended December 31,		
	2020	**2019**	**2018**
Supplemental disclosures of non-cash investing and financing information:			
Acquired lease liabilities arising from obtaining right-of-use assets	$ 18,775	$ 21,861	$ —
Stock-based compensation capitalized into ending inventory	$ 1,304	$ 1,206	$ 1,058
Costs of property and equipment included in accounts payable, accrued, and other liabilities	$ 8,515	$ 10,367	$ 1,192

See accompanying notes.

1. Organization and Basis of Presentation

Ultragenyx Pharmaceutical Inc. (the Company) is a biopharmaceutical company incorporated in California on April 22, 2010. The Company subsequently reincorporated in the state of Delaware in June 2011.

The Company is focused on the identification, acquisition, development, and commercialization of novel products for the treatment of serious rare and ultra-rare genetic diseases. The Company has three commercially approved products. Crysvita® (burosumab) is approved in the United States by the U.S. Food and Drug Administration (FDA) and in Canada for the treatment of X-linked hypophosphatemia (XLH) in adult and pediatric patients one year of age and older, and is approved in the European Union (EU) and the United Kingdom, for the treatment of XLH with radiographic evidence of bone disease in children one year of age and older, adolescents, and adults. In Brazil and Mexico, Crysvita is approved for treatment of XLH in adult and pediatric patients one year of age and older. Crysvita was approved by the FDA on June 18, 2020 for the treatment of fibroblast growth factor 23 (FGF23)-related hypophosphatemia in tumor-induced osteomalacia (TIO), associated with phosphaturic mesenchymal tumors that cannot be curatively resected or localized in adults and pediatric patients 2 years of age and older.

The Company has also received FDA approval for Mepsevii™ (vestronidase alfa), the first medicine approved for the treatment of children and adults with mucopolysaccharidosis VII (MPS VII), also known as Sly syndrome. In the European Union and the United Kingdom, Mepsevii is approved under exceptional circumstances for patients of all ages for the treatment of non-neurological manifestations of MPS VII. In Brazil, Mepsevii is approved for the treatment of MPS VII for patients of all ages.

Dojolvi, formerly known as UX007, was approved by FDA on June 30, 2020 for the treatment of pediatric and adult patients severely affected by long-chain fatty acid oxidation disorders (LC-FAOD).

In addition to the approved products, the Company has the following ongoing clinical development programs: DTX401 is an adeno-associated virus 8 (AAV8) gene therapy product candidate for the treatment of patients with glycogen storage disease type Ia (GSDIa); and DTX301 is an AAV8 gene therapy product candidate in development for the treatment of patients with ornithine transcarbamylase (OTC) deficiency, the most common urea cycle disorder. UX143 (setrusumab) which the Company began collaborating on the development with Mereo BioPharma 3 Limited (Mereo) beginning in January 2021, is a fully human monoclonal antibody that inhibits sclerostin, a protein that acts on a key bone-signaling pathway and inhibits the activity of bone-forming cells for the treatment of patients with osteogenesis imperfect (OI). GTX-102 is an antisense oligonucleotide, or ASO, which the Company is collaborating on the development with GeneTx Biotherapeutics LLC (GeneTx) for the treatment of Angelman syndrome, a debilitating and rare neurogenetic disorder caused by loss-of-function of the maternally inherited allele of the UBE3A gene. UX701 is an AAV type 9 gene therapy designed to deliver stable expression of a truncated version of the ATP7B copper transporter following a single intravenous infusion to improve copper distribution and excretion from the body and reverse pathological findings of Wilson liver disease. The Company operates as one reportable segment.

The Company has sustained operating losses and expects such annual losses to continue over the next several years. The Company's ultimate success depends on the outcome of its research and development and commercialization activities, for which it expects to incur additional losses in the future. Management recognizes that the Company will likely need to raise additional capital to fully implement its business plans. Through December 31, 2020, the Company has relied primarily on its sale of equity securities, its sale of future royalties, and strategic collaboration arrangements, to finance its operations.

The Company will likely raise additional capital through the issuance of equity, borrowings, or strategic alliances with partner companies. However, if such financing is not available at adequate levels, the Company would need to reevaluate its operating plans.

2. Summary of Significant Accounting Policies

Basis of Consolidation

The consolidated financial statements include the accounts of Ultragenyx Pharmaceutical Inc. and its wholly-owned subsidiaries. All intercompany balances and transactions have been eliminated.

Use of Estimates

The accompanying consolidated financial statements have been prepared in accordance with U.S. generally accepted accounting principles (GAAP). The preparation of the consolidated financial statements in conformity with GAAP requires management to make estimates and assumptions that affect the reported amounts of assets and liabilities, disclosure of contingent liabilities and the reported amounts of expenses in the consolidated financial statements and the accompanying notes. On an ongoing basis, management evaluates its estimates, including those related to clinical trial accruals, fair value of assets and liabilities, income taxes, stock-based compensation, and the liability related to the sale of future royalties. Management bases its estimates on historical experience and on various other market-specific and relevant assumptions that management believes to be reasonable under the circumstances. Actual results could differ from those estimates.

Cash, Cash Equivalents, and Restricted Cash

The Company considers all highly liquid investments with original maturities of three months or less from the date of purchase to be cash equivalents. Cash equivalents consist primarily of amounts invested in money market accounts.

Restricted cash primarily consists of money market accounts used as collateral for the Company's obligations under its facility leases and the gene therapy building construction project.

The following table provides a reconciliation of cash, cash equivalents, and restricted cash reported within the consolidated balance sheets that sum to the total of the amounts shown in the consolidated statement of cash flows (in thousands):

	December 31,		
	2020	2019	2018
Cash and cash equivalents	$ 713,526	$ 433,584	$ 113,432
Restricted cash included in prepaid expenses and other current assets	10,847	161	271
Restricted cash included in other assets	1,921	2,499	1,822
Total cash, cash equivalents, and restricted cash shown in the statements of cash flows	$ 726,294	$ 436,244	$ 115,525

Marketable Debt Securities

All marketable debt securities have been classified as "available-for-sale" and are carried at estimated fair value as determined based upon quoted market prices or pricing models for similar securities. Management determines the appropriate classification of its investments at the time of purchase and reevaluates such designation as of each balance sheet date. Investments with a maturity of one year or less from the balance sheet date are reported as current marketable debt securities and investments with a maturity of greater than one year from the balance sheet date are reported as non-current marketable debt securities. Unrealized gains and losses are excluded from earnings and are reported as a component of comprehensive loss. Realized gains and losses and declines in fair value judged to be other than temporary, if any, on available-for-sale securities are included in other income (expense). The cost of securities sold is based on the specific-identification method. Interest on investments is included in interest income.

Equity Investments

In June 2019, the Company entered into an amendment to the Research Collaboration and License Agreement and an Equity Purchase Agreement with Arcturus Therapeutics Holdings Inc. (Arcturus). Pursuant to the Equity Purchase Agreement, the Company purchased 2,400,000 shares of common stock and received an option to purchase an additional 600,000 shares of common stock, which was exercised in May 2020. In December 2020, the Company sold 800,000 shares. The Company elected to apply the fair value option to account for the equity investment in Arcturus. The option to purchase additional Arcturus stock was accounted for at fair value using the Black-Scholes option pricing method prior to the exercise of options.

In October 2020, the Company entered into a Research Collaboration and License Agreement, Stock Purchase Agreement and Investor Agreement, with Solid Biosciences Inc. (Solid). Pursuant to the Stock Purchase Agreement, the Company purchased 7,825,797 shares of Solid's common stock. The investment is being accounted at fair value based on quoted market prices.

The changes in fair value of the equity investments and an option to purchase additional stock are included in the Consolidated Statements of Operations. See "Note 7. License and Research Agreements" for additional details on the transaction.

Concentration of Credit Risk, Credit Losses, and Other Risks and Uncertainties

Financial instruments that potentially subject the Company to a concentration of credit risk consist of cash, cash equivalents, and investments. The Company's cash, cash equivalents, and investments are held by financial institutions that management believes are of high credit quality. The Company's investment policy limits investments to fixed income securities denominated and payable in U.S. dollars such as U.S. government obligations, money market instruments and funds, corporate bonds, commercial paper, and asset-backed securities and places restrictions on maturities and concentrations by type and issuer. Such deposits may, at times, exceed federally insured limits. The Company has not experienced any losses on its deposits of cash and cash equivalents and its accounts are monitored by management to mitigate risk. The Company is exposed to credit risk in the event of default by the financial institutions holding its cash and cash equivalents, corporate issuers, and other financial instruments, to the extent recorded in the balance sheets.

Effective January 1, 2020, the Company adopted Accounting Standards Update (ASU) 2016-13, Financial Instruments — Credit Losses, *(Topic 326): Measurement of Credit Losses on Financial Instruments,* which changed the impairment model for most financial assets and certain other instruments. For trade receivables and other instruments, the Company uses a new forward-looking

expected loss model that generally results in the earlier recognition of allowances for losses. For available-for-sale debt securities with unrealized losses, the losses are recognized as allowances rather than as reductions in the amortized cost of the securities.

The Company is exposed to credit losses primarily through receivables from customers and collaborators and through its available-for-sale debt securities. The Company's expected loss allowance methodology for the receivables is developed using historical collection experience, current and future economic market conditions, a review of the current aging status and financial condition of the entities. Specific allowance amounts are established to record the appropriate allowance for customers that have a higher probability of default. Balances are written off when determined to be uncollectible. The Company's expected loss allowance methodology for the debt securities is developed by reviewing the extent of the unrealized loss, the size, term, geographical location, and industry of the issuer, the issuers' credit ratings and any changes in those ratings, as well as reviewing current and future economic market conditions and the issuers' current status and financial condition. The Company considered the current and expected future economic and market conditions surrounding the novel coronavirus (COVID-19) pandemic and determined that the estimate of credit losses was not significantly impacted. The adoption of the guidance did not have a material impact on the Condensed Consolidated Financial Statements and related disclosures and there was no allowance for losses on available-for-sale debt securities which were attributable to credit risk for the year ended December 31, 2020.

The Company is dependent on third-party manufacturers to supply products for research and development activities in its programs. In particular, the Company relies and expects to continue to rely on a small number of manufacturers to supply it with its requirements for the active pharmaceutical ingredients and formulated drugs related to these programs. These programs could be adversely affected by a significant interruption in the supply of active pharmaceutical ingredients and formulated drugs.

Inventory

The Company values inventory at the lower of cost and net realizable value and determines the cost of inventory using the average-cost method. The Company expenses costs associated with the manufacture of product candidates prior to regulatory approval. Inventories consist of currently approved products. The Company periodically reviews its inventories for excess amounts or obsolescence and writes down obsolete or otherwise unmarketable inventory to its estimated net realizable value. Management determines excess inventory based on expected future demand. Estimates related to future demand are sensitive to significant inputs and assumptions such as acceptance by patients and physicians and the availability of formulary coverage and adequate reimbursement from private third-party payers for the product.

Property, Plant, and Equipment

Property, plant, and equipment are stated at cost, less accumulated depreciation and amortization. Depreciation and amortization is computed using the straight-line method over the estimated useful lives of the respective assets. Depreciation and amortization begins at the time the asset is placed in service. Maintenance and repairs are charged to operations as incurred. Upon sale or retirement of assets, the cost and related accumulated depreciation or amortization are removed from the balance sheet and the resulting gain or loss, if any, is reflected in operations.

The useful lives of property, plant, and equipment are as follows:

Research and development equipment	5 years
Furniture and office equipment	5 years
Computer equipment	3 years
Software	3-5 years
Land	Not applicable
Leasehold improvements	Shorter of lease term or estimated useful life

Intangible Assets

The Company's intangible assets consist of acquired in-process research and development (IPR&D) and contractual payments made for certain milestones achieved with collaboration partners.

IPR&D assets represent capitalized incomplete research projects that the Company acquired through business combinations. Such assets are initially measured at their acquisition date fair values and are tested for impairment, until the completion or abandonment of the associated research and development efforts. If and when development is complete, which generally occurs when regulatory approval to market a product is obtained, the associated assets will be deemed finite-lived and will be amortized over a period that best reflects the economic benefits provided by these assets. The contractual payments made for certain milestones achieved was recorded as an intangible and are amortized over its estimated useful life.

The Company tests its definite and indefinite-lived intangible assets for impairment annually during the fourth quarter and more frequently if events or changes in circumstances indicate that it is more likely than not that the asset is impaired. If it is determined that the asset becomes impaired, the carrying value is written down to its fair value with the related impairment charge recognized in consolidated statements of operations in the period in which the impairment occurs. The Company has not recorded any impairments of intangible assets.

Goodwill

Goodwill represents the excess of purchase price over fair value of net assets acquired in a business combination and is not amortized. Goodwill is subject to impairment testing at least annually during the fourth quarter or when a triggering event occurs that could indicate a potential impairment. If it is determined that the goodwill becomes impaired, the carrying value is written down to its fair value with the related impairment charge recognized in consolidated statements of operations in the period in which the impairment occurs. The Company has not recorded any impairments of goodwill.

Impairment of Long-Lived Assets

The Company evaluates its long-lived assets, including property and equipment, for impairment whenever events or changes in circumstances indicate that the carrying value of these assets may not be recoverable. Recoverability of these assets is measured by comparison of the carrying amount of each asset to the future undiscounted cash flows expected to result from the use of the asset and its eventual disposition. If the asset is considered to be impaired, the amount of any impairment is measured as the difference between the carrying value and the fair value of the impaired asset. The Company has not recorded impairment of any long-lived assets.

Accruals of Research and Development Costs

The Company records accruals for estimated costs of research, preclinical and clinical studies and manufacturing development. These costs are a significant component of the Company's research and development expenses. A substantial portion of the Company's ongoing research and development activities are conducted by third-party service providers, including contract research organizations. The Company accrues the costs incurred under its agreements with these third parties based on actual work completed in accordance with agreements established with these third parties. The Company determines the actual costs through obtaining information from external service providers as to the progress or stage of completion of the services and the agreed-upon fee to be paid for such services.

Revenue Recognition

Collaboration and license revenue

The Company has certain license and collaboration agreements that are within the scope of Accounting Standards Codification (ASC) 808, *Collaborative Agreements*, which provides guidance on the presentation and disclosure of collaborative arrangements. Generally, the classification of the transactions under the collaborative arrangements is determined based on the nature of contractual terms of the arrangement, along with the nature of the operations of the participants. The Company records its share of collaboration revenue, net of transfer pricing related to net sales in the period in which such sales occur, if the Company is considered as an agent in the arrangement. The Company is considered an agent when the collaboration partner controls the product before transfer to the customers and has the ability to direct the use of and obtain substantially all of the remaining benefits from the product. Funding received related to research and development services and commercialization costs is generally classified as a reduction of research and development expenses and selling, general and administrative expenses, respectively, in the consolidated statement of operations, because the provision of such services for collaborative partners are not considered to be part of the Company's ongoing major or central operations.

The Company also records royalty revenues under certain of the Company's license or collaboration agreements in exchange for license of intellectual property. If the Company does not have any future performance obligations for these license or collaboration agreements, royalty revenue is recorded as the underlying sales occur.

In order to record collaboration revenue, the Company utilizes certain information from its collaboration partners, including revenue from the sale of the product, associated reserves on revenue, and costs incurred for development and sales activities. For the periods covered in the financial statements presented, there have been no material changes to prior period estimates of revenues and expenses.

The terms of the Company's collaboration and license agreements may contain multiple performance obligations, which may include licenses and research and development activities. The Company evaluates these agreements under ASC 606, *Revenue from Contracts with Customers* (ASC 606), to determine the distinct performance obligations. The Company analogizes to ASC 606 for the accounting for distinct performance obligations for which there is a customer relationship. Prior to recognizing revenue, the Company makes estimates of the transaction price, including variable consideration that is subject to a constraint. Amounts of variable consideration are included in the transaction price to the extent that it is probable that a significant reversal in the amount of

cumulative revenue recognized will not occur and when the uncertainty associated with the variable consideration is subsequently resolved. Total consideration may include nonrefundable upfront license fees, payments for research and development activities, reimbursement of certain third-party costs, payments based upon the achievement of specified milestones, and royalty payments based on product sales derived from the collaboration.

If there are multiple distinct performance obligations, the Company allocates the transaction price to each distinct performance obligation based on its relative standalone selling price. The standalone selling price is generally determined based on the prices charged to customers or using expected cost-plus margin. The Company estimates the efforts needed to complete the performance obligations and recognizes revenue by measuring the progress towards complete satisfaction of the performance obligations using input measures.

Product sales

The Company sells its approved products through a limited number of distributors. Under ASC 606, revenue from product sales is recognized at the point in time when the delivery is made and when title and risk of loss transfers to these distributors. The Company also recognizes revenue from sales of certain products on a "named patient" basis, which are allowed in certain countries prior to the commercial approval of the product. Prior to recognizing revenue, the Company makes estimates of the transaction price, including any variable consideration that is subject to a constraint. Amounts of variable consideration are included in the transaction price to the extent that it is probable that a significant reversal in the amount of cumulative revenue recognized will not occur and when the uncertainty associated with the variable consideration is subsequently resolved. Product sales are recorded net of estimated government-mandated rebates and chargebacks, estimated product returns, and other deductions.

Provisions for returns and other adjustments are provided for in the period the related revenue is recorded, as estimated by management. These reserves are based on estimates of the amounts earned or to be claimed on the related sales and are reviewed periodically and adjusted as necessary. The Company's estimates of government mandated rebates, chargebacks, estimated product returns, and other deductions depends on the identification of key customer contract terms and conditions, as well as estimates of sales volumes to different classes of payors. If actual results vary, the Company may need to adjust these estimates, which could have an effect on earnings in the period of the adjustment.

Non-cash collaboration royalty revenue

Effective January 1, 2020, the Company sold the right to receive certain royalty payments from net sales of Crysvita in the European territories to RPI Finance Trust (RPI), an affiliate of Royalty Pharma, as further described in "Note 10. Liability Related to the Sale of Future Royalties". The Company records the royalty revenue from the net sales of Crysvita in the applicable European territories on a prospective basis as non-cash royalty revenue in the Consolidated Statements of Operations over the term of the arrangement.

Leases

The Company adopted Accounting Standards Update (ASU) No. 2016-02, *Leases (Topic 842)* as of January 1, 2019 using the modified retrospective method. The results for years ended December 31, 2019 and 2020 are presented under ASC 842. The results for the year ended December 31, 2018 were not adjusted and continue to be reported in accordance with historical accounting under prior lease guidance, ASC 840, *Leases (Topic 840)*. The Company also elected the package of practical expedients under the transition guidance that will retain the historical lease classification and initial direct costs for any leases that existed prior to adoption of the new guidance and the practical expedient to not separate lease and non-lease components.

The Company determines if an arrangement includes a lease at inception. Right-of-use lease assets and lease liabilities are recognized based on the present value of the future minimum lease payments over the lease term at the commencement date. The right-of-use lease asset includes any lease payments made and excludes lease incentives. Incremental borrowing rate is used in determining the present value of future payments. The Company applies a portfolio approach to the property leases to apply an incremental borrowing rate to leases with similar lease terms. The lease terms may include options to extend or terminate the lease. The Company recognizes the options to extend the lease as part of the right-of-use lease assets and lease liabilities only if it is reasonably certain that the option would be exercised. Lease expense for minimum lease payments is recognized on a straight-line basis over the non-cancelable lease term.

As a result of the adoption of the new guidance, effective January 1, 2019, the Company recorded a right-of-use lease asset of $16.2 million, a current lease liability of $4.5 million, and a non-current lease liability of $17.0 million and no cumulative effect adjustment was made to the retained earnings as of the adoption date. In addition, as of the adoption date, the Company derecognized a net deferred rent obligation of $5.2 million. See "Note 8. Leases" for further disclosure.

Comprehensive Loss

Comprehensive loss is the change in stockholders' equity from transactions and other events and circumstances other than those resulting from investments by stockholders and distributions to stockholders. The Company's other comprehensive loss is comprised of unrealized gains and losses on investments in available-for-sale securities and foreign currency translation adjustments.

Research and Development

Research and development costs are expensed as incurred and consist of salaries and benefits, stock-based compensation expense, lab supplies and facility costs, as well as fees paid to other nonemployees and entities that conduct certain research and development activities on the Company's behalf. Amounts incurred in connection with license agreements are also included in research and development expense. Nonrefundable advance payments for goods or services to be received in the future for use in research and development activities are deferred. The deferred amounts are expensed as the related goods are delivered or the services are performed.

Stock-Based Compensation

Stock-based awards issued to employees, including stock options, restricted stock units (RSUs), and performance stock units (PSUs) are recorded at fair value as of the grant date and recognized as expense on a straight-line basis over the employee's requisite service period (generally the vesting period). PSUs vest only if certain specified criteria are achieved and the employees' continued service requirements are met; therefore, the expense recognition occurs when the likelihood of the PSUs being earned is deemed probable. Stock compensation expense on awards expected to vest are recognized net of estimated forfeitures.

Income Taxes

The Company uses the liability method of accounting for income taxes. Under this method, deferred tax assets and liabilities are determined based on the differences between the financial reporting and the tax bases of assets and liabilities and are measured using the enacted tax rates and laws that will be in effect when the differences are expected to reverse. The Company must then assess the likelihood that the resulting deferred tax assets will be realized. A valuation allowance is provided when it is more likely than not that some portion or all of a deferred tax asset will not be realized. Due to the Company's lack of earnings history, the net deferred tax assets have been fully offset by a valuation allowance.

In conjunction with Dimension acquisition, a deferred tax liability was recorded reflecting the tax impact of the difference between the book basis and tax basis of acquired IPR&D. Such deferred income tax liability is not used to offset deferred tax assets when analyzing the Company's valuation allowance as the acquired IPR&D is considered to have an indefinite life until the Company completes or abandons development of the acquired IPR&D.

The Company recognizes benefits of uncertain tax positions if it is more likely than not that such positions will be sustained upon examination based solely on their technical merits, as the largest amount of benefit that is more likely than not to be realized upon the ultimate settlement. The Company's policy is to recognize interest and penalties related to the underpayment of income taxes as a component of income tax expense or benefit. To date, there have been no interest or penalties charged in relation to the unrecognized tax benefits.

Foreign Currency

Assets and liabilities of non-U.S. subsidiaries that operate in a local currency environment, where the local currency is the functional currency, are translated to U.S. dollars at exchange rates in effect at the balance sheet date, with the resulting translation adjustments directly recorded to a separate component of accumulated other comprehensive loss. Income and expense accounts are translated at average exchange rates for the period. Transactions which are not in the functional currency of the entity are remeasured into the functional currency and gains or losses resulting from the remeasurement recorded in other income (expense).

Net Loss per Share

Basic net loss per share is calculated by dividing the net loss by the weighted-average number of shares of common stock outstanding during the period, without consideration for common stock equivalents. Diluted net loss per share is the same as basic net loss per share, since the effects of potentially dilutive securities are antidilutive. In periods when we have incurred a net loss, options and warrants to purchase common stock are considered common stock equivalents, but have been excluded from the calculation of diluted net loss per share, as their effect is antidilutive.

3. Fair Value Measurements

Financial assets and liabilities are recorded at fair value. The carrying amount of certain financial instruments, including cash and cash equivalents, accounts receivable, accounts payable and accrued liabilities approximate fair value due to their relatively short maturities. Assets and liabilities recorded at fair value on a recurring basis in the balance sheets are categorized based upon the level of judgment associated with the inputs used to measure their fair values. Fair value is defined as the exchange price that would be received for an asset or an exit price that would be paid to transfer a liability in the principal or most advantageous market for the asset or liability in an orderly transaction between market participants on the measurement date. The authoritative guidance on fair value measurements establishes a three-tier fair value hierarchy for disclosure of fair value measurements as follows:

Level 1—Inputs are unadjusted, quoted prices in active markets for identical assets or liabilities at the measurement date;

Level 2—Inputs are observable, unadjusted quoted prices in active markets for similar assets or liabilities, unadjusted quoted prices for identical or similar assets or liabilities in markets that are not active, or other inputs that are observable or can be corroborated by observable market data for substantially the full term of the related assets or liabilities; and

Level 3—Unobservable inputs that are significant to the measurement of the fair value of the assets or liabilities that are supported by little or no market data.

The Company's financial instruments consist of Level 1, Level 2, and Level 3 assets. Where quoted prices are available in an active market, securities are classified as Level 1. Money market funds and U.S. Government treasury bills are classified as Level 1. Level 2 assets consist primarily of corporate bonds, asset backed securities, commercial paper and U.S. Government agency securities based upon quoted market prices for similar movements in active markets, quoted prices for identical or similar instruments in markets that are not active and model-based valuation techniques for which all significant inputs are observable in the market or can be corroborated by observable market data for substantially the full term of the assets. Where applicable these models project future cash flows and discount the future amounts to a present value using market-based observable inputs obtained from various third party data providers, including but not limited to, benchmark yields, interest rate curves, reported trades, broker/dealer quotes and reference data.

The Company determines the fair value of its equity investments in Arcturus and Solid by using the quoted market prices, which are Level 1 fair value measurements.

The fair value of the option to purchase additional shares of Arcturus common stock was based on unobservable inputs that are significant to the measurement of the fair value of the asset and is supported by little or no market data; accordingly, the fair value of the option is considered a Level 3 financial asset. The Company measures the Level 3 financial asset by applying the Black-Scholes option pricing method and utilizes the following inputs: stock price, strike price, volatility, risk free interest rate, and expected term. The expected term is the Company's estimated period to purchase additional stock. The option was exercised in May 2020 and converted to Arcturus common stock.

The following table sets forth the fair value of the Company's financial assets and liabilities remeasured on a recurring basis based on the three-tier fair value hierarchy (in thousands):

	December 31, 2020			
	Level 1	Level 2	Level 3	Total
Financial Assets:				
Money market funds	$ 598,392	$ —	$ —	$ 598,392
Time deposits	—	10,000	—	10,000
Corporate bonds	—	193,802	—	193,802
Commercial paper	—	173,859	—	173,859
Asset-backed securities	—	11,225	—	11,225
U.S. Government Treasury and agency securities	167,967	17,661	—	185,628
Investments in Arcturus and Solid common stock	154,756	—	—	154,756
Total	$ 921,115	$ 406,547	$ —	$ 1,327,662

	December 31, 2019			
	Level 1	Level 2	Level 3	Total
Financial Assets:				
Money market funds	$ 293,309	$ —	$ —	$ 293,309
Repurchase agreements	—	100,000	—	100,000
Time deposits	—	10,000	—	10,000
Corporate bonds	—	77,026	—	77,026
Commercial paper	—	80,119	—	80,119
Asset-backed securities	—	30,406	—	30,406
U.S. Government Treasury and agency securities	96,329	53,979	—	150,308
Equity investment in Arcturus	26,088	—	1,664	27,752
Total	$ 415,726	$ 351,530	$ 1,664	$ 768,920

In July 2020, the Company invested $2.5 million in a private diagnostic company in the form of a convertible promissory note that matures in two years, if not converted earlier. The Company was also issued a warrant to purchase up to $1.0 million of the entity's preferred stock. The fair value of the warrant to purchase shares of the entity was based on unobservable inputs that are significant to the measurement of the fair value of the asset and is supported by little or no market data; accordingly, the warrant is considered a Level 3 financial asset and is remeasured on a nonrecurring basis. The Company measured the fair value of the warrant by applying the Black-Scholes option pricing method and utilizing the following inputs: stock price, strike price, volatility, risk-free interest rate, and expected term. The Company will recognize interest income on the convertible promissory note based on the effective interest rate method over the life of the note. As of December 31, 2020, the balance of the convertible promissory note was $2.1 million, including $0.2 million in interest receivable, and was recorded in other assets, and the allocated fair value of the warrant was $0.6 million and was recorded in equity investments.

In December 2020, the Company invested $1.4 million in Mazi Therapeutics, Inc. (Mazi), a private pharmaceutical company founded by a current employee of the Company, in the form of a convertible promissory note that matures in two years, if not converted earlier.

4. Balance Sheet Components

Cash Equivalents and Marketable Debt Securities

The fair values of cash equivalents and marketable debt securities classified as available-for-sale securities consisted of the following (in thousands):

	December 31, 2020			
		Gross Unrealized		
	Amortized Cost	Gains	Losses	Estimated Fair Value
Money market funds	$ 598,392	$ —	$ —	$ 598,392
Time deposits	10,000	—	—	10,000
Corporate bonds	193,610	209	(17)	193,802
Commercial paper	173,859	—	—	173,859
Asset-backed securities	11,224	1	—	11,225
U.S. Government Treasury and agency securities	185,561	67	—	185,628
Total	$ 1,172,646	$ 277	$ (17)	$ 1,172,906

	December 31, 2019			
		Gross Unrealized		
	Amortized Cost	Gains	Losses	Estimated Fair Value
Money market funds	$ 293,309	$ —	$ —	$ 293,309
Repurchase agreements	100,000	—	—	100,000
Time deposits	10,000	—	—	10,000
Corporate bonds	77,022	17	(13)	77,026
Commercial paper	80,119	—	—	80,119
Asset-backed securities	30,375	31	—	30,406
U.S. Government Treasury and agency securities	150,184	124	—	150,308
Total	$ 741,009	$ 172	$ (13)	$ 741,168

At December 31, 2020, the remaining contractual maturities of available-for-sale securities were less than two years. There have been no significant realized gains or losses on available-for-sale securities for the periods presented. All marketable securities with unrealized losses at December 31, 2020 have been in a loss position for less than twelve months or the loss is not material and were temporary in nature. We do not intend to sell the investments that are in an unrealized loss position before recovery of their amortized cost basis.

Inventory

Inventory consists of the following (in thousands):

	December 31,	
	2020	2019
Work-in-process	$ 7,184	$ 8,191
Finished goods	5,864	3,355
Total	$ 13,048	$ 11,546

Property, Plant, and Equipment, net

Property, plant, and equipment, net consists of the following (in thousands):

	December 31,	
	2020	2019
Leasehold improvements	$ 39,356	$ 16,871
Research and development equipment	28,394	17,881
Furniture and office equipment	5,051	3,496
Computer equipment and software	8,181	7,817
Land	11,722	—
Construction-in-progress	17,649	24,271
Other	554	—
Property, plant, and equipment, gross	110,907	70,336
Less accumulated depreciation	(37,392)	(25,988)
Property, plant, and equipment, net	$ 73,515	$ 44,348

Depreciation expense for the years ended December 31, 2020, 2019 and 2018 was $12.1 million, $8.3 million and $7.2 million respectively. Amortization of leasehold improvements and software is included in depreciation expense. The construction-in-progress balance primarily relates to the construction costs for the gene therapy manufacturing plant in Bedford, Massachusetts.

Accrued Liabilities

Accrued liabilities consists of the following (in thousands):

	December 31,	
	2020	2019
Research, clinical study, and manufacturing expenses	$ 25,875	$ 22,894
Payroll and related expenses	58,176	41,324
Other	24,440	18,976
Total	$ 108,491	$ 83,194

5. Intangible Assets, net

Subsequent to the acquisition of Dimension Therapeutics, Inc. (Dimension) in November 2017, the Company recognized IPR&D assets of $129.0 million and a contract asset of $13.5 million. The estimated fair value of these intangible assets was measured using Level 3 inputs as of the acquisition date.

IPR&D assets represent the fair value of acquired programs to develop an AAV gene therapy for OTC deficiency and to develop an AAV gene therapy for glycogen storage disease type Ia. The fair value of IPR&D assets acquired was determined based on the discounted present value of each research project's projected cash flows using an income approach, including the application of probability factors related to the likelihood of success of the program reaching final development and commercialization. Additionally, the projections consider the relevant market sizes and growth factors, estimated future cash flows from product sales resulting from completed products and in-process projects and timing and costs to complete the in-process projects. The rates utilized to discount the net cash flows to their present value are commensurate with the stage of development of the projects and uncertainties in the economic estimates used in the projections. IPR&D assets are considered to be indefinite-life until the completion or abandonment of the associated research and development efforts.

The contract asset represented the fair value of the agreement with Bayer HealthCare LLC to research, develop, and commercialize AAV gene therapy products for treatment of hemophilia A. The fair value of the contract asset was determined based on the discounted present value of the estimated net future income and was amortized to research and development expense over the research term which was completed in 2019.

Subsequent to the FDA approval of Dojolvi for the treatment of LC-FAOD in June 2020, the Company recorded $2.3 million from contractual payments for the achievement of regulatory milestones to certain collaboration partners as intangible assets, which is being amortized over its useful life of seven years. The Company recorded research and development expense of $0.2 million, $0.2 million, and $12.3 million for the years ended December 31, 2020, 2019, and 2018, respectively, related to the amortization of the intangible assets.

The Company tests the intangible assets for impairment annually during its fourth quarter. No impairment charges have been recognized on intangible assets.

6. Revenue

The following table disaggregates total revenues from external customers by collaboration and license revenue and product sales (in thousands):

	Year Ended December 31,		
	2020	2019	2018
Collaboration and license revenue:			
Crysvita collaboration revenue in profit-share territory	$ 128,597	$ 74,869	$ 15,334
Crysvita royalty revenue in European territory	1,498	8,120	2,892
Daiichi Sankyo	89,220	—	—
Bayer	—	504	23,467
Total collaboration and license revenue	219,315	83,493	41,693
Product sales:			
Crysvita	10,350	4,286	644
Mepsevii	15,342	12,634	7,903
Dojolvi	13,028	3,301	1,255
Total product sales	38,720	20,221	9,802
Crysvita non-cash collaboration royalty revenue	12,995	—	—
Total revenues	$ 271,030	$ 103,714	$ 51,495

The following table disaggregates total revenues based on geographic location (in thousands):

	Year Ended December 31,		
	2020	2019	2018
North America	$ 237,666	$ 86,442	$ 45,339
Europe	21,318	12,085	5,293
All other	12,046	5,187	863
Total revenues	$ 271,030	$ 103,714	$ 51,495

The following table presents the activity and ending balances for sales-related accruals and allowances (in thousands):

	December 31,		
	2020	2019	2018
Balance of product sales reserve at beginning of year	$ 1,818	$ 1,240	$ 41
Provisions	5,763	3,846	2,148
Payments	(2,785)	(2,739)	(949)
Adjustments	(883)	(529)	—
Balance of product sales reserve at end of year	$ 3,913	$ 1,818	$ 1,240

The following table presents changes in the contract assets (liabilities) for the years ended December 31, 2020 and 2019 (in thousands):

	December 31,	
	2020	2019
Balance of contract assets at beginning of period	$ —	$ 2,979
Additions	(155,788)	504
Deductions	89,220	(3,483)
Balance of contract liabilities at end of period, net	$ (66,568)	$ —

See Note 7 for additional details on contract assets (liabilities) activities.

The Company's largest accounts receivable balance was from a collaboration partner and was 71% and 87% of the total accounts receivable balance as of December 31, 2020 and 2019, respectively.

7. License and Research Agreements

Kyowa Kirin Co., Ltd. Collaboration and License Agreement

In August 2013, the Company entered into a collaboration and license agreement with Kyowa Kirin Co., Ltd. (KKC or formerly Kyowa Hakko Kirin Co., Ltd. or KHK). Under the terms of this collaboration and license agreement, as amended, the Company and KKC 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 European Union, United Kingdom, and Switzerland, or the European territory, and the Company has the right to develop and commercialize such products in the field of orphan diseases in Mexico and Central and South America, or Latin America.

Development Activities

In the field of orphan diseases, and except for ongoing studies being conducted by KKC, the Company is the lead party for development activities in the profit-share territory and in the European territory until the applicable transition date; the Company is also 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 the Company and KKC. The Company shares the costs for development activities in the profit-share territory and the European territory conducted pursuant to the development plan before the applicable transition date equally with KKC. KKC is responsible for 100% of the costs for development activities in Japan and Korea. In April 2023, which is the transition date for the profit-share territory, and on the applicable transition date for the European territory, KKC will become the lead party and be responsible for the costs of the development activities. However, the Company will continue to share the costs of the studies commenced prior to the applicable transition date equally with KKC. Crysvita was approved in the European Union and United Kingdom in February 2018 and was approved by the FDA in April 2018.

The collaboration and license agreements are within the scope of ASC 808, which provides guidance on the presentation and disclosure of collaborative arrangements.

Collaboration revenue related to sales in profit-share territory

The Company and KKC share commercial responsibilities and profits in the profit-share territory until April 2023. Under the collaboration agreement, KKC manufactures and supplies Crysvita for commercial use in the profit-share territory and charges the Company the transfer price of 35% of net sales through December 31, 2022, and 30% thereafter. The remaining profit or loss after supply costs from commercializing products in the profit-share territory are shared between the Company and KKC on a 50/50 basis until April 2023. Thereafter, the Company will be entitled to receive a tiered double-digit revenue share in the mid-to-high 20% range.

As KKC is the principal in the sale transaction with the customer, the Company recognizes a pro-rata share of collaboration revenue, net of transfer pricing, in the period the sale occurs. The Company concluded that its portion of KKC's sales in the profit-share territory is analogous to a royalty and therefore recorded its share as collaboration revenue, similar to a royalty.

Royalty revenue related to sales in European territory

KKC has the commercial responsibility for Crysvita in the European territory. In December 2019, the Company sold its right to receive royalty payments based on sales in the European territory to Royalty Pharma, effective January 1, 2020, as further described in "Note 10. Liability Related to the Sale of Future Royalties." Prior to the Company's sale of the royalty, the Company received a royalty of up to 10% on net sales in the European territory, which was recognized as the underlying sales occur. Beginning in 2020, the Company records the royalty revenue as non-cash royalty revenues. During the year ended December 31, 2020, there was a change in estimate of the revenue reserves related to sales made prior to January 1, 2020, as a result of which, the Company recorded $1.5 million as royalty revenue in European territory.

The Company's share of collaboration and royalty revenue related to Crysvita was as follows (in thousands):

	Year Ended December 31,		
	2020	2019	2018
Company's share of revenue in profit-share territory	$ 128,597	$ 74,869	$ 15,334
Royalty revenue in European territory	1,498	8,120	2,892
Non-cash royalty revenue in European territory	12,995	—	—
Total	$ 143,090	$ 82,989	$ 18,226

Product revenue related to sales in other territories

The Company is responsible for commercializing Crysvita in Latin America and Turkey. The Company is considered the principal in these territories as the Company controls the product before it is transferred to the customer. Accordingly, the Company records revenue on a gross basis related to the sale of Crysvita once the product is delivered and the risk and title of the product is transferred to the distributor. The Company recorded product sales of $10.4 million, $4.3 million, and $0.6 million for the years ended December 31, 2020, 2019, and 2018, respectively, net of estimated product returns and other deductions. KKC has the option to assume responsibility for commercialization efforts in Turkey from the Company, after a certain minimum period.

Under the collaboration agreement, KKC manufactures and supplies Crysvita, which is purchased by the Company for sales in the above territories, and is based on 35% of the net sales through December 31, 2022 and 30% thereafter. The Company also pays to KKC a low single-digit royalty on net sales in Latin America.

Cost sharing payments

Under the collaboration agreement, KKC and the Company share certain development and commercialization costs. As a result, the Company was reimbursed for these costs and operating expenses were reduced as follows (in thousands):

	Year Ended December 31,		
	2020	2019	2018
Research and development	$ 21,476	$ 27,309	$ 32,240
Selling, general and administrative	25,186	21,828	14,228
Total	$ 46,662	$ 49,137	$ 46,468

Collaboration receivable and payable

The Company had accounts receivable from KKC in the amount of $16.4 million and $28.5 million from profit-share revenue and royalties and other receivables recorded in prepaid and other current assets of $9.6 million and $17.8 million and accrued liabilities of $2.4 million and $0.9 million from commercial and development activity reimbursements, as of December 31, 2020 and 2019, respectively.

Saint Louis University License Agreement

In November 2010, the Company entered into a license agreement with Saint Louis University (SLU). Under the terms of this license agreement, SLU granted the Company 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.

The Company made a milestone payment of $0.1 million upon approval of Mepsevii for treatment of MPS 7. The Company is required to pay to SLU a low single-digit royalty on net sales of the licensed products in any country or region, upon reaching a certain level of cumulative worldwide sales of the product.

Baylor Research Institute License Agreement

In September 2012, the Company entered into a license agreement with Baylor Research Institute (BRI). Under the terms of this license agreement, BRI exclusively licensed to the Company its territories for certain intellectual property related to Dojolvi (triheptanoin) for the treatment of LC-FAOD.

For the years ended December 31, 2020 and 2019, the Company paid $2.0 million and $0.8 million, respectively, for the attainment of various development milestones related to the development of LC-FAOD. The Company may be obligated to make additional future payments of up to $2.5 million contingent upon attainment of various development milestones relating to the development of LC-FAOD and $7.5 million contingent upon attainment of various sales milestones. Additionally, the Company is paying BRI a mid-single-digit royalty on net sales of the licensed product in the licensed territories.

REGENXBIO, Inc.

The Company has a license agreement with REGENX, for an exclusive, sublicensable, worldwide commercial license under certain intellectual property for preclinical and clinical research and development, and commercialization of drug therapies using REGENX 's licensed patents for the treatment of hemophilia A, OTC deficiency, and GSD1a. The Company will pay an annual 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 owed by REGENX to its licensors, contingent upon the attainment of certain development activities as outlined in the agreement.

The Company also has an option and license agreement with REGENX under which the Company has an exclusive, sublicensable, worldwide license to make, have made, use, import, sell, and offer for sale licensed products to treat Wilson disease and CDKL5 deficiency. For each disease indication, the Company is obligated to pay an annual maintenance fee of $0.1 million and up to $9.0 million upon achievement of various milestones, as well as mid to high single-digit royalties on net sales of licensed products and mid-single-digit to low double-digit percentage sublicenses fees, if any.

In March 2020, the Company entered into a license agreement with REGENX, for an exclusive, sublicensable, worldwide license to REGENX's NAV AAV8 and AAV9 vectors for the development and commercialization of gene therapy treatments for a rare metabolic disorder. In return for these rights, the Company made an upfront payment of $7.0 million, which was recorded as an in-process research and development expense during the year ended December 31, 2020. The Company will pay certain annual fees of $0.1 million, milestone payments of up to $14.0 million, and royalties on any net sales of products incorporating the licensed intellectual property that range from a high single-digit to low double-digit royalty.

Bayer HealthCare LLC

The Company has an agreement with Bayer Healthcare LLC (Bayer) to research, develop and commercialize AAV gene therapy products for the treatment of hemophilia A (DTX 201). Under this agreement, Bayer has been granted an exclusive license to develop and commercialize one or more novel gene therapies for hemophilia A. The agreement requires that Bayer use commercially reasonable efforts to conduct and fund a proof-of-concept (POC) clinical trial and 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.

Bayer is responsible for funding certain research and development services performed by the Company in the performance of its obligations under the annual research plan and budget. Under the terms of the agreement with Bayer, the Company is eligible to receive development and commercialization milestone payments of up to $232.0 million, as well as, royalty payments ranging in the high single-digit to low double-digit percentages, not exceeding the mid-teens, of net sales of licensed products. The Company achieved the first milestone in December 2017, the second milestone in April 2018, and has received $15.0 million for such milestones to date.

As of the acquisition date of Dimension on November 7, 2017, the Company valued the contract under ASC 805 and recorded an intangible asset of $13.5 million. The intangible asset was amortized to research and development expense over the research term and was completed in 2019. The Company recorded research and development expense of $0.2 million and $12.3 million for the years ended December 31, 2019 and 2018, respectively, for the amortization of the intangible asset.

The Company evaluated the agreement under ASC 606 and recorded a contract liability as of November 7, 2017 of $2.5 million. It was determined that the performance obligations under the agreement include (i) research and development services to be provided over the research term, (ii) a development and commercialization license, and (iii) the Company's participation in certain committees. It was determined that these performance obligations are not distinct in the context of the contract and therefore are a single performance obligation. The Company calculated the transaction price by including the unconstrained milestones along with the estimated payments for research and development services and recorded $0.5 million and $23.5 million as collaboration and license revenue for the years ended December 31, 2019 and 2018, respectively, by measuring the progress toward complete satisfaction of the performance obligation using an input measure.

University of Pennsylvania

The Company has an agreement with University of Pennsylvania School of Medicine (Penn) to sponsor certain research related to liver and hemophilia gene therapy. In consideration for funding such research, Penn granted the Company 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. The Company is required to reimburse Penn for filing, prosecuting and maintaining such patent rights unless and until the Company declines to exercise its option. Penn provides the Company with task-based, scientific reports of progress and results of the research, and granted the Company a royalty-free, nontransferable, non-exclusive right to copy and distribute any research reports furnished to the Company 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. Otherwise, the sponsored research agreement contains customary confidentiality provisions.

The Company also has a research, collaboration, and license agreement with Penn, which provides the terms for the Company and Penn to collaborate with respect to the pre-clinical development of gene therapy products for the treatment of certain indications. Under the agreement, Penn granted the Company an exclusive, worldwide license to certain patent rights arising out of the research program, subject to certain retained rights, and a non-exclusive, worldwide license to certain Penn intellectual property, in each case to research, develop, make, have made, use, sell, offer for sale, commercialize and import licensed products in each indication for the term of the agreement. The Company will fund the cost of the research program in accordance with a mutually agreed-upon research budget and will be responsible for clinical development, manufacturing and commercialization of each indication. The Company may be obligated to make milestone payments of up to $5.0 million for each indication, if certain development milestones are achieved over time, as well as low to mid-single-digit royalties on net sales of each licensed product. The Company may also be obligated to make milestone payments of up to $25.0 million per approved product if certain commercial milestones are achieved.

Arcturus Research Collaboration and License Agreement

In October 2015, the Company entered into a Research Collaboration and License Agreement with Arcturus. The Company and Arcturus are collaborating on the research and development of therapies for select rare diseases. As consideration for entering into the arrangement, the Company paid Arcturus an upfront fee of $10.0 million. Arcturus was responsible for conducting certain research services, funded by the Company, and the Company was responsible for development and commercialization costs. Pursuant to the agreement, the Company incurred $0.4 million, $0.8 million, and $1.9 million for the years ended December 31, 2020, 2019, and 2018, respectively, in research and development expense for the funding of certain research services received from Arcturus.

In June 2019, the Company entered into an Equity Purchase Agreement and an amendment to the Research Collaboration and License Agreement to expand the field of use and increase the number of disease targets to include mRNA, DNA and siRNA therapeutics for up to 12 rare diseases. Pursuant to the agreements, the Company paid $6.0 million in cash upfront to Arcturus and purchased 2,400,000 shares of Arcturus' common stock at a stated value of $10.00 per share, resulting in a total of $30.0 million of consideration paid at the close of the transaction. As a result, the Company received expanded license rights; the Arcturus common stock; an option to purchase an additional 600,000 shares of Arcturus' common stock at $16.00 per share. The Company also received the right to nominate one member to the Arcturus Board of Directors as well as one Board observer. In May 2020, the Company exercised the option to purchase 600,000 shares for a total purchase price of $9.6 million. Under the amended license agreement, certain early-stage milestone payments are reduced and the total potential milestone payments are increased due to the expanded number of targets. Arcturus is also entitled to reimbursement of related research expenses and royalties on commercial sales.

The Company recorded the common stock investment at $13.9 million on the transaction date, which was based on the quoted market price on the closing date. The Company elected to apply the fair value option to account for the equity investment in Arcturus. The Company also accounted for the option to purchase additional shares of Arcturus common stock at fair value, which was recorded at $0.5 million on the transaction date based on the Black-Scholes option pricing method. The remaining $15.6 million of the total $30.0 million paid as consideration was attributed to the additional license rights obtained and was recorded as in-process research and development expense.

In December 2020, the Company sold 800,000 shares of Arcturus' common stock at a weighted-average price of $100.81 per share and net proceeds of $79.8 million.

The changes in the fair value of the Company's equity investment in Arcturus were as follows (in thousands):

	Arcturus common stock	Option to purchase additional shares of Arcturus common stock	Total
Acquisition of equity investment in Arcturus in June 2019	$ 13,872	$ 467	$ 14,339
Change in fair value	12,216	1,197	13,413
December 31, 2019	26,088	1,664	27,752
Change in fair value	113,978	23,948	137,926
Transfer of value upon option exercise	35,212	(25,612)	9,600
Sale of shares	(79,842)	—	(79,842)
December 31, 2020	$ 95,436	$ —	$ 95,436

GeneTx

In August 2019, the Company entered into a Program Agreement and a Unitholder Option Agreement with GeneTx to collaborate on the development of GeneTx's GTX-102, an ASO for the treatment of Angelman syndrome.

Pursuant to the terms of the Unitholder Option Agreement, the Company made an upfront payment of $20.0 million for an exclusive option to acquire GeneTx, which was exercisable any time prior to 30 days following FDA acceptance of the IND for GTX-102. Pursuant to the agreement, upon acceptance of the IND, which occurred in January 2020, the Company elected to extend the option period by paying an option extension payment of $25.0 million (option extension premium) during the year ended December 31, 2020. The Company has a right to acquire GeneTx for a payment of $125.0 million, at any time, until the earlier of 30 months from the first dosing of a patient in a planned Phase 1/2 study (subject to extensions) or 90 days after results are available from that study. This exclusive option to acquire GeneTx can be extended under certain circumstances, by up to four additional three-month periods, by paying an additional extension fee for each three-month period.

During the exclusive option period, GeneTx is responsible for conducting the program based on the development plan agreed between the parties and, subject to the terms in the Program Agreement, has the decision-making authority on all matters in connection with the research, development, manufacturing and regulatory activities with respect to the Program. The Company will provide support, at its discretion, including strategic guidance and clinical expertise. The Company and GeneTx will collaborate on the management of the Phase 1/2 study in patients with Angelman syndrome. If the Company acquires GeneTx, the Company will then be responsible for all development and commercialization activities from the date of acquisition. The Company would also be required to make payments upon achievement of certain development and commercial milestones, as well as royalties, depending upon the success of the program.

Although GeneTx is a variable interest entity, the Company is not the primary beneficiary as it currently does not have the power to direct the activities that would most significantly impact the economic performance of GeneTx. Prior to product regulatory approval, all consideration paid to GeneTx represents rights to potential future benefits associated with GeneTx's in-process research and development activities, which have not reached technological feasibility and have no alternative future use. Accordingly, for the years ended December 31, 2020 and 2019, the Company recorded the option extension payment of $25.0 million and $20.0 million upfront payment as an in-process research and development expense, respectively.

Daiichi Sankyo

In March 2020, the Company entered into a License and Technology Access Agreement (the License Agreement) with Daiichi Sankyo Co., Ltd. (Daiichi Sankyo). Pursuant to the License Agreement, the Company granted Daiichi Sankyo a non-exclusive license to intellectual property, including know-how and patent applications, with respect to its HeLa producer cell line (PCL) and HEK293 transient transfection manufacturing technology platforms for AAV-based gene therapy products. The Company retains the exclusive right to use the manufacturing technology for its current target indications and additional indications identified now and in the future. The Company will provide certain technical assistance and technology transfer services during the technology transfer period of three years to enable Daiichi Sankyo to use the technologies for its internal gene therapy programs. Daiichi Sankyo has an option to extend the technology transfer period including know-how improvements by two additional one-year periods by paying a fixed amount for each additional year. Daiichi Sankyo will be responsible for the manufacturing, development, and commercialization of products manufactured with the licensed technology; however, the Company has the option to co-develop and co-commercialize rare disease products at the IND stage. Ultragenyx may also provide strategic consultation to Daiichi Sankyo on the development of both AAV-based gene therapy products and other products for rare diseases.

Under the terms of the License Agreement, Daiichi Sankyo made an upfront payment of $125.0 million and will pay an additional $25.0 million upon completion of the technology transfer of the HeLa PCL and HEK293 platforms, as well as single-digit royalties on net sales of products manufactured in either system. Daiichi Sankyo will reimburse the Company for all costs associated with the transfer of the manufacturing technology.

The Company also entered into a Stock Purchase Agreement with Daiichi Sankyo, pursuant to which Daiichi Sankyo purchased 1,243,913 shares of the Company's common stock in exchange for $75.0 million in cash during the first quarter of 2020. The fair market value of the common stock issued to Daiichi Sankyo was $55.3 million based on the stock price of $44.43 per share on the date of issuance, resulting in a $19.7 million premium on the Stock Purchase Agreement. Daiichi Sankyo is also subject to a three-year standstill and restrictions on sale of the shares (subject to customary exceptions or release).

In June 2020, the Company executed a subsequent license agreement (the Sublicense Agreement) with Daiichi Sankyo for transfer of certain technology in consideration for an upfront payment of $8.0 million and annual maintenance fees, milestone payments, and royalties on any net sales of products incorporating the licensed intellectual property.

The License Agreement, the Sublicense Agreement, and the Stock Purchase Agreement are being accounted for as one arrangement because they were entered into at or near the same time and negotiated in contemplation of one another. The Company evaluated the License Agreement and the Sublicense Agreement under ASC 606 and determined that the performance obligations under the agreements are (i) intellectual property with respect to its HeLa PCL and HEK293 transient transfection manufacturing technology platforms together with the initial technical assistance and technology transfer services, which are expected to be completed in the fourth quarter of 2021, and (ii) the transfer of any know-how and improvements after the completion of the initial technology transfer through the end of the three year technology transfer period ending March 2023.

The Company determined that the total transaction price of the License Agreement was $183.7 million which was comprised of the $19.7 million premium from the Stock Purchase Agreement, the $125.0 million upfront payment, the $25.0 million in unconstrained milestone payments, $8.0 million from the Sublicense Agreement, and the $6.0 million estimated reimbursement amount for delivering the license and technology services.

The Company allocated the total transaction price to the two performance obligations on a relative stand-alone selling price basis. Revenue allocated to the intellectual property and the technology transfer services will be recognized over an initial period which is estimated to end in the fourth quarter of 2021, measuring the progress toward complete satisfaction of the individual performance obligation using an input measure. Revenue for know-how and improvements after the completion of technology transfer will be recognized on a straight-line basis over the remaining technology transfer period, which ends in March 2023, as it is expected that Daiichi Sankyo will receive and consume the benefits consistently throughout the period. The estimated period to complete the technology transfer services and the related milestones payments, if any, are subject to revised estimates which could be impacted by limitations or delays from the COVID-19 pandemic, successful scale-up of the manufacturing, and other changes that may impact timing. Royalties from commercial sales will be accounted for as revenue upon achievement of such sales, assuming all other revenue recognition criteria are met.

For the year ended December 31, 2020, the Company recognized $89.2 million in revenue related to this arrangement. Accordingly, the Company had recorded $66.6 million as contract liabilities, net, as of December 31, 2020. The Company recorded an accounts receivable related to the License Agreement of $1.2 million as of December 31, 2020.

Solid Biosciences, Inc.

In October 2020, the Company entered into a strategic Collaboration and License Agreement with Solid Biosciences Inc., or Solid, and received an exclusive license for any pharmaceutical product that expresses Solid's proprietary microdystrophin construct from AAV8 and variants thereof in clade E for use in the treatment of Duchenne muscular dystrophy and other diseases resulting from lack of functional dystrophin, including Becker muscular dystrophy. The Company will collaborate to develop products that combine Solid's differentiated microdystrophin construct, the Company's HeLa PCL manufacturing platform, and the Company's AAV8 variants. Solid will also provide development support and was granted an exclusive option to co-invest in products the Company develops for profit share participation in certain territories. On a product-by-product basis, the Company may be obligated to make development milestone payments of up to $25.0 million, regulatory milestone payments of up to $65.0 million, and commercial milestone payments of up to $165.0 million, if such milestones are achieved, as well as royalties on any net sales of products incorporating the licensed intellectual property that range from a low to mid-double-digit percentage. The royalty rate changes to mid to high double-digit percentage if Solid decides to co-invest in the product.

The Company also entered into a Stock Purchase Agreement and the Investor Agreement with Solid, pursuant to which, the Company purchased 7,825,797 shares of Solid's common stock for an aggregate purchase price of $40.0 million. Subject to the terms of the Investor Agreement, the Company is restricted from selling, transferring or otherwise disposing of the shares without the prior approval of Solid until the earlier of (i) 18 months following the closing of the transaction, (ii) the termination of the Collaboration and License Agreement and (iii) certain other specified events. The Company also agreed to customary standstill restrictions in accordance with the terms of the Investor Agreement until the earlier of (a) 24 months after the closing of the transaction and (b) certain specified events.

The Company's investment in Solid is being accounted at fair value, as the fair value is readily determinable. The Company recorded the common stock investment at $26.8 million on the transaction date, which was based on the quoted market price on the closing date.

Although Solid is a variable interest entity, the Company is not the primary beneficiary as it does not have the power to direct the activities that would most significantly impact the economic performance of Solid. Prior to the achievement of certain development milestones, all consideration paid to Solid represents rights to potential future benefits associated with Solid's in-process research and development activities, which have not reached technological feasibility and have no alternative future use. Accordingly, the remaining $13.2 million of the total $40.0 million paid as consideration was attributed to the license rights obtained and was recorded as in-process research and development expense during the year ended December 31, 2020.

The changes in the fair value of the Company's investment in Solid's common stock were as follows (in thousands):

	Solid common stock
Acquisition of investment in Solid common stock in October 2020	$ 26,843
Change in fair value	32,477
December 31, 2020	$ 59,320

8. Leases

As described in "Note 2. Summary of Significant Accounting Policies", the Company adopted *Topic 842* as of January 1, 2019. Prior period amounts have not been adjusted and continue to be reported in accordance with historic accounting under *Topic 840*.

The Company leases office space and research, testing and manufacturing laboratory space in various facilities in Novato and Brisbane, California, in Cambridge and Woburn, Massachusetts, and in certain foreign countries, under operating agreements expiring at various dates through 2028. Certain lease agreements include options for the Company to extend the lease for multiple renewal periods and also provide for annual minimum increases in rent, usually based on a consumer price index or annual minimum increases. None of these optional periods have been considered in the determination of the right-of-use lease asset or the lease liability for the leases as the Company did not consider it reasonably certain that it would exercise any such options. The Company recognizes lease expense on a straight-line basis over the non-cancelable term of its operating leases. The variable lease expense primarily consists of common area maintenance and other operating costs.

The Company recognizes rent expense on a straight-line basis over the noncancelable term of its operating leases. Prior to adoption of *Topic 842*, under *Topic 840*, rent expense was $6.4 million during the year ended December 31, 2018.

The components of lease expense were as follows (in thousands):

	Year Ended December 31,	
	2020	2019
Operating lease expense	$ 10,164	$ 9,163
Variable lease expense	3,298	2,779
Financing:		
Amortization	158	—
Interest expense	40	—
Total	$ 13,660	$ 11,942

Cash paid for amounts included in the measurement of operating lease liabilities for the year ended December 31, 2020 was $10.3 million and was included in net cash used in operating activities in the Consolidated Statements of Cash Flows.

Future minimum lease payments under non-cancellable leases as of December 31, 2020 were as follows (in thousands):

Year Ending December 31,	Operating	Financing	Total
2021	$ 11,418	$ 513	$ 11,931
2022	11,904	495	12,399
2023	12,148	237	12,385
2024	10,319	—	10,319
2025	6,247	—	6,247
Thereafter	3,456	—	3,456
Total future lease payments	55,492	1,245	56,737
Less: Amount representing interest	(8,426)	(84)	(8,510)
Present value of future lease payments	47,066	1,161	48,227
Less: Lease liabilities, current	(8,516)	(460)	(8,976)
Lease liabilities, non-current	$ 38,550	$ 701	$ 39,251

Lease liabilities are based on the net present value of the remaining lease payments over the remaining lease term. As of December 31, 2020, the weighted-average remaining operating and financing lease terms were 4.82 years and 4.51 years, respectively, and the weighted-average discount rates used to determine the lease liability for operating and financing leases were 6.70% and 5.58%, respectively.

9. Gain from Sale of Priority Review Vouchers

In January 2018, the Company completed the sale of a Rare Pediatric Disease Priority Review Voucher (PRV) it received in connection with the approval of Mepsevii for $130.0 million. In June 2018, the Company also completed the sale of the PRV it received in connection with the approval of Crysvita for $80.6 million, net, which was shared equally with KKC. As the PRVs did not have a carrying value, the gain recognized was equal to the net proceeds received. The Company recorded $170.3 million for its portion of the net proceeds for the year ended December 31, 2018, as a gain from the sale of the priority review vouchers.

10. Liability Related to the Sale of Future Royalties

In December 2019, the Company entered into a Royalty Purchase Agreement with RPI and RPI paid $320.0 million to the Company in consideration for the right to receive royalty payments effective January 1, 2020, arising from the net sales of Crysvita in the European Union, the United Kingdom, and Switzerland under the terms of the Company's Collaboration and License Agreement with KKC dated August 29, 2013, as amended. The agreement with RPI will automatically terminate, and the payment of royalties to RPI will cease, in the event aggregate royalty payments received by RPI are equal to or greater than $608.0 million prior to December 31, 2030, or in the event aggregate royalty payments received by RPI are less than $608.0 million prior to December 31, 2030, when aggregate royalty payments received by RPI are equal to $800.0 million.

Proceeds from the transaction were recorded as a liability (liability related to sale of future royalties on the Consolidated Balance Sheets). The Company amortizes $320.0 million, net of transaction cost of $5.8 million using the effective interest method over the estimated life of the arrangement. In order to determine the amortization of the liability, the Company is required to estimate the total amount of future royalty payments to be received by the Company and paid to RPI, subject to the capped amount, over the life of the arrangement. The excess of future estimated royalty payments (subject to the capped amount), over the $314.2 million of net proceeds, is recorded as non-cash interest expense over the life of the arrangement. Consequently, the Company estimates an imputed interest on the unamortized portion of the liability and records interest expense relating to the transaction. The Company records the royalty revenue arising from the net sales of Crysvita in the applicable European territories as non-cash royalty revenue in the Consolidated Statements of Operations over the term of the arrangement.

The Company periodically assesses the expected royalty payments using a combination of historical results, internal projections and forecasts from external sources. To the extent such payments are greater or less than the Company's initial estimates or the timing of such payments is materially different than its original estimates, the Company will prospectively adjust the amortization of the liability and the effective interest rate. For the three months ended December 31, 2020, the effective annual interest rate was approximately 9.8%.

There are a number of factors that could materially affect the amount and timing of royalty payments from KKC in the applicable European territories, most of which are not within the Company's control. Such factors include, but are not limited to, the success of KKC's sales and promotion of Crysvita, changing standards of care, delays or disruptions related to the COVID-19 pandemic, the introduction of competing products, pricing for reimbursement in various European territories, manufacturing or other delays, intellectual property matters, adverse events that result in governmental health authority imposed restrictions on the use of Crysvita, significant changes in foreign exchange rates as the royalty payments are made in U.S. dollars (USD) while significant portions of the underlying European sales of Crysvita are made in currencies other than USD, and other events or circumstances that could result in reduced royalty payments from European sales of Crysvita, all of which would result in a reduction of non-cash royalty

revenue and the non-cash interest expense over the life of the arrangement. Conversely, if sales of Crysvita in Europe are more than expected, the non-cash royalty revenue and the non-cash interest expense recorded by the Company would be greater over the term of the arrangement.

The following table shows the activity within the liability account (in thousands):

	Liability related to the sale of future royalties
Proceeds from sale of future royalties in December 2019	$ 314,234
Non-cash interest expense	1,135
December 31, 2019	315,369
Non-cash collaboration royalty revenue	(12,995)
Non-cash interest expense	33,291
December 31, 2020	$ 335,665

11. Equity

At-the-Market Offerings

In July 2017, the Company entered into an additional ATM sales agreement with Cowen whereby the Company could sell up to $150.0 million in aggregate proceeds of common stock from time to time, through Cowen as its sales agent. During the years ended December 31, 2020, 2019, and 2018, the Company sold 283,333, 468,685, and 640,257 shares of common stock, respectively, resulting in net proceeds of approximately $20.4 million, $24.8 million, and $38.1 million, respectively, after commissions and other offering costs. As of June 30, 2020, the Company completed the sale of all available amounts under the ATM facility.

Underwritten Public Offering

In January 2018, the Company completed an underwritten public offering in which 5,043,860 shares of common stock were sold, which includes 657,895 shares purchased by the underwriters pursuant to an option granted to them in connection with the offering, at a public offering price of $57.00 per share. The total proceeds that the Company received from the offering were approximately $271.0 million, net of underwriting discounts and commissions.

In February 2019, the Company completed an underwritten public offering in which 5,833,333 shares of common stock were sold, which included 760,869 shares purchased by the underwriters pursuant to an option granted to them in connection with the offering, at a public offering price of $60.00 per share. The total proceeds that the Company received from the offering were approximately $330.4 million, net of underwriting discounts and commissions.

In October 2020, the Company completed an underwritten public offering in which 5,111,110 shares of common stock were sold, which included 666,666 shares purchased by the underwriters pursuant to an option granted to them in connection with the offering, at a public offering price of $90.00 per share. The total proceeds that the Company received from the offering were approximately $435.6 million, net of underwriting discounts and commissions.

Common Stock Warrants

As of December 31, 2019 and 2018, there was an aggregate of 149,700 of common stock warrants outstanding with exercise price of $3.01 and expiration dates in 2020 and 2021. In March 2020, all of the outstanding common stock warrants were exercised.

12. Stock-Based Awards

Equity Plan Awards

In 2011, the Company adopted the 2011 Equity Incentive Plan (the 2011 Plan). The 2011 Plan provides for the granting of stock-based awards to employees, directors, and consultants under terms and provisions established by the board of directors. In 2014, the Company adopted the 2014 Incentive Plan (the 2014 Plan). The 2014 Plan had 2,250,000 shares of common stock available for future issuance at the time of its inception, which included 655,038 shares available under the 2011 Plan, which were transferred to the 2014 Plan upon adoption. No further grants subsequent to the IPO were made under the 2011 Plan. The 2014 Plan provides for automatic annual increases in shares available for grant, beginning on January 1, 2015 through January 1, 2024. Under the terms of the 2014 Plan, awards may be granted at an exercise price not less than fair market value. For employees holding more than 10% of the voting rights of all classes of stock, the exercise prices for awards must be at least 110% of fair market of the common stock on the grant date, as determined by the board of directors. The term of an award granted under the 2014 Plan may not exceed ten years. Typically, the vesting schedule for option grants to the employees provides that 1/4 of the grant vests upon the first anniversary of the date of grant, with the remainder of the shares vesting monthly thereafter at a rate of 1/48 of the total shares subject to the option. Typically, the vesting schedule for RSU grants provides that 1/4 of the grant vests upon the annual anniversary of the date of grant over the period of four years.

As part of the acquisition of Dimension, the Company assumed an equivalent 639,897 options to purchase shares of common stock of the Company from the equity plans of Dimension. No further grants subsequent to the acquisition are available under these equity plans.

As of December 31, 2020, an aggregate of 10,878,499 shares of common stock have been authorized for issuance under the 2011 Plan, the 2014 Plan, and the assumed equity awards from the Dimension plans.

Stock Option Activity

The following table summarizes activity under the Company's stock option plans, including the 2011 Plan, the 2014 Plan, the assumed equity awards from the Dimension plans and related information:

	Options Outstanding			
	Number of Options	Weighted-Average Exercise Price	Weighted-Average Remaining Contractual Term (Years)	Aggregate Intrinsic Value
				(In thousands)
Outstanding — December 31, 2017	5,399,410	$ 62.75	7.40	$ 37,687
Options granted	1,479,451	55.54		
Options exercised	(713,263)	36.21		
Options cancelled	(812,474)	74.80		
Outstanding — December 31, 2018	5,353,124	$ 62.46	7.22	$ 23,243
Options granted	1,762,075	63.03		
Options exercised	(235,678)	32.87		
Options cancelled	(766,457)	72.48		
Outstanding — December 31, 2019	6,113,064	$ 62.51	7.00	$ 18,989
Options granted	1,849,106	62.51		
Options exercised	(1,505,486)	58.51		
Options cancelled	(452,081)	69.38		
Outstanding — December 31, 2020	6,004,603	$ 62.99	7.21	$ 453,253
Vested and exercisable — December 31, 2020	2,989,891	$ 64.35	5.68	$ 221,488
Vested and expected to vest — December 31, 2020	5,699,638	$ 62.99	7.12	$ 430,243

The aggregate intrinsic values of options outstanding, vested and exercisable, and vested and expected to vest were calculated as the difference between the exercise price of the options and the fair value of the Company's common stock. The total intrinsic value of options exercised during the years ended December 31, 2020, 2019, and 2018 was $56.9 million, $6.5 million and $22.9 million, respectively. Cash received from the exercise of options was $88.1 million, $7.7 million, and $25.8 million as of December 31, 2020, 2019, and 2018, respectively.

The weighted-average estimated fair value of stock options granted was $35.22, $37.15 and $33.32 per share of the Company's common stock during the years ended December 31, 2020, 2019, and 2018, respectively. The total estimated grant date fair value of options vested during the years ended December 31, 2020, 2019, and 2018 was $45.4 million, $45.3 million, and $51.7 million, respectively.

Restricted Stock Units

The following table summarizes activity under the Company's Restricted Stock Units (RSUs) from the 2014 Plan and related information:

	RSUs Outstanding	
	Number of Shares	Weighted- Average Grant Date Fair Value
Unvested — December 31, 2017	821,560	$ 70.71
RSUs granted	555,905	56.01
RSUs vested	(235,913)	71.01
RSUs cancelled	(187,475)	65.37
Unvested — December 31, 2018	954,077	$ 63.12
RSUs granted	863,065	62.78
RSUs vested	(313,682)	66.25
RSUs cancelled	(205,310)	64.28
Unvested — December 31, 2019	1,298,150	$ 61.96
RSUs granted	967,310	64.36
RSUs vested	(434,153)	62.65
RSUs cancelled	(150,140)	61.42
Unvested — December 31, 2020	1,681,167	$ 63.21

The fair value of the RSUs is determined on the grant date based on the fair value of the Company's common stock. The fair value of the RSUs is recognized as expense ratably over the vesting period of one to four years. The total grant date fair value of the RSUs vested during the years ended December 31, 2020, 2019, and 2018 was $27.2 million, $20.8 million, and $16.8 million, respectively. The aggregate intrinsic value of the shares of the RSUs vested during the years ended December 31, 2020, 2019, and 2018 was $29.5 million, $18.4 million, and $14.9 million, respectively.

Performance Stock Units

In December 2017, the Company began granting performance stock units (PSUs) to certain employees. The following table summarizes activity under the Company's PSUs from the 2014 Plan and related information:

	PSUs Outstanding	
	Number of Shares	Weighted- Average Grant Date Fair Value
Unvested — December 31, 2017	508,850	$ 48.03
PSUs granted	71,725	59.67
PSUs cancelled	(97,375)	48.58
Unvested — December 31, 2018	483,200	$ 49.65
PSUs granted	61,500	67.31
PSUs vested	(65,643)	48.03
PSUs cancelled	(79,517)	50.01
Unvested — December 31, 2019	399,540	$ 52.56
PSUs granted	47,600	56.08
PSUs vested	(200,867)	51.21
PSUs cancelled	(33,707)	52.48
Unvested — December 31, 2020	212,566	$ 54.64

The fair value of the PSUs is determined on the grant date based on the fair value of the Company's common stock. PSUs are subject to vest only if certain specified criteria are achieved and the employees' continued service with the Company after achievement of the specified criteria. For certain PSUs, the number of PSUs that may vest are also subject to the achievement of certain specified criteria. As of December 31, 2020, the specified criteria were deemed probable of achievement or already achieved. Stock-based compensation for these PSUs is recognized over the service period beginning in the period the Company determines it is probable that the performance criteria will be achieved. The total grant date fair value of the PSUs vested during the years ended December 31, 2020 and 2019 was $10.3 million and $3.2 million, respectively, with an aggregate intrinsic value of the shares of $14.4 million and $4.2 million, respectively.

Employee Stock Purchase Plan

In January 2014, the Company adopted the 2014 Employee Stock Purchase Plan (ESPP) and reserved a total of 600,000 shares of common stock for issuance under the ESPP. The ESPP provides for automatic annual increases in shares available for grant, beginning on January 1, 2015 through January 1, 2024. Eligible employees may purchase common stock at 85% of the lesser of the fair market value of common stock on the offering date or the purchase date with a six-month look-back feature. ESPP purchases are settled with common stock from the ESPP's previously authorized and available pool of shares. During the year ended December 31, 2020, the Company issued 112,857 shares of common stock under the ESPP. As of December 31, 2020, an aggregate of 3,248,367 shares of common stock have been authorized for future issuance on the ESPP.

Stock-Based Compensation Expense

Total stock-based compensation recognized was as follows (in thousands):

	Year Ended December 31,		
	2020	2019	2018
Cost of sales	$ 827	$ 1,084	$ 146
Research and development	47,949	44,205	45,572
Selling, general and administrative	36,959	36,706	34,389
Total stock-based compensation expense	$ 85,735	$ 81,995	$ 80,107

Stock-based compensation of $1.2 million, $1.4 million, and $1.1 million was capitalized into inventory for the years ended December 31, 2020, 2019, and 2018, respectively. Capitalized stock-based compensation is recognized as cost of sales when the related product is sold. As of December 31, 2020, the total unrecognized compensation expense related to unvested equity awards, net of estimated forfeitures, was $155.6 million, which the Company expects to recognize over an estimated weighted-average period of 2.48 years. In determining the estimated fair value of the stock options and ESPP, the Company uses the Black-Scholes option-pricing model and assumptions discussed below. Each of these inputs is subjective and generally requires significant judgment to determine.

Expected Term—The Company's expected term represents the period that the Company's stock-based awards are expected to be outstanding and is determined using the simplified method (based on the mid-point between the vesting date and the end of the contractual term).

Expected Volatility—The Company's expected volatility is based on historical volatility over the look-back period corresponding to the expected term.

Risk-Free Interest Rate—The risk-free interest rate is based on the U.S. Treasury zero coupon issues in effect at the time of grant for periods corresponding with the expected term of option.

Expected Dividend—The Company has never paid dividends on its common stock and has no plans to pay dividends on its common stock. Therefore, the Company used an expected dividend yield of zero.

The fair value of stock option awards granted was estimated at the date of grant using a Black-Scholes option-pricing model with the following weighted-average assumptions:

	Year Ended December 31,		
	2020	2019	2018
Expected term (years)	6.20	6.22	6.23
Expected volatility	61%	61%	62%
Risk-free interest rate	0.8%	2.4%	2.7%
Expected dividend rate	0.0%	0.0%	0.0%

13. Defined Contribution Plan

The Company sponsors a retirement plan in which substantially all of its full-time employees in the United States and certain other foreign countries are eligible to participate. Eligible participants may contribute a percentage of their annual compensation to this plan, subject to statutory limitations. The Company recorded $4.3 million, $3.6 million, and $2.9 million as contribution expenses for the years ended December 31, 2020, 2019, and 2018, respectively.

14. Income Taxes

The components of the Company's loss before income taxes were as follows (in thousands):

	Year Ended December 31,		
	2020	2019	2018
Domestic	$ 189,449	$ 399,709	$ 205,440
Foreign	(4,090)	(265)	(8,343)
Total loss before income taxes	$ 185,359	$ 399,444	$ 197,097

The components of the Company's income tax provision were as follows (in thousands):

	Year Ended December 31,		
	2020	2019	2018
Current provision for income taxes:			
Federal	$ —	$ —	$ —
State	15	51	14
International	1,192	1,092	500
Total current tax provision	1,207	1,143	514
Deferred tax provision:			
Federal	—	—	—
State	—	2,140	—
International	—	—	—
Total deferred tax provision	—	2,140	—
Total provision for income taxes	$ 1,207	$ 3,283	$ 514

The Company has incurred net operating losses since inception. The Company has not reflected any benefit of such net operating loss carryforwards in the accompanying financial statements. The Company has established a full valuation allowance against its deferred tax assets due to the uncertainty surrounding the realization of such assets.

The effective tax rate of our provision for income taxes differs from the federal statutory rate as follows:

	Year Ended December 31,		
	2020	2019	2018
Federal statutory income tax rate	21.0 %	21.0 %	21.0 %
State income taxes, net of federal benefit	—	(0.5)	—
Federal tax credits	13.7	5.2	9.5
Other	(0.5)	(0.2)	(0.2)
Premium on equity issuance	2.2	—	—
Nondeductible permanent items	(0.9)	(0.4)	(0.8)
Stock-based compensation	0.9	(1.0)	(0.8)
Uncertain tax positions	(2.7)	(1.0)	(1.9)
Change in valuation allowance	(33.9)	(23.6)	(26.8)
Foreign rate differential	(0.5)	(0.3)	(0.3)
Provision for income taxes	(0.7)%	(0.8)%	(0.3)%

The tax effect of temporary differences that give rise to significant portions of the deferred tax assets is presented below (in thousands):

	Year Ended December 31,	
	2020	2019
Deferred tax assets:		
Loss carryforwards	$ 222,902	$ 185,892
Tax credits	184,961	158,791
Stock options	39,154	40,676
Accruals and reserves	24,922	19,622
Fixed assets and intangibles	7,242	3,870
Liability related to sale of future royalties	86,664	81,424
Other	28,642	4,183
Gross deferred tax assets	594,487	494,458
Valuation allowance	(561,139)	(486,796)
Total deferred tax assets	33,348	7,662
Deferred tax liabilities:		
In-process research and development	(33,306)	(33,306)
Basis difference in equity investments	(23,019)	—
Right-of-use lease assets	(10,329)	(7,662)
Gross deferred tax liabilities	(66,654)	(40,968)
Net deferred tax liabilities	$ (33,306)	$ (33,306)

As of December 31, 2020 and 2019, the Company had approximately $750.2 million and $549.9 million of federal net operating loss carryforwards available to reduce future taxable income that will begin to expire in 2032. As of December 31, 2020 and 2019, the Company had approximately $616.8 million and $520.2 million of state net operating loss carryforwards available to reduce future taxable income that will begin to expire in 2031.

As of December 31, 2020 and 2019, the Company had federal research tax credit carryforwards of $17.7 million and $11.7 million available to reduce future tax liabilities that will begin to expire in 2030. As of December 31, 2020 and 2019, the Company had state research credit carryforwards of $34.5 million and $25.5 million available to reduce future tax liabilities that will be carried forward indefinitely.

As of December 31, 2020 and 2019, the Company had federal Orphan Drug Credits of $179.8 million and $160.0 million available to reduce future tax liabilities that will begin to expire in 2031.

The Company's ability to use net operating loss and tax credit carryforwards to reduce future taxable income and liabilities may be subject to annual limitations pursuant to Internal Revenue Code Sections 382 and 383 as a result of ownership changes in the past and future. As a result of ownership changes in 2012 and 2011, $3.6 million of federal net operating loss carryforwards, $3.6 million of state net operating loss carryforwards, and $0.2 million of federal tax credits are permanently limited. Deferred tax assets for net operating losses and tax credits have been reduced and a corresponding adjustment to the valuation allowance has been recorded. Based upon information available through the reporting date, the Company is not aware of any other changes in ownership that would result in material limitations under Section 382 as of December 31, 2020.

The valuation allowance increased by $74.3 million and $125.1 million during the year ended December 31, 2020 and 2019, respectively.

The Company recorded unrecognized tax benefits for uncertainties in income taxes. A reconciliation of the Company's unrecognized tax benefits follows (in thousands):

	December 31,		
	2020	2019	2018
Balance at beginning of year	$ 39,954	$ 33,727	$ 28,377
Additions based on tax positions related to current year	6,950	5,575	4,750
Additions for tax positions of prior years	382	652	600
Reductions for tax positions of prior years	(624)	—	—
Balance at end of year	$ 46,662	$ 39,954	$ 33,727

The entire amount of the unrecognized tax benefits would not impact the Company's effective tax rate if recognized. The Company has elected to include interest and penalties as a component of tax expense. During the years ended December 31, 2020 and 2019, the Company did not recognize accrued interest and penalties related to unrecognized tax benefits. The Company does not anticipate that the amount of existing unrecognized tax benefits will significantly increase or decrease during the next year.

It is the Company's intention to reinvest the earnings of its non-U.S. subsidiaries in their operations. As of December 31, 2020, the Company had not made a provision for any incremental foreign withholding taxes on approximately $6.3 million of the excess of the amount of net income for financial reporting over the tax basis of investments in foreign subsidiaries that are essentially permanent in duration. If these earnings were repatriated to the U.S., the deferred tax liability associated with these temporary differences would result in a nominal amount of withholding taxes.

The Company files income tax returns in the U.S. federal, California, and other state tax jurisdictions. The federal and state income tax returns from inception to December 31, 2020 remain subject to examination.

15. Commitments and Contingencies

The Company has various manufacturing, clinical, research, and other contracts with vendors in the conduct of the normal course of its business. Other than as noted below, contracts are terminable, with varying provisions regarding termination. If a contract with a specific vendor were to be terminated, the Company would only be obligated for the products or services that the Company had received at the time the termination became effective.

As of December 31, 2020, the aggregate payments under contractually binding manufacturing and service agreements are as follows (in thousands):

	Year Ended December 31,	
	2021	2022
Manufacturing and Services	$ 4,330	$ 472
Land and Building Construction	26,078	382
Total	$ 30,408	$ 854

See "Note 8. Leases" for lease commitments.

Contingencies

While there are no material legal proceedings the Company is aware of, the Company may become party to various claims and complaints arising in the ordinary course of business. Management does not believe that any ultimate liability resulting from any of these claims will have a material adverse effect on its results of operations, financial position, or liquidity. However, management cannot give any assurance regarding the ultimate outcome of these claims, and their resolution could be material to operating results for any particular period, depending upon the level of income for the period.

Guarantees and Indemnifications

The Company indemnifies each of its directors and officers for certain events or occurrences, subject to certain limits, while the director is or was serving at the Company's request in such capacity, as permitted under Delaware law and in accordance with its certificate of incorporation and bylaws. The term of the indemnification period lasts as long as a director may be subject to any proceeding arising out of acts or omissions of such director in such capacity. The maximum amount of potential future indemnification is unlimited; however, the Company currently holds director liability insurance. This insurance allows the transfer of risk associated with the Company's exposure and may enable it to recover a portion of any future amounts paid. The Company believes that the fair value of these indemnification obligations is minimal. Accordingly, it has not recognized any liabilities relating to these obligations for any period presented.

16. Net Loss per Share

The following table sets forth the computation of the basic and diluted net loss per share during the years ended December 31, 2020, 2019, and 2018 (in thousands, except share and per share data):

	Year Ended December 31,		
	2020	2019	2018
Numerator:			
Net loss	$ (186,566)	$ (402,727)	$ (197,611)
Denominator:			
Weighted-average shares used to compute net loss per share, basic and diluted	60,845,550	56,576,885	49,775,223
Net loss per share, basic and diluted	$ (3.07)	$ (7.12)	$ (3.97)

The following weighted-average outstanding common stock equivalents were excluded from the computation of diluted net loss per share for the periods presented because including them would have been antidilutive:

	Year Ended December 31,		
	2020	2019	2018
Options to purchase common stock, RSUs, and PSUs	8,532,236	7,978,666	7,301,431
Employee stock purchase plan	2,626	3,953	3,345
Common stock warrants	29,449	149,700	149,700
	8,564,311	8,132,319	7,454,476

17. Accumulated Other Comprehensive Income (Loss)

Total accumulated other comprehensive income (loss) consisted of the following (in thousands):

	Year Ended December 31,	
	2020	2019
Cumulative foreign currency translation adjustment	$ 429	$ (306)
Unrealized gain on securities available-for-sale	260	159
Total accumulated other comprehensive income (loss)	$ 689	$ (147)

18. Quarterly Financial Data (unaudited)

The following table presents certain unaudited quarterly financial information. This information has been prepared on the same basis as the audited financial statements and includes all adjustments (consisting only of normal recurring adjustments) necessary to present fairly the unaudited quarterly results of operations set forth herein (in thousands, except per share data):

	2020			
	March 31,	June 30,	September 30,	December 31,
Revenue	$ 36,309	$ 61,709	$ 81,470	$ 91,542
Operating expenses	$ 156,974	$ 124,764	$ 131,785	$ 187,623
Change in fair value of equity investments	$ 7,668	$ 95,200	$ (11,520)	$ 79,055
Net income (loss)	$ (119,025)	$ 25,315	$ (68,845)	$ (24,011)
Net income (loss) per share, basic	$ (2.05)	$ 0.42	$ (1.13)	$ (0.37)
Net income (loss) per share, diluted	$ (2.05)	$ 0.41	$ (1.13)	$ (0.37)

	2019			
	March 31,	June 30,	September 30,	December 31,
Revenue	$ 18,172	$ 24,149	$ 25,800	$ 35,593
Operating expenses	$ 117,386	$ 136,623	$ 143,833	$ 130,045
Change in fair value of equity investments	$ —	$ 9,828	$ 2,166	$ 1,419
Net loss	$ (96,756)	$ (99,172)	$ (112,994)	$ (93,805)
Net loss per share, basic and diluted	$ (1.82)	$ (1.72)	$ (1.96)	$ (1.62)

19. Subsequent Event

In December 2020, the Company entered into a License and Collaboration Agreement with Mereo BioPharma 3 Limited (Mereo) to collaborate on the development of setrusumab. Under the terms of the agreement, the Company will lead future global development of setrusumab in both pediatric and adult patients with Osteogenesis Imperfecta, and was granted an exclusive license to develop and commercialize setrusumab in the U.S., Turkey, and the rest of the world, excluding the European Economic Area, United Kingdom, and Switzerland (the Mereo territory), where Mereo retains commercial rights. Each party will be responsible for post-marketing commitments and commercial supply in their respective territories.

Upon the closing of the transaction under the agreement in January 2021, the Company made a payment of $50.0 million to Mereo and will be required to make payments of up to $254.0 million upon the achievement of certain clinical, regulatory, and commercial milestones. The Company will pay for all global development costs as well as tiered double-digit percentage royalties to Mereo on net sales in the U.S., Turkey, and the rest of the world, and Mereo will pay the Company a fixed double-digit percentage royalty on net sales in the Mereo Territory.

[***] = CERTAIN CONFIDENTIAL INFORMATION CONTAINED IN THIS DOCUMENT, MARKED BY BRACKETS, HAS BEEN OMITTED BECAUSE THE INFORMATION (I) IS NOT MATERIAL AND (II) WOULD BE COMPETITIVELY HARMFUL IF PUBLICLY DISCLOSED

License Agreement

This License Agreement (this " **Agreement** ") is made as of September 20, 2012 (the " **Effective Date** "), by and between Ultragenyx Pharmaceutical Inc., a corporation organized and existing under the laws of the State of Delaware, having its principal place of business at 60 Leveroni Court, Novato, CA 94949 (" **Ultragenyx** "), and Baylor Research Institute, a non-profit corporation organized and existing under the laws of the State of Texas, having its principal place of business at 3310 Live Oak Street, Suite 501, Dallas, Texas 75204 (" **BRI** "). Ultragenyx and BRI are referred to in this Agreement individually as a " **Party** " and collectively as the " **Parties** ."

Recitals

WHEREAS, Ultragenyx is a biotechnology company focused on the discovery and development of innovative therapeutics for patients with rare and ultra-rare genetic diseases;

WHEREAS, BRI is a research center focused on finding prevention therapies and treatments for diseases and illnesses;

WHEREAS, BRI owns or controls certain intellectual property related to the Compound (as defined below); and

WHEREAS, the Parties desire for Ultragenyx to obtain certain rights and licenses to such intellectual property pertaining to the Compound in order to develop, manufacture and commercialize prophylactic, therapeutic and diagnostic products pursuant to the terms and conditions set forth herein.

NOW, THEREFORE, in consideration of the foregoing premises and the mutual covenants herein contained, the receipt and sufficiency of which are hereby acknowledged, Ultragenyx and BRI hereby agree as follows:

Article 1

Definitions

The terms in this Agreement with initial letters capitalized, shall have the meanings set forth below, or the meaning as designated in the indicated places throughout this Agreement.

1.1 "Active Ingredient" means a therapeutically active material that provides pharmacological activity in a nutritional or pharmaceutical product (excluding formulation components such as coatings, stabilizers, excipients or solvents, adjuvants or controlled release technologies).

1.2 "Affiliate" means, with respect to a Party, any Entity that controls, is controlled by, or is under common control with that Party. For the purpose of this definition, "control" means, direct or indirect, ownership of more than fifty percent (50%) of the shares of stock entitled to vote for the election of directors, in the case of a corporation, or more than fifty percent (50%) of the equity interest in the case of any other type of legal entity, status as a general partner in any partnership, or any other arrangement whereby the Entity controls or has the right to control the board of directors or equivalent governing body of a corporation or other entity, or the ability to cause the direction of the management or policies of a corporation or other entity.

1.3 "[***]" means [***].

1.4 "[***] Option" means that certain option pursuant to the option and license agreement between BRI and [***], dated [***] and as amended by the amendment agreement dated [***], which grants [***] the option to obtain a license to develop, manufacture and commercialize Compound and Product in the [***].

1.5 "[***] Option Termination" is defined in Section 2.2(a).

1.6 "BRI Indemnitee" is defined in Section 9.2.

1.7 "BRI Know-How" means, subject to Section 10.2(b), any and all Know-How Controlled by BRI or any of its Affiliates as of the Effective Date or thereafter during the Term that relates to, or is otherwise reasonably necessary or reasonably useful for, the use, development, manufacture or commercialization of any Compound or Product.

1.8 "BRI Patents" means any and all Patents Controlled by BRI or its Affiliate(s) as of the Effective Date or thereafter during the Term that: (i) claim the composition of matter of, or the method of manufacturing or using, any Compound or Product; or (ii) that otherwise relate to, or are reasonably necessary for, the use, development, manufacture or commercialization of any Compound or Product, including the Patents set forth in Exhibit A .

1.9 "BRI Technology" means BRI Know-How and BRI Patents.

1.10 "Business Day" means a day other than (a) a Saturday or Sunday, or (b) a day on which commercial banks located in San Francisco, California are authorized or required by law to be closed.

1.11 "Calendar Quarter" means the respective periods of three (3) consecutive calendar months ending on March 31, June 30, September 30 and December 31.

1.12 "Calendar Year" means a period of twelve (12) consecutive months ending on December 31.

1.13 "Claims" means all Third Party demands, claims, actions, proceedings, orders, findings and verdicts (in contract, tort or otherwise), as well as losses of any type, damages and legal costs resulting therefrom, including, without limitation, any product liability or substantially equivalent claims.

1.14 "Combination Product" means:

(i) a Product that contains both a Compound and one or more other Active Ingredients that are not Compounds;

(ii) a product consisting of one or more separate products packaged together with a Product in a single package or as a unit; or

(iii) a drug, device, test, kit or biological product packaged separately that is sold as a unit with a Product.

1.15 "Commencement" means, with respect to a clinical trial of any Compound or Product, the [***].

1.16 "Commercially Reasonable Efforts" means: (a) where applied to carrying out specific tasks and obligations of a Party under this Agreement other than development, manufacture or commercialization of a Product, expending reasonable, diligent, good faith efforts and resources to accomplish such task or obligation as a similarly situated pharmaceutical or biotechnology company (on its own or acting through any of its Affiliates, sublicensees or subcontractors) would normally use to accomplish a similar task or obligation under similar circumstances; and (b) where applied to the development, manufacture or commercialization of a Product, those reasonable efforts and resources customarily used by such Party with respect to a similar pharmaceutical product Controlled by such Party, which product is at a similar stage in its development or product life and is of similar market potential in the applicable market taking into account efficacy, safety profile, labeling, the then-current and expected competition in the applicable market, the likely timing of entry into the market, the expected extent and speed of market penetration, the patent and other proprietary position of the Product, the likelihood of regulatory approval given the regulatory structure involved, the profitability of the Product, including the cost of manufacture,

royalties payable to licensors of patent or other intellectual property rights, alternative products and other relevant factors and other scientific, clinical or commercial factors. With respect to subpart (b) of this definition, Commercially Reasonable Efforts shall be determined on a market-by-market and indication-by-indication basis for a particular Product, and it is anticipated that the level of effort shall be different for different markets and different indications, and shall change over time, reflecting changes in the status of the Product and the market(s) and indication(s) involved.

1.17 "Compound" means any of the following: (a) Triheptanoin; (b) [***], and in each case of (a) and (b), including any [***] thereof.

1.18 "Confidential Information" means all proprietary Know-How, unpublished patent applications and other information and data of a financial, commercial, business, operational or technical nature which: (a) the disclosing Party or any of its Affiliates has supplied or otherwise made available to the other Party or any of its Affiliates in connection with this Agreement, whether prior to or during the Term and whether made available orally, by observation, in writing or in electronic form; or (b) the receiving Party has learned from the disclosing Party in the course of this Agreement, in each case including information comprising or relating to concepts, discoveries, inventions, data, designs or formulae in relation to this Agreement.

1.19 "Control" or **"Controlled"** means, with respect to any Know-How, molecule, material, Patents, other intellectual property, or any proprietary or trade secret information, the legal authority or right (whether by ownership, license or otherwise), as of the Effective Date or during the Term, to: (i) grant ownership of or a license or sublicense to make, use, offer to sell, sell or import such molecule or material; (ii) grant ownership of or a license or a sublicense under such Know-How, Patents, or intellectual property; or (iii) otherwise disclose such proprietary or trade secret information, in each case without breaching the terms of any agreement with, obligation to or other arrangement with a Third Party, or misappropriating the proprietary or trade secret information of a Third Party; in each case as provided in this Agreement.

1.20 "Disclosing Party" is defined in Section 6.1(a).

1.21 "Dollar" or **"$"** means the legal tender of the United States.

1.22 "EMA" means the European Medicines Agency or any successor entity thereto performing substantially the same functions.

1.23 "Entity" means a partnership, limited partnership, limited liability partnership, corporation, limited liability company, business trust, joint stock company, trust, incorporated association, joint venture or similar entity or organization.

1.24 "European Union" means the European Union member states as then constituted; provided, as of the Effective Date, the European Union member states are Austria, Belgium, Bulgaria, Cyprus, the Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, the Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, and the United Kingdom.

1.25 "Fatty Acid Oxidation Disorder" or **"FAOD"** means a group of inherited metabolic disorders associated with a specific enzyme defect in the fatty acid metabolic pathway and affecting utilization of dietary and stored fat. Fatty Acid Oxidation Disorders include, without limitation, disorders of the following enzymes: Carnitine-Acylcarnitine Translocase (CATR), Carnitine Palmitoyltransferase I and II (CPT I, CPT II), Very-Long Chain Acyl-CoA dehydrogenase (VLCAD), L-3-Hydroxy-Acyl-CoA Dehydrogenase (LCHAD), and Mitochondrial Trifunctional Protein (TFP).

1.26 "FD&C Act" means the federal Food, Drug and Cosmetic Act, as amended, and the regulations promulgated thereunder from time to time.

1.27 "FDA" means the United States Food and Drug Administration or any successor entity thereto performing substantially the same functions.

1.28 "Field" means [***].

1.29 "First Commercial Sale" means, with respect to any Product in any country or jurisdiction in the Licensed Territory, the first (1st) *bona fide* commercial sale by or on behalf of Ultragenyx, its Affiliates or sublicensees to a Third Party other than sublicensees for distribution, use or consumption of any such Product in such country or jurisdiction after the Regulatory Approvals and any applicable Pricing Approvals have been obtained for such Product in such country or jurisdiction.

1.30 "Generic Product" means, with respect to a particular Product, and on a country-by-country basis, any nutritional or pharmaceutical product, other than a Product, that contains the same Active Ingredient as such Product and that is commercialized by a Third Party, which Third Party is not a licensee or sublicensee of Ultragenyx or its Affiliates, or any of their licensees or sublicensees, and has not obtained such pharmaceutical product from a chain of distribution including Ultragenyx or any of its Affiliates, licensees or sublicensees or further sublicensees. The term Generic Product does not include any Product licensed or produced by Ultragenyx or any of its Affiliates or sublicensees (i. e. an authorized generic product).

1.31 "Government Authority" means any federal, state, national, regional, provincial or local government, or political subdivision thereof, or any multinational organization or any authority, agency or commission entitled to exercise any administrative, executive, judicial, legislative, police, regulatory or taxing authority or power, any court or tribunal (or any department, bureau or division thereof, or any governmental arbitrator or arbitral body).

1.32 "IND" means an Investigational New Drug Application submitted to the FDA in conformance with applicable laws and regulations, or the foreign equivalent of any such application in any other country (such as a clinical trial application in the European Union).

1.33 "Indemnified Party" is defined in Section 9.4.

1.34 "Indemnifying Party" is defined in Section 9.4.

1.35 "IMD" is defined in Section 2.4.

1.36 "Know-How" means any and all tangible and intangible information and materials, including research and development data, regulatory submissions and correspondence, manufacturing information and processes, formulations, assays, cell lines, sequences, composition of matter, constructs, discoveries, improvements, modifications, processes, methods, protocols, formulas, utility, data (including physical, chemical, biological, toxicological, pharmacological, analytical, quality control, preclinical, clinical, and veterinary data), results, inventions, know-how and trade secrets, patentable or otherwise, and all other scientific, marketing, financial and commercial information or data, but excluding any of the foregoing to the extent described or claimed in any Patents.

1.37 "Law" means any federal, state, local, foreign or multinational law, statute, standard, ordinance, code, rule, regulation, resolution or promulgation, or any order by any Government Authority, or any license, franchise, permit or similar right granted under any of the foregoing, or any similar provision having the force or effect of law.

1.38 "Licensed Territory" means (a) as of the Effective Date, the United States, Canada and Mexico; or (b) if Ultragenyx exercises the Ultragenyx Option pursuant to Section 2.2(a), worldwide after the Licensed Territory is expanded pursuant to Section 2.2(d).

1.39 "Licensed Territory Product Infringement" is defined in Section 5.3(a).

1.40 "MAA" means a marketing approval application for Regulatory Approval of a Product that is filed with the EMA.

1.41 "Major European Market" means any of the following: [***].

1.42 "Major Market" means [***].

1.43 "Marketing Approval Application" means a BLA, NDA, MAA or similar application for Regulatory Approval that is filed with the applicable Regulatory Authority(ies) in any country or jurisdiction.

1.44 "Net Sales" means, with respect to any Product, the aggregate gross amount invoiced by Ultragenyx, any Affiliate, or sublicensee for sales of such Product to independent, unrelated Third Parties in *bona fide* arms' length transactions, less deductions for:

(a) the costs of packing, transportation, importation, postage, shipping and handling charges, and other charges, such as insurance and customs duties, relating thereto;

(b) any sales, excise or value added taxes imposed on or charged to the selling party and any other charges imposed by a Governmental Authority upon the sale of such Product and actually paid;

(c) trade, quantity, prompt settlement or similar discounts (including chargebacks and allowances) actually granted, allowed or incurred in connection with the sale of such Product that are customary in the trade;

(d) amounts repaid or credited on account of price adjustments, rejection, outdating, billing errors, recalls or return of such Product;

(e) bad debts that have been written off within twelve (12) months after the date of invoice; and

(f) rebates, reimbursements, fees or similar payments to (i) wholesalers and other distributors, pharmacies and other retailers, buying groups (including group purchasing organizations), health care insurance carriers, pharmacy benefit management companies, health maintenance organizations, Governmental Authorities, or other institutions or health care organizations; or (ii) to patients and other Third Parties arising in connection with any program applicable to a Product under which Ultragenyx, its Affiliates, or its sublicensees provides to low income, uninsured or other patients the opportunity to obtain Ultragenyx's pharmaceutical products at no cost or reduced cost.

Sales between Ultragenyx and its Affiliates and sublicensees shall be disregarded for purposes of calculating Net Sales, except if such purchaser is an end user.

If a Product is sold as part of a Combination Product, the Net Sales of such Product for the purpose of calculating royalties owed under this Agreement for sales of such Product under Section 4.4 or determining whether a sales-based milestone payment is due under Section 4.3(a), shall be determined as follows: first, Ultragenyx shall determine the actual Net Sales of such Combination Product (using the above provisions) and then such amount shall be multiplied by the fraction A/(A+B), where A is the invoice price of such Product, if sold separately, and B is the aggregate invoice price for an equivalent dose amount or unit of each other Active Ingredient, drug, device, test, kit or biological product in the Combination Product, if sold separately. If any other Active Ingredient, drug, device, test, kit or biological product in the Combination Product is not sold separately, Net Sales shall be calculated by multiplying actual Net Sales of such Combination Product by a fraction A/C where A is the invoice price of such Product if sold separately, and C is the invoice price of the Combination Product. If neither the Product nor any other Active Ingredient, drug, device, test, kit or biological product in the Combination Product is sold separately, the adjustment to Net Sales shall be determined by the Parties in good faith to reasonably reflect the fair market value of the contribution of such Product in the Combination Product to the total fair market value of such Combination Product.

1.45 "Option Exercise Fee" is defined in Section 2.2(b).

1.46 "Option Exercise Notice" is defined in Section 2.2(b).

1.47 "Option Period" is defined in Section 2.2(a).

1.48 "Option Territory" means worldwide except for the United States, Canada and Mexico.

1.49 "Patent Counsel" is defined in Section 5.1(a).

1.50 "Patents" means all patents and patent applications and any patents issuing therefrom (which for the purpose of this Agreement shall be deemed to include certificates of invention and applications for certificates of invention), including all divisionals, continuations, substitutions, continuations-in-part, converted provisionals, continued prosecution applications, adjustments, re-examinations, reissues, additions, renewals, revalidations, extensions (including patent term extensions, and supplemental certificates and the like), registrations, pediatric exclusivity periods of any such patents and patent applications, and any and all foreign equivalents of the foregoing.

1.51 "Person" means any individual, Entity or Governmental Authority.

1.52 "Phase 3 Clinical Trial" means a human clinical trial, the principal purpose of which is to establish safety and efficacy in patients and which is designed and intended to serve as a pivotal study to support the filing of an NDA for the indication being studied, all in accordance with the trial protocol.

1.53 "Pricing Approvals" means, with respect to a Product in any country or jurisdiction, all pricing and reimbursement approvals for the Product from Government Authorities required by applicable Law or Governmental Authorities.

1.54 "Product" means any nutritional or pharmaceutical product, including all dosage forms and formulations, containing one or more Compound(s) as an Active Ingredient(s) (alone or as part of a Combination Product). Except when referred to in the Net Sales definition in describing how to calculate the Net Sales of Combination Products, all references to Product in this Agreement shall be deemed to include Combination Products. Two Products shall be deemed the same Product if they contain the same Compound as the Active Ingredient.

1.55 "Product Marks" is defined in Section 3.6(b).

1.56 "Proof of Concept Study" or "POC Study" means a human clinical trial of a Compound or Product conducted by Ultragenyx or any Affiliate to demonstrate preliminary clinical safety and efficacy with a small number of strictly selected patients.

1.57 "Receiving Party" is defined in Section 6.1(a).

1.58 "Regulatory Approval" means, with respect to a Product in any country or jurisdiction, the approvals by the applicable Regulatory Authority in such country or jurisdiction (other than Pricing Approvals) necessary for the commercialization of such Product.

1.59 "Regulatory Authority" means any applicable Government Authority responsible for granting Regulatory Approvals for Products, including the FDA, the EMA and any corresponding national or regional regulatory authorities.

1.60 "Regulatory Exclusivity" means, with respect to a Product, any market exclusivity granted by government or Regulatory Authority to exclude Third Parties from the development and/or commercialization of any Products containing as its Active Ingredient the same Compound as the Product.

1.61 "Regulatory Filings" means, with respect to the Compounds or Products, any submission to a Regulatory Authority of any appropriate regulatory application specific to Compounds or Products, and shall include any submission to a regulatory advisory board and any supplement or amendment thereto. **"Regulatory Filings"** includes any IND, NDA, BLA and any Marketing Approval Application.

1.62 "Retained Territory" means all countries of the world other than the Licensed Territory. For clarity, if Ultragenyx exercises the Ultragenyx Option pursuant to Section 2.2(a), there will be no countries, jurisdictions or territories in the Retained Territory.

1.63 "Retained Territory Product Infringement" is defined in Section 5.4(a).

1.64 "Royalty Report" means a written report or reports showing, with respect to a given Calendar Quarter, on a Product-by-Product basis: (a) the calculation of Net Sales for each such Product during such Calendar Quarter; (b) any applicable currency conversions; and (c) the royalties payable with respect to such Net Sales in United States Dollars.

1.65 "Royalty Term" has the meaning set forth in Section 4.4(b).

1.66 "Safety Data Exchange Agreement" has the meaning set forth in Section 3.4.

1.67 "Term" is defined in Section 7.1.

1.68 "Third Party" means any Person other than a Party or an Affiliate of a Party.

1.69 "Third Party License" is defined in Section 4.4(d).

1.70 "Third Party Patent Proceeding" is defined in Section 5.5.

1.71 "Ultra Orphan Indication" means, on a country-by-country basis, an indication other than FAOD for which a Product has been granted orphan drug exclusivity under Section 527 of the FD&C Act, or has been granted a corresponding exclusivity under the applicable Laws of another country or jurisdiction within the Licensed Territory, and which affects fewer than 20,000 people in the US.

1.72 "Ultragenyx Indemnitee" is defined in Section 9.1.

1.73 "Ultragenyx Option" is defined in Section 2.2(a).

1.74 "Ultragenyx Option Notice" is defined in Section 2.2(a).

1.75 "United States" or **"US"** means the United States of America including its territories and possessions.

1.76 "Valid Claim" means, with respect to any country a claim of any issued and unexpired patent included in the BRI Patents (as may be extended through supplementary protection certificate or patent term extension or the like) that has not been revoked, abandoned, held invalid, unpatentable or unenforceable by a patent office, court or other governmental agency of competent jurisdiction in a final and non-appealable judgment (or judgment from which no appeal was taken within the allowable time period) and which claim has not been disclaimed, denied or admitted to be invalid or unenforceable through reissue, re-examination, opposition or disclaimer or otherwise, or lost in an interference proceeding.

1.77 Interpretation . In this Agreement, unless otherwise specified:

(a) "includes" and "including" means respectively includes and including without limitation;

(b) words denoting the singular shall include the plural and vice versa and words denoting any gender shall include all genders;

(c) the word "or" shall not be deemed to be used in the exclusive sense and shall instead be used in the inclusive sense to mean "and/or";

(d) words such as "herein", "hereof", and "hereunder" refer to this Agreement as a whole and not merely to the particular provision in which such words appear; and

(e) the Exhibits and other attachments form part of the operative provision of this Agreement and references to this Agreement shall include references to the Exhibits and attachments.

Article 2

License

2.1 License to Ultragenyx.

(a) BRI hereby grants to Ultragenyx (i) an exclusive license, with the right to grant sublicenses in multiple tiers, under the BRI Technology to research, develop, make, have made, use, offer to sell, sell, have sold, import and export Compounds and Products in the Field in the Licensed Territory; and (ii) a non-exclusive license, with the right to grant sublicenses in multiple tiers, to use BRI Know-How relating to Products for research purposes, and for commercial purposes for exploitation of any BRI Patents not otherwise exclusively committed to a Third Party outside of the Licensed Territory. For clarity, the license granted to Ultragenyx under this Section 2.1(a) does not include the right for Ultragenyx to practice any BRI Patent or use any BRI Know-How to develop, make, use or sell compounds or products that are proprietary to BRI other than Compounds or Products.

(b) Ultragenyx may exercise its rights and perform its obligations under this Agreement by itself or through any of its Affiliates or Third Party sublicensees or contractors without the prior written consent of BRI. Ultragenyx shall remain responsible for all of its obligations under this Agreement that have been delegated, subcontracted or sublicensed to any of its Affiliates, sublicensees or contractors.

(c) After the expiration of the Royalty Term for a particular Product in a country within the Licensed Territory, the licenses granted to Ultragenyx by BRI under this Section 2.1 shall become fully paid-up, irrevocable and perpetual licenses for such Product in the Field in such country.

(d) All licenses granted to Ultragenyx under this Agreement are granted subject to (i) any limitations imposed by the terms of any government grant, government contract, or government cooperative agreement applicable to the BRI Patent Rights and (ii) applicable requirements of 35 U.S.C. Sections 200 et seq., as amended, and implementing regulations and policies.

2.2 Ultragenyx Option to Expand Licensed Territory.

(a) The Parties acknowledge and agree that, as of the Effective Date, the Licensed Territory is limited to the United States, Canada and Mexico as a result of the [***] Option. The [***] Option, if not exercised by [***], will expire on December 31, 2012. BRI shall promptly provide Ultragenyx with written notice if (i) the [***] Option lapses either as a result of (A) [***] not exercising such [***] Option; or (B) any waiver or early termination of the [***] Option or otherwise (the "[***] **Option Termination** "), and/or (ii) [***] exercising the [***] Option and the resulting license agreement between [***] and BRI subsequently terminating or expiring (such notice in each of (i) and (ii), the " **Ultragenyx Option Notice** "). BRI hereby grants to Ultragenyx an exclusive option, to expand the Licensed Territory to be worldwide (the " **Ultragenyx Option** "), exercisable in the case of (i) above at any time after Ultragenyx receives the Ultragenyx Option Notice and before June 30, 2013 and in the case of (ii) above within three (3) months after Ultragenyx receives the Ultragenyx Option Notice (the " **Option Period** "). If [***] exercises the [***] Option and subsequently obtains a license to develop, manufacture and commercialize Compound and Product in the Option Territory, BRI and Ultragenyx shall use reasonable efforts to approach [***] to discuss in good faith the coordination of such development, manufacture and commercialization of Compound and Product by [***] and Ultragenyx in separate territories, provided, that there is no obligation for any party to agree to any such coordination, except that neither [***] nor Ultragenyx can commercialize Compound or Product in the other party's territory.

(b) Ultragenyx may exercise the Ultragenyx Option by providing written notice to BRI (an " **Option Exercise Notice** ") at any during the Option Period and by paying BRI the one-time option exercise fee of Seven Hundred Fifty Thousand Dollars ($750,000) (the " **Option Exercise Fee** ").

(c) Within ten (10) days of the date of the Ultragenyx Option Notice, BRI shall provide Ultragenyx with a good faith estimate of the BRI Patent related costs and expenses that BRI anticipates incurring for the BRI Patents for the Option Territory from the date of the Ultragenyx Option Notice through the Option Expiration Date. Upon its receipt of Ultragenyx's Option Exercise Notice, BRI shall provide Ultragenyx with a final reasonably detailed accounting of all BRI Patent related costs and expenses incurred after the date of the Ultragenyx Option Notice until the date of receipt of such Option Exercise Notice. Within thirty (30) days of

receipt of such final accounting, Ultragenyx shall reimburse BRI for any such reasonable BRI Patent related costs and expenses to the extent BRI has not been otherwise reimbursed for such costs and expenses.

(d) Upon BRI's receipt of the Option Exercise Notice and the Option Exercise Fee, the definition of Licensed Territory shall automatically be expanded to be worldwide.

2.3 BRI's Retained Rights. BRI retains the right to practice the BRI Technology outside the scope of the license granted to Ultragenyx in Section 2.1 (as may be expanded by Section 2.2), and the right to use the BRI Know-How for internal, not-for-profit research purposes. In addition, BRI shall have the right to continue to hold the IND for and conduct and complete the clinical trial that is being sponsored by BRI as of the Effective Date titled: "[***]" (the " **BRI Ongoing Study** ") in accordance with the protocol existing as of the Effective Date; provided, that BRI may only (i) modify the protocol for the Ongoing Study, (ii) increase enrollment for the Ongoing Study or (iii) change the enrollment criteria for the Ongoing Study as follows: BRI shall discuss any such matters with Ultragenyx in good faith and BRI shall use best efforts to incorporate any of Ultragenyx's comments on such matters. During the Term, BRI shall have the right to conduct additional clinical trials using the Compound under the direct supervision of [***]; provided, that BRI shall first notify Ultragenyx of any such proposed clinical trial and discuss any opportunity for collaboration on such clinical trial between BRI and Ultragenyx and, in the event the Parties agree for BRI to conduct such clinical trial independently, BRI shall conduct such clinical trial pursuant to a protocol to be agreed upon by Ultragenyx and BRI.

2.4 Collaborative Research Agreement. The Parties shall negotiate in good faith the terms and conditions for a collaborative research agreement between Ultragenyx and BRI's Institute of Metabolic Disease (" **IMD** ") regarding the Compound and such terms and conditions shall include (i) financial and technical support from Ultragenyx for the ongoing Phase 2 Clinical Trial in adult polyglucosan body disease and/or other development work at IMD and (ii) technical and scientific support from IMD to Ultragenyx in support of its development of the Compound and the Products. Neither Party shall be obligated to enter into such collaborative research agreement if the Ultragenyx and BRI cannot reach agreement on such terms and conditions after such good faith negotiations.

2.5 No Implied Licenses. Except as set forth herein, neither Party shall acquire any license or other intellectual property interest, by implication or otherwise, under any trademarks, Patents, Know-How or other intellectual property Controlled by the other Party.

2.6 Technology Transfer. In addition to BRI's obligation to provide information and documents related to BRI Know-How in accordance with Section 3.5(b), promptly after the Effective Date, BRI shall use best efforts, at no additional cost to Ultragenyx, to disclose and provide to Ultragenyx all BRI Know-How pertaining to the manufacture and development of any Compounds or Products that are Controlled by BRI as of the Effective Date, including all data from any and all clinical trials and preclinical studies, to the extent such BRI Know-How has not previously been provided to Ultragenyx. On a continuing basis during the Term, BRI shall, at no additional cost to Ultragenyx, disclose and provide to Ultragenyx additional BRI Know-How pertaining to the manufacture and development of any Compounds or Products that comes into existence or comes to BRI's attention after the Effective Date.

Article 3

Development, Manufacture and Commercialization

3.1 General. Subject to the terms and conditions of this Agreement, as between the Parties, Ultragenyx (on its own or acting through or together with any of its Affiliates, sublicensees or contractor manufacturers) shall have the sole and exclusive right to develop (including making Regulatory Filings and seeking Regulatory Approvals), manufacture and commercialize Compounds and Products in the Field in the Licensed Territory, at its sole discretion and at its cost and expense. The Parties acknowledge and agree that except as otherwise expressly provided in this Agreement, Ultragenyx shall have no obligation to disclose or share with BRI any preclinical or clinical data and information unless or until Ultragenyx exercises the Ultragenyx Option pursuant to Section 2.2(b).

3.2 Diligence.

(a) Ultragenyx (on its own or acting through any of its Affiliates, sublicensees or subcontractors) shall use Commercially Reasonable Efforts to develop and commercialize at least one (1) Product in FAOD and at least (1) Product in [***]. Specifically, Ultragenyx will use Commercially Reasonable Efforts to (a) [***]; (b) [***]; (c) [***]; and (d) within [***] after the Effective Date, perform at least one of the following: (i) [***]; or (ii) [***]; in each case of (a)-(d) above, provided that each such timeline shall be extended to account for any delay resulting from factors beyond Ultragenyx's reasonable control, including regulatory, medical, safety or efficacy delays.

(b) If Ultragenyx shall fail to achieve such milestones within such applicable time frame(s) (as such time frame(s) may be extended pursuant to 3.2(a) above), BRI may provide written notice to Ultragenyx and upon receipt of any such notice, the Parties shall discuss in good faith Ultragenyx's progress for the development of such Product in the applicable jurisdiction and the Parties may agree on an amended timeline or a plan for Ultragenyx to continue its development of the Product. Each agreed upon [***] extension of the timeline shall be subject to the payment by Ultragenyx of an extension fee of [***]. For clarity, if a delay in timeline is due to new regulatory, development, or safety requirements or other similar actions by regulatory authorities or other government agencies, such timeline is not subject to the payment by Ultragenyx of an extension fee.

(c) For the purposes of this Section 3.2(c), all FAOD indications shall be deemed one "Indication Cluster" and all [***] shall be deemed another "Indication Cluster." On an Indication Cluster-by-Indication Cluster basis, in the event Ultragenyx fails to satisfy such new timeline or plan that is specific to a particular Indication Cluster, then upon written notice by BRI, the license granted to Ultragenyx pursuant to Section 2.1(a) shall become non-exclusive solely for such Indication Cluster, provided that all obligations for payment of royalties or milestones remain the same for such Indication Cluster and provided, that, if Ultragenyx subsequently obtains Regulatory Approval for the Product for such Indication Cluster, the license under Section 2.1(a) shall thereupon automatically convert back to an exclusive license for such Indication Cluster so long as BRI still maintains the right to grant an exclusive license to Ultragenyx at such time. In the event of the conversion of the license to non-exclusive, any sole and/or exclusive rights that Ultragenyx has under this Agreement with respect to such non-exclusive Indication Cluster, including without limitation such rights under Section 3.1, this Section 3.2, and Section 3.3 shall also automatically become non-exclusive. Further, on an Indication Cluster-by-Indication Cluster basis, Ultragenyx's rights regarding BRI Independent Studies under Sections 3.3 (i)-(iv), and Ultragenyx's rights under Sections 5.1(a), 5.3(b), Section 5.4(b), Section 5.5 (a) and (b), and Section 5.6, as well as BRI's corresponding obligations to Ultragenyx with respect to those Sections, in each case as such rights and obligations apply to any non-exclusive Indication Cluster, shall be suspended for so long as such license remains non-exclusive and shall be automatically reinstated if and when such license becomes exclusive pursuant to the foregoing. Failure to achieve such milestones shall not be a material breach of this Agreement. The remedy provided for pursuant to this Section 3.2 shall be BRI's sole and exclusive remedy for or relating to Ultragenyx's failure to achieve any milestone. If the license granted to Ultragenyx pursuant to Section 2.1(a) is converted to a non-exclusive license for a particular Indication Cluster pursuant to the terms of this Section 3.2, BRI shall promptly provide Ultragenyx with written notice of any Third Party license that BRI grants under the BRI Technology relating to Compounds or Products for such Indication Cluster.

3.3 Regulatory. As between the Parties, Ultragenyx (on its own or acting through or together with any of its Affiliates, sublicensees or contractor manufacturers) has the sole right to: (a) make all Regulatory Filings, submissions, reports, updates and supplements with any Regulatory Authority with respect to any Compound or Product in the Licensed Territory; (b) obtain, hold and maintain all INDs (other than the IND for the BRI Ongoing Study), Regulatory Approvals and Pricing Approvals in the Field in the Licensed Territory in the name of Ultragenyx or any of its Affiliates or sublicensees; and (c) conduct all meeting and discussions and handle all correspondence with any Regulatory Authority related to any Compound or Product in the Licensed Territory. For the BRI Ongoing Study and any additional study that BRI independently conducts pursuant to Section 2.3 (" **BRI Independent Studies** "): (i) BRI shall promptly provide Ultragenyx with copies of all material documents, information and correspondence that are received from any Regulatory Authority; (ii) BRI shall provide Ultragenyx with copies of all material documents, information and correspondence that are planned for submission to any Regulatory Authority and BRI shall cooperate with and consider in good faith any input from Ultragenyx in preparing such submission; (iii) BRI shall provide Ultragenyx with reasonable advance notice of all meetings, conferences and discussions scheduled with any Regulatory Authority concerning such study(ies) and BRI shall consider in good faith any input from Ultragenyx in preparing for such meetings, conferences or discussions; and

(iv) to the extent permitted by applicable Laws and by any obligations to Third Parties that (A) exist as of the Effective Date or (B) come into existence after the Effective Date, provided that BRI shall use Commercially Reasonable Efforts to obtain such rights for Ultragenyx in its negotiations with Third Parties after the Effective Date, Ultragenyx shall have the right to participate in any such meetings, conferences or discussions and BRI shall facilitate such participation. If either (x) [***] exercises the [***] Option or (y) Ultragenyx does not exercise the Ultragenyx Option, then, in each case, BRI and Ultragenyx shall each use reasonable efforts to facilitate global coordination of clinical data and safety data between Ultragenyx and [***] and/or any other applicable Third Party licensee of BRI in the Retained Territory in order for Ultragenyx, [***] and/or any Third Party licensee to comply with regulatory requirements.

3.4 Pharmacovigilance. If either (a) [***] exercises the [***] Option or (b) Ultragenyx does not exercise the Ultragenyx Option, then, in each case, BRI and Ultragenyx shall use reasonable efforts to facilitate BRI, Ultragenyx and [***] and/or any other applicable Third Party licensee of BRI in the Retained Territory entering into a safety data exchange agreement (" ***Safety Data Exchange Agreement*** ") setting forth in detail the pharmacovigilance alert process and data exchange with respect to the Product to comply with all applicable legal obligations of Regulatory Authorities in the Licensed Territory and in the Retained Territory. For the Ongoing Study and any additional study that BRI independently conducts pursuant to Section 2.3, BRI shall cooperate with Ultragenyx and BRI shall transfer all safety data relating to the Product to Ultragenyx pursuant to a procedure to be agreed upon by the Parties; in the event of conversion of the license to non-exclusive, Ultragenyx shall also provide a reciprocal transfer of all its safety data to BRI.

3.5 Manufacture; Provision of Know-How.

(a) Subject to Section 3.5(b), Ultragenyx (on its own or acting through any of its Affiliates, sublicensees or subcontractors) shall be responsible for the manufacture and supply of Compounds and Products in the Licensed Territory for use by Ultragenyx, its Affiliates and sublicensees, at its cost and expense, itself or through one or more contract manufacturers or sublicensees. BRI shall use Commercially Reasonable Efforts to assist Ultragenyx in establishing a direct relationship with BRI's current supplier of Compounds.

(b) Promptly after the Effective Date, BRI shall provide Ultragenyx with all BRI Know-How that is necessary or reasonably useful to manufacture Compound or Product, including any and all reports and documentation from BRI's current or former supplier of Compounds that BRI does not have the ability to disclose to Ultragenyx under express or implied obligations of confidentiality.

3.6 Commercialization.

(a) Ultragenyx (on its own or acting through any of its Affiliates, sublicensees or subcontractors) shall book sales for the Products in the Licensed Territory and shall have sole control over pricing and other commercialization decisions with respect to the Products in the Licensed Territory.

(b) As between the Parties, Ultragenyx (on its own or acting through any of its Affiliates, sublicensees or subcontractors) shall have the right to brand commercialized Products using Ultragenyx trademarks and any other trademarks and trade names it determines appropriate for the Products, which may vary by country or within a country (" **Product Marks** "). Ultragenyx (on its own or acting through any of its Affiliates, sublicensees or subcontractors) shall own all rights in the Product Marks and shall be responsible for registration, maintenance, and defense of the Product Marks at its own costs and expense.

Article 4

Financial Provisions

4.1 Upfront Payment. In consideration for the license granted under this Agreement, Ultragenyx shall pay to BRI a one-time, non-refundable, non-creditable upfront payment of Two Hundred Fifty Thousand Dollars ($250,000) within thirty (30) days after the Effective Date.

4.2 Milestone Payments.

(a) Development and Regulatory Milestones. Ultragenyx shall pay to BRI the following one-time, non-refundable, non-creditable development and regulatory milestone payments upon the achievement of the corresponding milestone by Ultragenyx or any of its Affiliates or sublicensees:

Development and Regulatory Milestones	Payments
(i) [***]	$ [***]
(ii) [***]	$ [***]
(iii) [***]	$ [***]
(iv) [***]	$ [***]
(v) [***]	$ [***]
(vi) [***]	$ [***]
(vii) [***]	$ [***]
(viii) [***]	$ [***]
(ix) [***]	$ [***]
(x) [***]	$ [***]

(b) The Parties acknowledge and agree that the milestones set forth in Section 4.2(a)(ii), (vii), (viii), (ix) and (x) above will not be due if such Product triggering the milestone is in an indication that is not covered by a Valid Claim and if Ultragenyx has a financial obligation to pay a milestone pursuant to a Third Party License (as defined in Section 4.4(d) below) on such Product for such indication.

(c) The milestones set forth in Section 4.2(a) shall each be due after the first (1st) achievement of such milestone for the first Product to achieve such milestone by or on behalf of Ultragenyx or any of its Affiliates or sublicensees, and each such milestone payment shall be payable only once, regardless of how many Products or how many indications for which such milestone has been achieved.

(d) For clarity, the milestones set forth in sub-Section 4.2(a)(i), (ii), (v), (vi), (ix) and (x) above may only be due if Ultragenyx exercises the Ultragenyx Option pursuant to Section 2.2(b).

(e) Ultragenyx shall notify BRI in writing promptly upon each milestone event set forth in this Section 4.2 and BRI shall thereafter submit an invoice to Ultragenyx for the milestone payment corresponding to such milestone event as set forth in this Section 4.2. Ultragenyx shall make such applicable milestone payment within [***] days after receipt of such invoice from BRI.

4.3 Sales Milestone Payments.

(a) Ultragenyx shall pay to BRI the non-refundable, non-creditable sales milestone payments set forth below. The sales milestones shall each be due after the first achievement of such milestone for annual aggregate Net Sales of all Products by or on behalf of Ultragenyx or any of its Affiliates or sublicensees, and each such milestone payment shall be payable only once, regardless of how many Calendar Years during which such sales milestone have been reached.

Sales Milestones	Payments
First (1st) Calendar Year in which aggregate total Net Sales by Ultragenyx, its Affiliates and sublicensees for all Products throughout the Licensed Territory exceed $[***]	[***]
First (1st) Calendar Year in which aggregate total Net Sales by Ultragenyx, its Affiliates and sublicensees for all Products throughout the Licensed Territory exceed $[***]	$ [***]

(b) Ultragenyx shall notify BRI in writing within [***] days following the end of the Calendar Year during which any milestone event is achieved and BRI shall thereafter submit an invoice to Ultragenyx for the corresponding milestone payment as set forth in Section 4.4(a). Ultragenyx shall make such applicable milestone payment within [***] days following receipt of such invoice.

4.4 Royalty Payments.

(a) Royalty Rates for Products. Subject to the other terms of this Section 4.4, during the Royalty Term, Ultragenyx shall make quarterly royalty payments to BRI equal to [***] percent ([***]%) of the Net Sales of the Products in the Licensed Territory by Ultragenyx and any of its Affiliates or sublicensees.

(b) Royalty Term. On a Product-by-Product basis and country-by-country basis, Ultragenyx's royalty payment obligations under this Section 4.4 shall commence upon the First Commercial Sale of such Product in such country and expire upon the later of: (i) the expiration of the period of the first Regulatory Exclusivity granted by the applicable Regulatory Authority applicable to such Product in such country in connection with approval in such country for either FAOD or an Ultra Orphan Indication; or (ii) the expiration of the last-to-expire Valid Claim included in BRI Patents claiming the composition of matter of, or the method of making or using, such Product in such country in connection with approval in such country for FAOD or an Ultra Orphan Indication ("**Royalty Term**").

(c) Royalty Reduction for a Product Subject to Generic Competition. For a particular Product in a particular country, during any period during the Royalty Term if one (1) or more Generic Product(s) with respect to such Product is being sold in such country then the applicable royalty rate under this Section 4.4 shall be reduced by [***] percent ([***]%) for such Product in such country.

(d) Royalty Reduction for Third Party Payment Obligations. If Ultragenyx (or any of its Affiliates or sublicensees) enters into any agreement with a Third Party under which Ultragenyx obtains rights under any intellectual property (including any Patent or Know-How) Controlled by a Third Party, which is necessary to the use, development, manufacture, commercialization or import of any Compound or Product (including for the use or commercialization of any Compound or Product in a particular indication) (each, a " **Third Party License** "), Ultragenyx shall have the right to credit up to [***] percent ([***]%) of the amounts owed by Ultragenyx under any such Third Party License against Ultragenyx's royalty payments to BRI under this Section 4.4 for the same Product, on a country-by-country basis, provided that, by operation of this Section 4.4(d), Ultragenyx's royalty payment obligation to BRI shall not be reduced by more than [***] percent ([***]%) for the first such Third Party License or [***] percent ([***]%) for the second and any subsequent such Third Party License(s). For clarity, any applicable royalty reduction pursuant to Section 4.4(c) shall be in addition to any applicable royalty reduction pursuant to this Section 4.4(d) and such royalty reduction is not included within the aforementioned limits.

4.5 Reports; Payment of Royalty; Annual Reconciliation. During the Term, following the First Commercial Sale of a Product and on a Calendar Quarter basis, Ultragenyx shall furnish to BRI a Royalty Report. Reports shall be due within [***] days following the close of each Calendar Quarter. Royalties shown to have accrued by each Royalty Report shall be due and payable on the date such royalty report is due. Ultragenyx shall keep complete and accurate records in sufficient detail to enable the royalties payable hereunder to be determined.

4.6 Currency; Exchange Rate.

(a) All payments to be made by Ultragenyx to BRI under this Agreement shall be made in Dollars by bank wire transfer in immediately available funds to a bank account designated by written notice from BRI to Ultragenyx. In the case of sales outside the United States, the rate of exchange to be used in computing the monthly amount of currency equivalent in Dollars due BRI shall be made at the monthly rate of exchange published in *The Wall Street Journal* (U.S., Eastern Edition), prevailing on the last Business Day of the month preceding the month in which such sales are recorded by Ultragenyx.

(b) If pursuant to applicable Law or fiscal policy of a particular country, a remittance of royalties in the currency stipulated in this Section 4.6 is restricted or forbidden, Ultragenyx shall provide notice thereof to BRI, and payment of such royalty shall be made by the deposit thereof in local currency to the credit of BRI in a recognized banking institution designated by BRI or its Affiliates. When in any such country the applicable Law or fiscal policy would then allow the transmittal of such royalty payments, all royalties or other sums that Ultragenyx would have been under obligation to transmit but for the prohibition, shall promptly be transmitted to BRI to the extent allowable.

4.7 Late Payments. If a Party does not receive payment of any sum due to it on or before the due date therefor, simple interest shall thereafter accrue on the sum due to such Party from the due date until the date of payment at a per-annum rate of prime plus [***] percentage points or the maximum rate allowable by applicable Law, whichever is less.

4.8 Taxes.

(a) Taxes on Income. Each Party shall be solely responsible for the payment of all taxes imposed on its share of income arising directly or indirectly from the activities of the Parties under this Agreement.

(b) Tax Cooperation. The Parties agree to cooperate with one another and use reasonable efforts to avoid or reduce tax withholding or similar obligations in respect of royalties, milestone payments, and other payments made by Ultragenyx to BRI under this Agreement. To the extent Ultragenyx is required to deduct and withhold taxes on any payment to BRI, Ultragenyx shall pay the amounts of such taxes to the proper Governmental Authority in a timely manner, and the sum payable to BRI shall be decreased by the same amount. BRI shall provide Ultragenyx any tax forms that may be reasonably necessary in order for Ultragenyx to not withhold tax or to withhold tax at a reduced rate under an applicable bilateral income tax treaty. BRI shall use reasonable efforts to provide any such tax forms to Ultragenyx in advance of the due date. Each Party shall provide the other with reasonable assistance to enable the recovery, as permitted by Law, of withholding taxes or similar obligations resulting from payments made under this Agreement, such recovery to be for the benefit of BRI as the Party bearing such withholding tax under this Section 4.8(b).

4.9 Records and Audit Rights.

(a) Ultragenyx shall keep complete, true and accurate books and records in relation to this Agreement. Upon the written request of BRI and not more than [***] in each Calendar Year, Ultragenyx shall permit an independent certified public accounting firm selected by BRI, and reasonably acceptable to Ultragenyx, to have access during normal business hours to such of the records of Ultragenyx as may be reasonably necessary to verify the accuracy of the royalty reports hereunder for any Calendar Year ending not more than [***] prior to the date of such request. BRI shall treat all financial information subject to review under this Section 4.9 or under any sublicense agreement in accordance with the confidentiality and non-use provisions of this Agreement.

(b) Ultragenyx may require an accounting firm conducting an audit hereunder to sign a non-disclosure agreement to protect the confidentiality of Ultragenyx's Confidential Information before providing such accounting firm access to Ultragenyx's facilities, books or records. Upon completion of any audit hereunder, the accounting firm shall provide both Ultragenyx and BRI a written report disclosing whether the royalty reports submitted by Ultragenyx are correct or incorrect, whether the amounts paid are correct or incorrect, and in each case, the specific details concerning any discrepancies.

(c) BRI shall bear its internal expenses and the out-of-pocket costs for engaging such accounting firm in connection with performing such audits; provided , however , that if any such audit uncovers an underpayment of milestones payments or royalties by Ultragenyx that exceeds [***] percent ([***]%) of the total owed for such payment or payment period, as applicable, then Ultragenyx shall reimburse BRI for the expenses and costs for such audit.

(d) If such accounting firm identifies an underpayment by Ultragenyx during such period, Ultragenyx shall pay BRI the amount of the discrepancy within [***] days of the date BRI delivers to Ultragenyx such accounting firm's written report with the amount of underpayment accruing interest at the rate such forth in Section 4.7. If such accounting firm identifies an overpayment by Ultragenyx during such period, Ultragenyx shall, at its option, have the right to request a refund of such overpaid amount, or credit such overpaid amount against subsequent payment obligations to BRI, and BRI shall make such refund to Ultragenyx within [***] days of Ultragenyx's request if so requested. If Ultragenyx has no future payment obligations under this Agreement, then Ultragenyx may require BRI to refund such overpayment and BRI shall pay such overpaid amount to Ultragenyx within [***] days of Ultragenyx's request.

Article 5

Intellectual Property Rights

5.1 Patent Prosecution in the Licensed Territory.

(a) As between the Parties, Ultragenyx, acting through outside patent counsel of its choice (" **Patent Counsel** "), shall have the first right, but not the obligation, to take the lead in the preparation, filing, prosecution and maintenance of the BRI Patents in the Licensed Territory, at Ultragenyx's cost and expense. BRI shall cooperate with Ultragenyx in filing and prosecution of such BRI Patents in the Licensed Territory, including by providing Ultragenyx with data and other information as appropriate and executing all necessary paperwork. Within [***] days after the Effective Date, BRI shall provide to Ultragenyx those copies of all patent filings, and the correspondence between BRI and patent authorities, for BRI Patents in the Licensed Territory existing as of the Effective Date. Within [***] days after Ultragenyx exercises the Ultragenyx Option pursuant to Section 2.2(a), BRI shall provide Ultragenyx those copies of all patent filings, and the correspondence between BRI and patent authorities, for BRI Patents in the Licensed Territory existing as of the date of exercise of the Ultragenyx Option that have not already been provided to Ultragenyx pursuant to this Section 5.1(a). Ultragenyx will keep BRI reasonably informed of the status of the prosecution of such BRI Patents in the Licensed Territory. For the purpose of this Article 6, "prosecution" shall include any pre-grant and post-grant proceeding including patent interference proceeding, opposition proceeding and other similar proceedings, appeals or petitions to any Board of Appeals in the patent office, appeals to any court for any patent office decisions, reissues and reexamination proceedings, and applications for patent term extensions and the like.

(b) Ultragenyx will notify BRI of any decision not to file for, prosecute or maintain, or not to continue to pay the expenses of prosecution or maintenance of (collectively, "Patent Support"), any BRI Patents in the Licensed Territory. Ultragenyx will provide such notice at least [***] days prior to any filing or payment due date, or any other due date that requires action, in connection with such BRI Patent. In such event, BRI shall have the right, but not the obligation, to file for, or continue prosecution or maintenance of, such BRI Patent in the Licensed Territory, at its expense. In the event BRI does maintain such BRI Patent in the Licensed Territory and such BRI Patent in the Licensed Territory covers the applicable Product that triggers any royalty or milestone payment, Ultragenyx shall continue payment of the applicable royalties and milestones.

5.2 Patent Prosecution in the Retained Territory.

(a) If the Licensed Territory does not expand pursuant to Section 2.2(a), BRI shall use Commercially Reasonable Efforts to prosecute and maintain all of the patents and applications included within the BRI Patents in the Retained Territory. BRI shall: (i) keep Ultragenyx advised of the status of all communications and actual and prospective filings regarding such BRI Patents in the Retained Territory, (ii) give Ultragenyx a reasonable opportunity (but in no event less than [***] business days) to review and comment on any such communications and filings proposed to be sent to any patent authority, and (iii) incorporate all reasonable

comments of Ultragenyx before making any such communication or filing related to such BRI Patents in the Retained Territory.

(b) Should BRI (and [***] if the [***] Option has been exercised and [***] has the right) decide that it is no longer interested in maintaining or prosecuting any BRI Patent in the Retained Territory, BRI shall promptly advise Ultragenyx thereof and, upon written notice by Ultragenyx, BRI agrees that Ultragenyx may prosecute and maintain such BRI Patent in its own name, and BRI shall execute all required documents in order to assign any such BRI Patent to Ultragenyx; provided, however, that any such assignment by BRI shall be subject to the [***] Option.

5.3 Patent Enforcement and Defense in the Licensed Territory.

(a) Each Party shall give the other Party written notice of any infringement by a Third Party of any BRI Patents through the development or commercialization of a Product in the Field in the Licensed Territory (a " **Licensed Territory Product Infringement** "), within [***] Business Days after such Licensed Territory Product Infringement comes to such Party's attention.

(b) Ultragenyx shall have the sole and exclusive right, but not the obligation, to bring and control any legal action in connection with such Licensed Territory Product Infringement in the Licensed Territory at its own expense and discretion as it reasonably determines appropriate. BRI shall have the right to be represented in any such action by counsel of its choice at its own expense. Should Ultragenyx decline to bring a legal action in connection with a Licensed Territory Product Infringement in the Licensed Territory, BRI shall have the right, but not the obligation, to bring such a legal action. In the event that the Licensed Territory Product Infringement involves a Generic Product, and Ultragenyx declines to bring a legal action, Ultragenyx shall not be permitted to reduce royalties due BRI pursuant to Section 4.4(c). For clarity, Ultragenyx's right to bring and control any legal action under this Section 5.3(b)shall not apply to a Licensed Territory Product Infringement in an Indication Cluster during the period of time in which Ultragenyx has a non-exclusive license.

(c) At the request of a party bringing a legal action under Section 5.2(b) (the " **Litigating Party** "), the other Party shall reasonably cooperate and provide any information or assistance in connection with any legal action under this Section 5.3, including executing reasonably appropriate documents, cooperating in discovery and joining as a party to the action if required, all at the Litigating Party's expense.

(d) Any recoveries resulting from such an action relating to a claim of Licensed Territory Product Infringement shall be first applied against payment of costs and expenses in connection with the action of the Party which initiated and prosecuted the action. The other Party shall then, to the extent possible, recover its costs and expenses incurred in connection with the action. Solely in the case in which Ultragenyx is the Litigating Party, any such recoveries in excess of such costs and expenses of the Parties shall be retained by Ultragenyx and shall be deemed Net Sales subject to Ultragenyx's royalty payment obligation to BRI under Section 4.4. In the event BRI is the Litigating Party, all recoveries in excess of such costs and expenses of the Parties shall be retained by BRI.

5.4 Patent Enforcement and Defense in the Retained Territory.

(a) If the Licensed Territory does not expand pursuant to Section 2.2(a), each Party shall give the other Party written notice of any infringement by a Third Party of any BRI Patents through the development or commercialization of a Product in the Field in the Retained Territory (a " **Retained Territory Product Infringement** "), within [***] Business Days after such Retained Territory Product Infringement comes to such Party's attention.

(b) As between the Parties, BRI shall have the right, but not the obligation, to bring and control any legal action in connection with such Retained Territory Product Infringement in the Retained Territory at its own expense. BRI shall, if it has brought or controls such legal action, use Commercially Reasonable Efforts to: (i) keep Ultragenyx advised of the status of all such legal actions, (ii) give Ultragenyx a reasonable opportunity to review and comment on any filings, motions, pleadings or other strategic decisions relating to such legal action, and (iii) incorporate all reasonable comments of Ultragenyx in conducting such legal action, and, in each case, BRI shall use Commercially Reasonable Efforts to require [***] or any other applicable Third Party licensee of BRI in the Retained Territory to do so.

5.5 Third Party Patent Proceedings. Each Party will notify the other Party in writing prior to challenging any Patents controlled by a Third Party that are necessary or reasonably useful to use, develop, manufacture, commercialize or import any Compound or Product. Such challenges include declaratory judgment actions, inter parties re-examinations, interferences, oppositions and other similar proceedings (collectively " **Third Party Patent Proceeding** ").

(a) Except as the Parties otherwise agree, Ultragenyx shall have the first right to bring and control any legal action in connection with such Third Party Patent Proceeding in the Field in the Licensed Territory, at its own expense and discretion as it reasonably determines appropriate.

(b) At the request of Ultragenyx, BRI shall reasonably cooperate and provide any information or assistance in connection with any legal action under this Section 5.3, including executing reasonably appropriate documents, cooperating in discovery and joining as a party to the action if required, all at Ultragenyx's expense. Ultragenyx shall keep BRI reasonably informed of the status of such action.

5.6 Patent Extensions. The Parties shall cooperate in obtaining patent term restoration (under but not limited to Drug Price Competition and Patent Term Restoration Act), supplemental protection certificates or their equivalents, and patent term extensions with respect to the BRI Patents in any country or region in the Licensed Territory where applicable, provided, that Ultragenyx shall have the final decision making authority on the foregoing.

Article 6

Confidentiality; Publication

6.1 Duty of Confidence. Subject to the other provisions of this Article 6:

(a) all Confidential Information disclosed by or on behalf of a Party or its Affiliates (" **Disclosing Party**") under this Agreement, or in the course of contemplating a transaction under this Agreement prior to the execution of this Agreement, shall be maintained in confidence and otherwise safeguarded by the recipient Party and its Affiliates ("**Receiving Party**"), in the same manner and with the same protection as such Receiving Party maintains its own confidential information, but at least with reasonable protection;

(b) the Receiving Party may only use any such Confidential Information for the purposes of performing its obligations or exercising its rights under this Agreement; and

(c) the Receiving Party may disclose Confidential Information of the other Party to: (i) its Affiliates and sublicensees; and (ii) employees, directors, agents, contractors, consultants and advisers of the Party and its Affiliates, licensees and sublicensees, in each case to the extent reasonably necessary for the purposes of, and for those matters undertaken pursuant to, this Agreement; provided that such Persons are bound to maintain the confidentiality of the Confidential Information in a manner consistent with the confidentiality provisions of this Agreement. Notwithstanding the foregoing, the Parties acknowledge and agree that BRI may not disclose any Confidential Information of Ultragenyx to [***] or any other licensee or sublicensee of the Compound and/or Product in the Option Territory without Ultragenyx's prior written consent. Ultragenyx acknowledges that, pursuant to the [***] Option as amended on February 22, 2012, BRI is required to disclose preclinical and clinical data and information regarding regulatory submissions in the Licensed Territories to [***], and with respect to BRI Independent Studies, shall require no consent from Ultragenyx to do so.

6.2 Exceptions. The foregoing obligations as to particular Confidential Information of a Disclosing Party shall not apply to the extent that the Receiving Party can demonstrate that such Confidential Information:

(a) was known by the Receiving Party at the time of its receipt, and not through a prior disclosure by the Disclosing Party, as documented by the Receiving Party's written records;

(b) was in the public domain before its receipt from the Disclosing Party, or thereafter enters the public domain through no fault of the Receiving Party;

(c) is subsequently disclosed to the Receiving Party by a Third Party who is not under a direct or indirect obligation of confidentiality to the Disclosing Party; or

(d) is developed by the Receiving Party independently and without use of or reference to any Confidential Information received from the Disclosing Party, as documented by the Receiving Party's written records.

Any combination of features or disclosures shall not be deemed to fall within the foregoing exclusions merely because individual features are published or available to the general public or in the rightful possession of the Receiving Party unless the combination itself and principle of operation are published or available to the general public or in the rightful possession of the Receiving Party.

6.3 Authorized Disclosures. Notwithstanding the obligations set forth in Sections 6.2 and 6.5, a Party may disclose the other Party's Confidential Information (including this Agreement and the terms herein) solely to the extent:

(a) such disclosure: (i) is reasonably necessary for the filing or prosecuting Patents as contemplated by this Agreement; (ii) is reasonably necessary in connection with Regulatory Filings for Products; (iii) is reasonably necessary for the prosecuting or defending of legal actions, including litigation, as contemplated by this Agreement; or (iv) is made to any Third Party bound by written obligation of confidentiality and non-use similar to those set forth under this Article 6, to the extent otherwise necessary or appropriate in connection with the exercise of its rights or the performance of its obligations hereunder;

(b) such disclosure is reasonably necessary: (i) to such Party's directors, attorneys, independent accountants or financial advisors for the sole purpose of enabling such directors, attorneys, independent accountants or financial advisors to provide advice to the Receiving Party, provided that in each such case on the condition that such directors, attorneys, independent accountants and financial advisors are bound by confidentiality and non-use obligations substantially consistent with those contained in this Agreement; provided , however , that the term of confidentiality for such directors, attorneys, independent accountants and financial advisors shall be no less than [***]; or (ii) to actual or potential investors, sublicensees or acquirors solely for the purpose of evaluating an actual or potential investment, sublicense or acquisition; provided that in each such case on the condition that such actual or potential investors, sublicensees and acquirers are bound by confidentiality and non-use obligations substantially consistent with those contained in this Agreement; provided , however , that the term of confidentiality for such actual or potential investors and acquirers shall be no less than [***]; or

(c) such disclosure is required by judicial or administrative process, provided that in such event such Party shall promptly inform the other Party of such required disclosure and provide the other Party an opportunity to challenge or limit the disclosure obligations. Confidential Information that is disclosed by judicial or administrative process shall remain otherwise subject to the confidentiality and non-use provisions of this Article 7, and the Party disclosing Confidential Information pursuant to law or court order shall take all steps reasonably necessary, including seeking of confidential treatment or a protective order to ensure the continued confidential treatment of such Confidential Information.

6.4 Scientific Publications. Subject to Section 6.3, Ultragenyx or its sublicensee(s) shall have the sole right to make any public publication or presentation of any data regarding any Compound or Product, provided, however, that to the extent such data arises as a result of work performed by a BRI employee or contractor, or with financial support by BRI, BRI shall be provided with a copy of any proposed publication at least [***] days prior to submission for BRI's review and comment, and as appropriate in accordance with scientific journal standards, shall designate the appropriate BRI personnel as co-authors. However, such publication or presentation shall not include any Confidential Information of BRI without the prior written consent of BRI. Subject to Section 6.3, BRI shall make no public publication or presentation of any data regarding any Compound or Product without the prior written consent of Ultragenyx. Notwithstanding the foregoing, this Section 6.4 shall not apply to any publication or presentation of data relating to BRI Know-How or BRI Patents existing as of the Effective Date, provided that BRI shall provide Ultragenyx with a copy of any proposed publication or presentation at least [***] days prior to submission, for Ultragenyx's review and comment.

6.5 Publicity; Use of Names. Notwithstanding anything to the contrary in this Agreement, until the expiration of the [***] Option and Ultragenyx's receipt of the Ultragenyx Option Notice, the existence and the terms of this Agreement are each Party's Confidential Information and such shall be held in strict confidence and not disclosed by

either Party, except with the prior express written permission of the other Party or as may be required by applicable Law. Subject to Sections 6.1, 6.2 and 6.3, no other disclosure of the existence or the terms of this Agreement may be made by either Party or its Affiliates except as provided in this Section 6.5, and no Party shall use the name, trademark, trade name or logo of the other Party, its Affiliates or their respective employees in any publicity, promotion, news release or disclosure relating to this Agreement or its subject matter, except as provided in this Section 6.5 or with the prior express written permission of the other Party, except as may be required by applicable Law.

(a) A Party may disclose this Agreement and its terms, and material developments or material information generated under this Agreement, in securities filings with the US Securities and Exchange Commission (or equivalent foreign agency) to the extent required by applicable Law after complying with the procedure set forth in this Section 6.5(a). In such event, the Party seeking such disclosure will prepare a draft confidential treatment request and proposed redacted version of this Agreement to request confidential treatment for this Agreement, and the other Party agrees to promptly (and in any event, no more than seven (7) days after receipt of such confidential treatment request and proposed redactions) give its input in a reasonable manner in order to allow the Party seeking disclosure to file its request within the time lines proscribed by applicable Law. The Party seeking such disclosure shall exercise Commercially Reasonable Efforts to obtain confidential treatment of this Agreement from the US Securities and Exchange Commission (or equivalent foreign agency) as represented by the redacted version reviewed by the other Party.

(b) The Parties agree that any news release or other public announcement relating to the terms and conditions of this Agreement or the performance hereunder shall not be made until after the earlier of (i) expiration or termination of the [***] Option and (ii) [***] exercise of the [***] Option. Any such news release, any further news release or other public disclosure that would disclose information other than that already in the public domain, shall first be reviewed and approved by both Parties (with such approval not to be unreasonably withheld or delayed).

(c) The Parties agree that after a disclosure pursuant to Section 6.5(b), a press release or other public announcement pursuant to Section 6.5(c) has been reviewed and approved by the other Party, the disclosing Party may make subsequent public disclosures reiterating such information without having to obtain the other Party's prior consent and approval.

Article 7

Term and Termination

7.1 Term. The term of this Agreement will commence upon the Effective Date and continue in full force and effect, on a Product-by-Product and country-country basis, until the expiration of the royalty obligations of Ultragenyx with respect to the applicable Product, unless earlier terminated as set forth in Section 7.2 (the " **Term** "). After the expiration of this Agreement for a particular Product in a particular country, Ultragenyx's license in such country shall become fully paid, royalty-free, perpetual and irrevocable.

7.2 Termination.

(a) Termination by Ultragenyx for Convenience. At any time, Ultragenyx may terminate this Agreement, in its entirety or on a Product-by-Product basis, by providing written notice of termination to BRI, which notice includes an effective date of termination at least ninety (90) days after the date of the notice.

(b) Termination for Material Breach. If either Party believes that the other is in breach of its material obligations hereunder (other than Ultragenyx's nonfulfillment of its obligations under Section 3.2, the remedy of which is set forth in Section 3.2), then the non-breaching Party may deliver notice of such breach to the other Party. The allegedly breaching Party shall have ninety (90) days from such notice to dispute or cure such breach. If the Party receiving notice of breach fails to cure, or fails to dispute, that breach within the period set forth above, then the Party originally delivering the notice of breach may terminate this Agreement effective on written notice of termination to the other Party, provided that such non-breaching Party delivers such notice of termination within sixty (60) days of the end of such one hundred ninety(90)-day cure period. If the allegedly breaching Party in good faith disputes such material breach or disputes the failure to cure or remedy such material breach and provides written notice of that dispute to the other Party within the period set forth

above, the notifying Party may not terminate this Agreement until one independent industry expert mutually agreeable to both Parties has determined that the allegedly breaching Party is in material breach of this Agreement, and such breaching Party further fails to cure such breach within thirty (30) days after such determination by the independent industry expert (and such termination shall then be effective upon written notification from the notifying Party to the breaching Party).

(c) Termination for Bankruptcy. Either party may terminate this Agreement in the event the other Party ceases doing business as a going concern, makes an assignment for the benefit of creditors, shall not be paying its debts in the ordinary course, shall have become insolvent or shall, voluntarily or involuntarily, become party to insolvency proceeding, or commits any act of bankruptcy. Notwithstanding any other provision of this Agreement to the contrary, in the event that BRI becomes a debtor under the United States Bankruptcy Code (11 U.S.C. §101 et. seq. or any similar law in any other country (the " **Bankruptcy Code** ")) and rejects this Agreement pursuant to Section 365 of the Bankruptcy Code (a " **Bankruptcy Rejection** "), (i) the license to the BRI Technology described under this Agreement shall be deemed fully retained by and vested in Ultragenyx as protected intellectual property rights under Section 365(n)(1)(B) of the Bankruptcy Code and further shall be deemed to exist immediately before the commencement of the bankruptcy case in which BRI is the debtor; and (ii) Ultragenyx shall have all of the rights afforded to non-debtor licensees under Section 365(n) of the Bankruptcy Code, subject to its continued compliance with all its obligations under this Agreement. All rights and licenses now or hereinafter granted by BRI to Ultragenyx under or pursuant to any section of this Agreement, including Section 2.1 are rights to "intellectual property" (as defined in the Bankruptcy Code).

7.3 Effect of Termination.

(a) Termination by Ultragenyx for Convenience; Termination by BRI for Breach or Bankruptcy . Upon termination of this Agreement by Ultragenyx pursuant to Section 7.2(a) or by BRI pursuant to Sections 7.2(b) or 7.2(c), the following consequences shall apply to the termination and shall be effective as of the effective date of such termination:

(i) Each Party shall pay all amounts then due and owing to the other Party as of the termination date;

(ii) All licenses and other rights granted to Ultragenyx under the BRI Technology will terminate, and Ultragenyx shall immediately discontinue sales of Product;

(iii) No later than thirty (30) days after the effective date of such termination, Ultragenyx shall return or cause to be returned to BRI all Confidential Information in tangible form received from BRI and all copies thereof and all materials substances or compositions delivered or provided by BRI; provided , however , that Ultragenyx may keep one copy of Confidential Information received from the other Party in its confidential files for record purposes;

(iv) No later than thirty (30) days after the effective date of termination, at BRI's option, the Parties shall negotiate in good faith the terms and conditions (including financial compensation to Ultragenyx) for a license under patent applications, patents, Know-How, and any other information and documentation Controlled by Ultragenyx as of the effective date of such termination necessary for BRI to continue development and commercialization of Products in the Licensed Territory, but solely for those indications, the use of which are claimed by a Valid Claim in the BRI Technology as of the date of such termination. If the Parties have failed to agree upon such terms of compensation within ninety (90) days of initiation of such negotiation, the matter shall be referred to three independent industry experts having expertise in intellectual property valuation and who are mutually agreeable to both Parties. The industry experts shall take into account all pertinent factors, including but not limited to each party's relative contribution to the Ultragenyx Technology, and within thirty (30) days make a joint recommendation of appropriate compensation for the license ("License Compensation"). BRI shall have the right, but not the obligation, to accept the license at the recommended License Compensation. If BRI does not accept the license at the recommended License Compensation, then Ultragenyx shall have no further obligation to negotiate with BRI regarding the terms and conditions for a license pursuant to this Section 7.3(a)(iv) and Ultragenyx shall have no obligation to grant BRI any such license. If BRI does accept the license at the recommended License Compensation, then Ultragenyx shall have the obligation to grant BRI the license at the recommended License Compensation; and

(v) At the written request of any of Ultragenyx's sublicensees under this Agreement, BRI shall negotiate in good faith with such sublicensee an agreement between BRI and such sublicensee under which such sublicensee will obtain a direct license under the BRI Technology. For clarity, under no circumstances shall BRI be required to grant a direct license to any sublicensee which does not compensate BRI at a level substantially equivalent to the compensation received by BRI under this Agreement with respect to the applicable technology, taking into consideration any costs associated with BRI's license to Ultragenyx Technology. Ultragenyx shall indemnify, defend and hold BRI Indemnitees harmless from and against any Claims brought by any sublicensee in connection with the termination of an Ultragenyx sublicense, or the inability of BRI and any sublicensee to negotiate a mutually acceptable license to BRI Technology, provided that Ultragenyx shall have no indemnification obligation to BRI under this Section 7.3(a)(v) to the extent such Claim arises as a result of BRI's bad faith in negotiation with an Ultragenyx sublicensee.

(b) Termination by Ultragenyx for Breach or Bankruptcy. Upon termination of this Agreement by Ultragenyx pursuant to Sections 7.2(b) or 7.2(c), the following consequences shall apply to the termination and shall be effective as of the effective date of such termination:

(i) Each Party shall pay all amounts then due and owing to the other Party as of the termination date;

(ii) The licenses and other rights granted by BRI to Ultragenyx under the BRI Technology will remain in full force and effect as set forth in Sections 2.1; provided that Ultragenyx fulfills its payment obligations to BRI under Article 4 pursuant to the terms and conditions set forth in Article 4, further provided that, on a Product-by-Product and country by country basis, for any Product that is the subject of the underlying breach, milestone payments under Sections 4.2 and 4.3 and royalty payments under Section 4.4 with respect to such Product shall be reduced by [***] percent ([***]%);

(iii) No later than thirty (30) days after the effective date of such termination, BRI shall return or cause to be returned to Ultragenyx all Confidential Information in tangible form received from Ultragenyx and all copies thereof and all materials, substances or compositions delivered or provided by Ultragenyx; provided , however , that BRI may keep one copy of Confidential Information received from Ultragenyx in its confidential files for record purposes; and

(iv) In addition to the provisions set forth in Section 7.5, the provisions relating to BRI Patents in Sections 6.1, 6.2, 6.3 and 6.4 shall survive the termination of this Agreement for so long as the license to Ultragenyx survives under this Section 7.3(b).

7.4 Survival. Expiration or termination of this Agreement shall not relieve the Parties of any obligation accruing prior to such expiration or termination. Without limiting the foregoing, the provisions of Articles 1, 6, 9 (to the extent the Claims arise out of actions or omissions during the Term) and 10, and Sections 5.1, 7.3, 7.4 and 7.5, and any other provisions which by their nature are intended to survive, shall survive the expiration or termination of this Agreement.

7.5 Termination Not Sole Remedy. Termination is not the sole remedy under this Agreement and, whether or not termination is effected and notwithstanding anything contained in this Agreement to the contrary, all other remedies will remain available except as agreed to otherwise herein.

Article 8

Representations and Warranties

8.1 Representations and Warranties of Each Party. Each Party represents and warrants to the other Party as of the Effective Date that:

(a) it has the full right, power and authority to enter into this Agreement, to perform its obligations hereunder; and

(b) this Agreement has been duly executed by it and is legally binding upon it, enforceable in accordance with its terms, and does not conflict with any agreement, instrument or understanding, oral or written, to which

it is a party or by which it may be bound, nor violate any material law or regulation of any court, governmental body or administrative or other agency having jurisdiction over it.

8.2 Representations and Warranties by BRI. BRI represents and warrants to Ultragenyx as of the Effective Date that:

(a) it has not previously assigned, transferred, conveyed or otherwise encumbered its right, title and interest in BRI Patents or BRI Know-How with respect to any of the Compounds or Products other than pursuant to the [***] Option;

(b) it has the right to grant the license and rights herein to Ultragenyx and it has not granted any license, right or interest in, to or under the BRI Patents or BRI Know-How to any Third Party with respect to any of the Compounds or Products other than pursuant to the [***] Option;

(c) to the best of its knowledge, it has provided to Ultragenyx all of the following information relating to the Compound or Product: all communications to and from Regulatory Authorities, all protocols and amendments for any human clinical studies, all safety reports sent to the FDA or other Regulatory Authorities, all Regulatory Filings filed with Regulatory Authorities, including all INDs filed with the FDA, and all clinical, non-clinical, and research study reports in its possession;

(d) the [***] Option does not grant [***] any license rights to BRI Know-How and BRI Patents with respect to the United States, Canada or Mexico;

(e) to the best of its knowledge, except as otherwise stated in this Section 8.2(e), the development, use, sale and import of Compounds or Products in the Licensed Territory do not infringe any valid intellectual property rights owned or possessed by any Third Party and do not breach any obligation of confidentiality or non-use owed by BRI to a Third Party, provided however, that the Parties acknowledge and agree that the following Third Parties may own or possess intellectual property rights covering the method of use of the Compound and/or Product: [***];

(f) there are no claims, judgments or settlements against or owed by BRI and to the best of BRI's knowledge, there are no pending or threatened claims or litigation, in each case relating to any Compounds or Products, or to the BRI Patents or BRI Know-How in the Licensed Territory;

(g) there is no provision in the [***] Option or the agreement to be entered into between BRI and [***] upon [***] exercise of the [***] Option that expressly addresses the performance of clinical trials by BRI or any other party in the Option Territory and during the Term BRI shall not extend the duration of the [***] Option, or amend the terms of such [***] Option or the agreement to be entered into between BRI and [***] upon [***] exercise of the [***] Option (other than financial), in each case without Ultragenyx's prior written consent; and

(h) the list of Patents contained in Exhibit A is a complete list of all BRI Patents.

8.3 No Other Warranties. EXCEPT AS EXPRESSLY STATED IN THIS ARTICLE 8, (A) NO REPRESENTATION, CONDITION OR WARRANTY WHATSOEVER IS MADE OR GIVEN BY OR ON BEHALF OF ULTRAGENYX OR BRI; AND (B) ALL OTHER CONDITIONS AND WARRANTIES WHETHER ARISING BY OPERATION OF LAW OR OTHERWISE ARE HEREBY EXPRESSLY EXCLUDED, INCLUDING ANY CONDITIONS AND WARRANTIES OF MERCHANTABILITY, FITNESS FOR A PARTICULAR PURPOSE OR NON-INFRINGEMENT.

Article 9

Indemnification; Liability

9.1 Indemnification by BRI. BRI shall indemnify and hold Ultragenyx and its Affiliates, and their respective officers, directors, agents and employees (" **Ultragenyx Indemnitees** ") harmless from and against any Claims arising under or related to this Agreement against them to the extent arising or resulting from:

(a) the negligence or willful misconduct of any of the BRI Indemnitees; or

(b) the breach of any of the warranties or representations made by BRI to Ultragenyx under this Agreement; or

(c) any breach by BRI of its material obligations pursuant to this Agreement

except in each case, to the extent such Claims result from the material breach by any Ultragenyx Indemnitee of any covenant, representation, warranty or other agreement made by Ultragenyx in this Agreement or the negligence or willful misconduct of any Ultragenyx Indemnitee.

9.2 Indemnification by Ultragenyx. Ultragenyx shall indemnify and hold BRI, its Affiliates, and their respective officers, directors, agents and employees (" **BRI Indemnitees** ") harmless from and against any Claims arising under or related to this Agreement against them to the extent arising or resulting from:

(a) the development, manufacture, packaging, use, sale or commercialization of the Compounds or Products, or use of the BRI Technology, by or on behalf Ultragenyx or any of its Affiliates, sublicensees or contractors in the Field in the Licensed Territory; or

(b) the negligence or willful misconduct of any of the Ultragenyx Indemnitees, sublicensees, or contractors; or

(c) the breach of any of the warranties or representations made by Ultragenyx to BRI under this Agreement;

(d) any representation made or warranty given by Ultragenyx, or any of its Affiliates, sublicensees or contractors with respect to Compounds, Products, BRI Patents or BRI Know-How;

(e) any infringement claims relating to Compounds or Products;

(f) any asserted violation of applicable Laws by any Ultragenyx Indemnitees, sublicensees or contractors; or

(g) any breach by Ultragenyx of its material obligations pursuant to this Agreement;

except in each case, to the extent such Claims result from the material breach by any BRI Indemnitee of any covenant, representation, warranty or other agreement made by BRI in this Agreement or the negligence or willful misconduct of any BRI Indemnitee.

9.3 Insurance. From and after the Effective Date, Ultragenyx shall maintain for a period of [***] after the expiration or termination of this Agreement, commercial product liability insurance (including contractual liability insurance and clinical trial insurance) with insurance carriers with, at least, an AM BEST rating of A- VII to cover the activities of Ultragenyx Indemnitees, for minimum limits of [***] dollars ($[***]) per claim and [***] dollars ($[***]) in the aggregate. Such insurance shall cover BRI Indemnitees as additional insureds. Ultragenyx shall furnish a certificate of insurance evidencing such coverage. Ultragenyx will provide thirty days' written notice to BRI of cancellation or material change in coverage. The minimum amounts of insurance coverage required herein shall not be construed as creating any limitation on the Ultragenyx's indemnity obligation under Section 9.2. of this Agreement. If any coverage is written on a Claims Made policy form, the Retroactive Date is to be the first date that the first Claims Made policy was effective and is not to be advanced during the term of the project. Additionally, if the coverage is written on a Claims Made form, the insurance policies will remain in full force and effect, or if canceled or non renewed Ultragenyx shall purchase an Extended Reporting Period "Tail Coverage", for a minimum period of [***] after the termination of this Agreement.

9.4 Indemnification Procedure. If either Party is seeking indemnification under Sections 9.1 or 9.2 (the "**Indemnified Party**"), it shall inform the other Party (the "**Indemnifying Party**") of the claim giving rise to the obligation to indemnify pursuant to such section as soon as reasonably practicable after receiving notice of the claim. The Indemnifying Party shall have the right to assume the defense of any such claim for which it is obligated to indemnify the Indemnified Party. The Indemnified Party shall cooperate with the Indemnifying Party and the Indemnifying Party's insurer as the Indemnifying Party may reasonably request, and at the Indemnifying Party's cost and expense. The Indemnified Party shall have the right to participate, at its own expense and with counsel of its choice, in the defense of any claim or suit that has been assumed by the Indemnifying Party. Neither Party shall have the obligation to indemnify the other Party in connection with any settlement made without the Indemnifying Party's written consent, which consent shall not be unreasonably withheld, conditioned or delayed. If the Parties

cannot agree as to the application of Section 9.1 or 9.2 as to any claim, pending resolution of the dispute pursuant to Section 10.6, the Parties may conduct separate defenses of such claims, with each Party retaining the right to claim indemnification from the other Party in accordance with Section 9.1 or 9.2 upon resolution of the underlying claim.

9.5 Mitigation of Loss. Each Indemnified Party will take and will procure that its Affiliates take all such reasonable steps and action as are reasonably necessary or as the Indemnifying Party may reasonably require in order to mitigate any Claims (or potential losses or damages) under this Article 9. Nothing in this Agreement shall or shall be deemed to relieve any Party of any common law or other duty to mitigate any losses incurred by it.

9.6 Special, Indirect and Other Losses. NEITHER PARTY NOR ANY OF ITS AFFILIATES SHALL BE LIABLE IN CONTRACT, TORT, NEGLIGENCE, BREACH OF STATUTORY DUTY OR OTHERWISE FOR ANY CONSEQUENTIAL, SPECIAL OR PUNITIVE DAMAGES OR FOR LOSS OF PROFITS SUFFERED BY THE OTHER PARTY, EXCEPT TO THE EXTENT ANY SUCH DAMAGES ARE REQUIRED TO BE PAID TO A THIRD PARTY AS PART OF A CLAIM FOR WHICH A PARTY PROVIDES INDEMNIFICATION UNDER THIS ARTICLE 9.

Article 10

General Provisions

10.1 Force Majeure. Neither Party shall be held liable to the other Party nor be deemed to have defaulted under or breached this Agreement for failure or delay in performing any obligation under this Agreement to the extent such failure or delay is caused by or results from causes beyond the reasonable control of the affected Party, potentially including embargoes, war, acts of war (whether war be declared or not), acts of terrorism, insurrections, riots, civil commotions, strikes, lockouts or other labor disturbances, fire, floods, earthquakes or other acts of God, or acts, omissions or delays in acting by any Government Authority or the other Party or unavailability of materials related to the manufacture of Compounds or Products. The affected Party shall notify the other Party in writing of such force majeure circumstances as soon as reasonably practical, and shall promptly undertake and continue diligently all reasonable efforts necessary to cure such force majeure circumstances or to perform its obligations in spite of the ongoing circumstances. Notwithstanding the foregoing, neither Party shall be excused from making payments owed hereunder because of a force majeure affecting such Party unless such force majeure event affects the method of payment.

10.2 Assignment.

(a) This Agreement may not be assigned or otherwise transferred, nor may any right or obligation hereunder be assigned or transferred, by either Party without the prior written consent of the other Party. Notwithstanding the foregoing, either Party may, without consent of the other Party, assign this Agreement and its rights and obligations hereunder in whole or in part to an Affiliate of such Party, or to its successor in interest by way of merger, acquisition, or sale of all or substantially all of its assets to which this Agreement relates. Any attempted assignment not in accordance with this Section 10.2 shall be null and void and of no legal effect. Any permitted assignee shall assume all assigned obligations of its assignor under this Agreement. The terms and conditions of this Agreement shall be binding upon, and shall inure to the benefit of, the Parties and their respected successors and permitted assigns.

(b) Notwithstanding anything to the contrary in this Agreement, in the event that a Party undergoes a merger, acquisition, or sale of all or substantially all of its assets to which this Agreement relates, no intellectual property rights of the Third Party assignee, acquiror or successor of such Party or any Affiliate of such Third Party shall be included in the subject matter licensed hereunder, to the extent that such intellectual property rights were held by such Third Party prior to the merger, acquisition or sale, or are created outside of any activities under this Agreement by personnel who were not employees of the acquired Party at the time of the acquisition.

10.3 Severability. If any one or more of the provisions contained in this Agreement is held invalid, illegal or unenforceable in any respect, the validity, legality and enforceability of the remaining provisions contained herein shall not in any way be affected or impaired thereby, unless the absence of the invalidated provision(s) adversely

affects the substantive rights of the Parties. The Parties shall in such an instance use their best efforts to replace the invalid, illegal or unenforceable provision(s) with valid, legal and enforceable provision(s) which, insofar as practical, implement the purposes of this Agreement.

10.4 Notices. All notices which are required or permitted hereunder shall be in writing and sufficient if delivered personally, sent by facsimile (and promptly confirmed by personal delivery, registered or certified mail or courier), sent by internationally recognized courier or sent by registered or certified mail, postage prepaid, return receipt requested, addressed as follows:

If to BRI:

Baylor Research Institute
3310 Live Oak Street, Suite 501
Dallas, TX 75204
Attn: Chief Operating Officer
Fax: (214) 820-4952

with a copy to:

Law Department
Baylor Health Care System
4005 Crutcher Street
Dallas, TX 75246
Attn: BRI Attorney
Fax: (214) 820-1535

If to Ultragenyx:

Ultragenyx Pharmaceutical Inc.
60 Leveroni Court
Novato, CA 94949
Attn: Tom Kassberg, Chief Business Officer
Fax: (415) 483-8820

with a copy to:

Cooley LLP
3175 Hanover Street
Palo Alto, CA 94304
Attn: Lila Hope, Esq.
Fax: (650) 849-7400

or to such other address(es) as the Party to whom notice is to be given may have furnished to the other Party in writing in accordance herewith. Any such notice shall be deemed to have been given: (a) when delivered if personally delivered or sent by facsimile on a Business Day (or if delivered or sent on a non-Business Day, then on the next Business Day); (b) on the Business Day after dispatch if sent by internationally recognized overnight courier; or (c) on the fifth (5th) Business Day following the date of mailing, if sent by mail.

10.5 Applicable Law. This Agreement shall be governed by and construed in accordance with the laws of the State of New York and the patent laws of the United States without reference to any rules of conflict of laws.

10.6 Dispute Resolution. The Parties shall negotiate in good faith and use reasonable efforts to settle any dispute, controversy or claim ("**Dispute**") arising from or related to this Agreement or the breach thereof. If any Dispute has not been resolved within [***] days of written notice detailing the nature of the Dispute by one Party to the other, the Parties shall each immediately refer such dispute to respective senior executives at the level of Senior Vice President or above for consideration and resolution. If the Dispute has not been resolved within [***] days of referral to such senior executives, either party may bring an action in a court of competent jurisdiction.

10.7 Compliance. Each Party agrees that in performing its obligations or exercising its rights under this Agreement: (a) it shall comply in all material respects with all applicable Laws; (b) it will not employ or engage any Person who has been debarred by any Regulatory Authority, or, to such Party's knowledge, is the subject of debarment proceedings by a Regulatory Authority; and (c) it will be primarily responsible for any activities performed on its behalf by an Affiliate, licensee, sublicensee, contractor or subcontractor.

10.8 Entire Agreement.

(a) This Agreement, together with the Exhibits, contains the entire understanding of the Parties with respect to the licenses granted hereunder. Any other express or implied agreements and understandings, negotiations, writings and commitments, either oral or written, in respect to the licenses granted hereunder are superseded by the terms of this Agreement. The Exhibits to this Agreement are incorporated herein by reference and shall be deemed a part of this Agreement.

(b) This Agreement supersedes the Mutual Nondisclosure Agreement, dated February 8th, 2012, between Ultragenyx and BRI (the " **Prior NDA** "). All Confidential Information disclosed by one Party to the other Party under the Prior NDA shall be deemed Confidential Information of such disclosing Party under this Agreement and shall be subject to the terms of this Agreement.

10.9 Amendments. This Agreement may be amended, or any term hereof modified, only by a written instrument duly executed by authorized representative(s) of both Parties.

10.10 Headings. The captions to the several Articles, Sections and subsections hereof are not a part of this Agreement, but are merely for convenience to assist in locating and reading the several Articles and Sections hereof.

10.11 Independent Contractors. It is expressly agreed that BRI and Ultragenyx shall be independent contractors and that the relationship between the two Parties shall not constitute a partnership, joint venture or agency. Neither BRI nor Ultragenyx shall have the authority to make any statements, representations or commitments of any kind, or to take any action, which shall be binding on the other Party, without the prior written consent of the other Party.

10.12 Waiver. The waiver by either Party of any right hereunder, or of any failure of the other Party to perform, or of any breach by the other Party, shall not be deemed a waiver of any other right hereunder or of any other breach by or failure of such other Party whether of a similar nature or otherwise.

10.13 Cumulative Remedies. No remedy referred to in this Agreement is intended to be exclusive, but each shall be cumulative and in addition to any other remedy referred to in this Agreement or otherwise available under law.

10.14 Waiver of Rule of Construction. The rule of construction that any ambiguity in this Agreement shall be construed against the drafting Party shall not apply.

10.15 Business Day Requirements. In the event that any notice or other action or omission is required to be taken by a Party under this Agreement on a day that is not a Business Day then such notice or other action or omission shall be deemed to be required to be taken on the next occurring Business Day.

10.16 Counterparts. This Agreement may be executed in counterparts by original signature, facsimile or PDF files, each of which shall be deemed an original, but all of which together shall constitute one and the same instrument.

[Remainder of page intentionally left blank; signature page follows.]

IN WITNESS WHEREOF, the Parties intending to be bound have caused this Agreement to be executed by their duly authorized representatives.

Baylor Research Institute

By: /s/ Jaime Walkawiak
Name: Jaime Walkawiak
Title: VP Research Operations

Ultragenyx Pharmaceutical Inc.

By: /s/ Emil Kakkis
Name: Emil Kakkis MD PhD
Title: Chief Executive Officer

Exhibit A

BRI Patents Existing as of the Effective Date

Case Type	Country	Priority Case Number	Inventor Name	Status, Filing Date, App. Serial No. Pub No. & Date	Pat/Reg No., Issue/Reg Date	Title
		[***]				

Exhibit 10.13

[***] = CERTAIN CONFIDENTIAL INFORMATION CONTAINED IN THIS DOCUMENT, MARKED BY BRACKETS, HAS BEEN OMITTED BECAUSE THE INFORMATION (I) IS NOT MATERIAL AND (II) WOULD BE COMPETITIVELY HARMFUL IF PUBLICLY DISCLOSED

AMENDMENT LICENSE AGREEMENT

This Amendment to the License Agreement ("Amendment") is made and entered into by and between Ultragenyx Pharmaceutical Inc., a corporation organized and existing under the laws of the State of Delaware, having its principal place of business at 60 Leveroni Court, Novato, CA 94949 (" **Ultragenyx**"), and Baylor Research Institute, a non-profit corporation organized and existing under the laws of the State of Texas, having its principal place of business at 3310 Live Oak Street, Suite 501, Dallas, Texas 75204 ("**BRI** ").

RECITALS

A. WHEREAS, Ultragenyx and BRI entered into a License Agreement ("Agreement") dated September 20, 2012.

B. WHEREAS, Both Parties wish to amend the Agreement as set forth below to further clarify the intent of the Parties when the Agreement was initially entered into.

NOW, THEREFORE, in consideration of the mutual covenants and premises herein contained, the parties agree as follows;

1. This Amendment shall be effective as of March 22, 2013 ("the Effective Date")

2. The following shall be inserted to replace Section 5.1 in the Agreement

(a) As between the Parties, Ultragenyx, acting through outside patent counsel of its choice **("Patent Counsel")** , shall have the first right, but not the obligation, to take the lead in the preparation, filing, prosecution and maintenance of the BRI Patents in the Licensed Territory, at Ultragenyx's cost and expense. BRI shall cooperate with Ultragenyx in filing and prosecution of such BRI Patents in the Licensed Territory, including by providing Ultragenyx with data and other information as appropriate and executing all necessary paperwork to enable Patent Counsel to file, prosecute, and defend BRI Patents directly with patent offices. Within [***] days after the Effective Date, BRI shall provide to Ultragenyx those copies of all patent filings, and the correspondence between BRI and patent authorities, for BRI Patents in the Licensed Territory existing as of the Effective Date. Within [***] days after Ultragenyx exercises the Ultragenyx Option pursuant to Section 2.2(a), BRI shall provide Ultragenyx those copies of all patent filings, and the correspondence between BRI and patent authorities, for BRI Patents in the Licensed Territory existing as of the date of exercise of the Ultragenyx Option that have not already been provided to Ultragenyx pursuant to this Section 5.1(a). Ultragenyx will keep BRI reasonably informed of the status of the prosecution of such BRI Patents in the Licensed Territory by providing a copy of any written response to be filed with the USPTO or a copy of any instruction letter to a foreign associate with respect to preparation of a response to be filed with the pertinent foreign patent office to counsel of BRI's choice prior to such filing. BRI has the right to provide comment to Patent Counsel at BRI's cost and expense. Ultragenyx will consider any comment provided by BRI counsel in good faith, but shall not be required to incorporate any such comment.

For the purpose of this Article 6, "prosecution" shall include any pre-grant and post-grant proceeding including patent interference proceeding, opposition proceeding and other similar proceedings, appeals or petitions to any Board of Appeals in the patent office, appeals to any court for any patent office decisions, reissues and reexamination proceedings, and applications for patent term extensions and the like.

(b) Ultragenyx will notify BRI of any decision not to file for, prosecute or maintain, or not to continue to pay the expenses of prosecution or maintenance of (collectively, "Patent Support"), any BRI Patents in the Licensed Territory. Ultragenyx will provide such notice at least [***] days prior to any filing or payment due date, or any other due date that requires action, in connection with such BRI Patent. In such event, BRI shall have the right, but not the obligation, to file for, or continue prosecution or maintenance of, such BRI Patent in the Licensed Territory, at its expense. In the event BRI does maintain such BRI Patent in the Licensed Territory and such BRI Patent in the Licensed Territory covers the applicable Product that triggers any royalty or milestone payment, Ultragenyx shall continue payment of the applicable royalties and milestones.

3. Except as expressly provided in this Amendment, all other terms, conditions and provisions of the Agreement shall continue in full force and effect as provided therein. Capitalized terms used in this Amendment that are not otherwise defined herein shall have the same meanings as such terms are defined in the Agreement

IN WITNESS WHEREOF, the Parties intending to be bound have caused this Amendment to be executed by their duly authorized representatives.

Baylor Research Institute

By: /s/ Paul Convery
Name: Paul Convery
Title: Interim CO

Ultragenyx Pharmaceutical Inc.

By: /s/ Thomas Kassberg
Name: Thomas Kassberg
Title: CBO

[***] = CERTAIN CONFIDENTIAL INFORMATION CONTAINED IN THIS DOCUMENT, MARKED BY BRACKETS, HAS BEEN OMITTED BECAUSE THE INFORMATION (I) IS NOT MATERIAL AND (II) WOULD BE COMPETITIVELY HARMFUL IF PUBLICLY DISCLOSED

MASTER SERVICES AGREEMENT

This Master Services Agreement (the "Agreement") is entered into

Between

(1) Aenova Haupt Pharma Wolfratshausen GmbH, Pfaffenrieder Straße 5, 82515 Wolfratshausen Germany

- hereinafter referred to as "**AENOVA**" -

and

(2) Ultragenyx Pharmaceuticals Inc., 60 Leveroni Ct Novato, CA 94949

- hereinafter referred to as "**Customer**" -

The entities listed in no. (1) to (2) above are also referred to collectively as the "Parties" and each as a "Party".

Preamble

WHEREAS, Customer is a company active in the pharmaceutical field focussing on development of rare disease therapies, including Product (as defined hereinafter); and

WHEREAS, AENOVA is a contract manufacturing organization part of the AENOVA Group of companies that develops, manufactures, and markets solid, semi-solid, and liquid pharmaceutical products for the healthcare industries worldwide; and

WHEREAS, Customer wishes to engage AENOVA as contract manufacturing organization for the manufacturing of Product for which Customer is planning to receive marketing authorization in multiple jurisdictions globally; and

WHEREAS, AENOVA, that has affirmed to have the know-how, expertise, capability, experience and the infrastructure necessary to manufacture Product, has agreed to manufacture and supply certain amounts of Product to Customer for clinical trials and general, including commercial where possible, demands in the Territory (as defined hereinafter) subject to the terms and conditions set forth herein; and

WHEREAS, the Parties have agreed in a separate agreement on a certain capital investment of Customer in a sealing equipment to be placed at AENOVA's site in Wolfratshausen (under **Schedule A**); and

WHEREAS, both Parties agree to cooperate with the appropriate level of trust and transparency. Each Party hereto has a duty of good faith and fair dealing in connection with its performance under this Agreement. Each Party shall perform its obligations under this Agreement in a diligent, lawful, ethical and professional manner so as to advance the purposes and intent of this Agreement.

NOW, THEREFORE, in consideration of the mutual covenants contained herein, and for other good and valuable consideration, the Parties agree as follows:

1. Definitions and Interpretation

In this Agreement, including the preamble and except where set forth otherwise, the following terms and abbreviations shall be construed as follows:

1.1 **"Additional Services"** means any service specifically qualified as an additional service (see **Section 6** and **Schedule C** for reference) in any approved Offer following approval process set forth in **Section 5**, except all activities involved in converting FOC Material into Product and according to the quality standards set forth in Quality Agreement including costs of in-process control, quality assurance, quality control and release, deviation and complaint handling, storage of FOC Material until delivery notice, storage of purchased material procured by AENOVA and of Product until delivery notice, disposal of waste.

1.2 **"Affiliate"** shall mean with respect to a Party, any person, corporation, company, partnership or other entity that controls, is controlled by, or is under common control with that Party. For the purpose of this definition, "control" shall mean direct ownership of fifty (50%) or more of the shares of stock entitled to vote for the election of directors, in the case of a corporation, or fifty percent (50%) of more of the equity interest in the case of any other type of legal entity, status as a general partner in any partnership, or any other arrangement whereby the entity or person controls or has the right to control the board of directors or equivalent governing body of a corporation or other entity, or the ability to cause the direction of the management or policies of a corporation or other entity.

1.3 **"Business Day"** shall mean each day of the week excluding Saturday, Sunday and public holidays in Germany or Switzerland or the United States of America.

1.4 **"Calendar Year"** shall mean a period of 12 (twelve) consecutive months corresponding to the calendar year commencing on the first day of January.

1.5 **"Confidential Information"** means contents of this Agreement and any information regarding the other Party's business and / or its Affiliates' business as well as information relating to Product disclosed by one Party and / or its Affiliates to the other Party pursuant to this Agreement.

1.6 **“Critical Materials”** means primary packaging components and materials defined in **Section 11**.

1.7 **“Delivery Date”** means the date of delivery requested by Customer in a Purchase Order, including release of Product for further use.

1.8 **“Drug Substance”** means Customer’s active pharmaceutical ingredient Triheptanoin, manufactured under GMP condition for human use.

1.9 **“Equipment”** means any equipment system to support manufacturing and / or packaging of Product.

1.10 **“Executive Collaborative Leadership”** shall mean for the purpose of this Agreement, on Customer’s side, a professional holding a role not lower than the [***] and a professional holding a role not lower than the [***]; on AENOVA’s side, the [***] and [***] (or whoever is on these roles ad interim).

1.11 **“Facility”** shall mean AENOVA’s manufacturing facilities located in Wolfratshausen, Germany.

1.12 **“Final Release”** shall mean Product is quality released by Customer or Customer’s delegate as per Quality Agreement in **Schedule D**.

1.13 **“FOC Material”** means materials, including but not limited to the Drug Substance, supplied by Customer to AENOVA free of charge (FOC).

1.14 **“Force Majeure”** shall have the meaning as provided in **Section 21** of this Agreement.

1.15 **“Good Manufacturing Practices”** or “**cGMP”** means the current Good Manufacturing Practices including EU GMP Guide, 21 CFR, ICH guidelines, EU guide and their current official interpretations applicable to the manufacturing of drug substances and products.

1.16 **“Hidden Defects”** means a defect of FOC Material or Product already present at the time of respective delivery but not detectable at the time of the inspection.

1.17 **“Improvement”** means technical and business process optimization that is beneficial for the manufacturing process, product quality, financial aspect or supply of Product.

1.18 **“Intellectual Property Rights”** means rights in patents, patent applications (including all utility and design patents and patent applications), inventions, trademarks, service marks, trade names, internet domain names, rights in designs, rights in get-up and trade dress, goodwill and the right to sue for passing off or unfair competition, copyrights, (including all computer applications, programs and other software, including without limitation operating software, network software, firmware, middleware, and design software rights in computer software and databases), database rights,

industrial property rights, moral rights of authors, rights to use, and protect the confidentiality of, confidential information (including know-how and trade secrets), utility models, any other rights (including common law rights) arising from use of the foregoing, all rights of renewal, continuations, divisions, extensions and the like relating to the foregoing, and other intellectual property rights, in each case whether registered or unregistered and including any applications and rights to apply for the grant of any such rights and all rights and forms of protection having an equivalent or similar effect anywhere in the world.

1.19 **"Joint Working Team Members"** shall mean the team selected by the Executive Collaborative Leadership in accordance with the criteria set out under **Section 7** of this Agreement.

1.20 **"Key Performance Indicators"**, shall mean a quantifiable measure used to evaluate the performance of AENOVA in meeting the objectives of this Agreement as defined by the Joint Working Team and approved by the Executive Collaborative Leadership.

1.21 **"Manufacture"** or "**Manufacturing"** means filling or processing, producing, testing and packaging of FOC Material and purchased material to obtain Product by AENOVA in accordance to Specifications.

1.22 **"Material Change in Control or Business Model"** shall mean any of the following: (i) the sale or disposition of all or substantially all of the assets of a Party to a Third Party, (ii) the acquisition by a Third Party, of more than 50% of a Party's outstanding shares of voting capital stock (e.g. capital stock entitled to vote generally for the election of directors), or (iii) the merger or consolidation of a Party with or into another corporation. References in this definition to a Third Party shall also include Affiliates in case Affiliate has no comparable financial resources and financial reputation as Customer or AENOVA has.

1.23 **"Offer"** shall mean AENOVA's quotation containing the details of the proposed Services subject to Customer's binding order.

1.24 "**Person in Plant**" shall mean Customer's representative present on Facility.

1.25 **"Product"** shall mean the product that contains Drug Substance, manufactured by AENOVA and to be delivered to Customer the ownership of which belongs to Customer.

1.26 **"Purchase Order"** shall mean a firm order placed and issued by Customer with a corresponding purchase order number to AENOVA reflecting Services provided by AENOVA.

1.27 **"Quality Agreement"** shall mean the Quality Agreement as referenced in **Schedule D**.

1.28 **“Quarantined Production”** means a Manufacturing of Product with any material not released by the quality department of AENOVA before such Manufacturing. Such Manufacturing requires explicit request by Customer.

1.29 **“Quarantined Shipment”** means a shipment of Product before the quality release by AENOVA and / or Customer in accordance with Quality Agreement.

1.30 **“AENOVA Know-How”** means all know-how or intellectual property relating to AENOVA’s background know-how in the field of the manufacturing and AENOVA’s operations of process development services as well as regulatory, packaging and quality issues.

1.31 **“AENOVA Offer”** means any quote proposed for Additional Services approved by the Customer in accordance with the procedure set forth in **Section 5** of this Agreement.

1.32 **“Services”** means all activities related to Manufacturing of Product as described in this Agreement and **Schedule C** which do not include Additional Services.

1.33 **“Service Fee”** means the fee paid by Customer for each Services as itemized in **Schedule B** in this Agreement and includes all activities involved in converting FOC Material into Product and according to the quality standards set forth in Quality Agreement including costs of in-process control, quality assurance, quality control and release, packaging, storage of FOC Material. Fees for Third Party Materials and Third Party Services are not included and are covered separately.

1.34 **“Specifications”** means the written Product specifications as mutually agreed.

1.35 **“Third Party”** means any person –either individual or legal- other than Customer, AENOVA and their respective Affiliates.

1.36 **“Third Party Material”** means all materials procured by AENOVA for Manufacturing of Product.

1.37 **“Third Party Services”** means all services procured by AENOVA for Manufacturing of Product (e.g. laboratory services, hazardous waste disposal etc.).

1.38 **“Technical Release”** means the release of Product for transport by AENOVA in accordance with **Schedule D**.

1.39 **“Yield”** shall mean the amount of Product manufactured in a production batch, as agreed in writing by the Joint Working Team in compliance with **Section 7.4.iii (iii)** of this Agreement

2. Scope of this Agreement & Schedules

2.1. AENOVA will perform on a non-exclusive basis Services and / or Additional Services upon the terms and conditions of this Agreement as well as its Schedules.

2.2. Attached to this Agreement are the following Schedules which form an integral part of this Agreement:

Schedule B: Service Fee

Schedule C: Description of Services and Additional Services

Schedule D: Quality Agreement

Schedule E: Compliance

Schedule F: Storage Terms

2.3. In the case of any inconsistencies between this Agreement, the Schedules and / or an Offer referring to it, this Agreement shall prevail, except for quality aspects after the Effective Date for which **Schedule D** shall prevail.

2.4. Neither Party shall alter or adjust this Agreement or any Schedule to it without the prior written permission of the other Party.

3. Customer Responsibilities

3.1. Customer shall be responsible to:

(i) provide complete and accurate requirements to define the Specifications;

(ii) provide AENOVA in a timely manner with complete and accurate information and sufficient FOC Material necessary to perform Services;

(iii) provide AENOVA in a timely manner with complete and accurate information to perform Additional Services.

3.2. Customer shall supply FOC Material to AENOVA according to **Schedule B** in line with [***] (Incoterm 2010). Customer is responsible that such material (i) is suitable for the Manufacturing of the Product, (ii) fits for Services and (iii) is pharmaceutically compliant.

3.3. Customer shall strictly comply with **Schedule E**.

4. AENOVA Responsibilities

4.1. AENOVA shall perform Services listed under **Schedule C** and / or Additional Services described under **Section 6** and **Schedule C** in accordance with this Agreement, including Quality Agreement, and with the standard of professional skill, care and diligence customarily applied in respect of services of the same quality and character as the Services listed under **Schedule C** and / or Additional Services described under **Section 6** and **Schedule C** in

similar industry manufacturing processes.

4.2. In particular, AENOVA shall comply with cGMP and with recognized industry standards, including, but not limited to applicable ICH guidelines and the pertaining laws and regulations.

4.3. AENOVA will make available and maintain an adequate manufacturing site and facilities to perform Services and/or approved Additional Services, validated processing equipment if needed, maintain the manufacturing processes for Product in a validated state if needed, trained and competent personnel with relevant knowledge and experience, and will ensure sufficient capacity to store the FOC material and the excipients needed and render Services, and Manufacture of Product.

4.4. All the responsibilities and obligation listed under **Sections 4.1**, **4.2.** and **4.3.** will be covered by AENOVA at their own expenses.

4.5. AENOVA will notify Customer immediately but not later than within [***] Business Days in the event of any potential failure to deliver Product within the agreed time lines.

4.6. AENOVA will manufacture Product in accordance with the terms of this Agreement and the responsibilities as set out in Quality Agreement.

4.7. Until Product is approved either by the FDA or the EMA but not later than [***], AENOVA has to provide Customer with a [***] FOC Material inventory report by the [***] Business Day of [***] reflecting the inventory of FOC Material on the [***] of the [***]. After preceding condition is met, the Parties will discuss in good faith AENOVA's FOC Material reporting obligation.

4.8. AENOVA shall strictly comply with **Schedule E**.

5. Order Processing

5.1. AENOVA will quote Additional Services to Customer by written AENOVA Offer referring to this Agreement.

5.2. Upon agreement between the Parties about such AENOVA Offer, Costumer will place a related PO and AENOVA will provide Additional Services as described in the respective AENOVA Offer.

6. Additional Services

Provided that Order Processing under **Section 5** has been followed, AENOVA will perform Additional Services such as but not limited to those under **Schedule C** and the followings:

(i) [***];

(ii) [***];

(iii) [***];

(iv) [***].

7. Governance Model

7.1. The Parties shall establish a Joint Working Team, consisting of [***] ("Joint Working Team Members"). Joint Working Team will be co-chaired by a representative designated by each Party.

7.2. Either Party may replace its Joint Working Team Members by notice to the other Party.

7.3. Joint Working Team Members shall be appropriately qualified and experienced in order to make a meaningful contribution to the Joint Working Team meetings.

7.4. The purpose of Joint Working Team is to:

(i) drive and improve performance of Services and / or Additional Services, including Yield and Joint Working Team;

(ii) deliver on Service and / or Additional Services goals;

(iii) track yield of the delivered batches. The acceptable product yield in the commercial phase of manufacturing is [***]%. If the yield was below the [***]% the JWT Team shall conduct its discussion in good faith with a view to operating to the mutual benefit of the Parties.

(iv) manage and reduce aggregate risk, including lead times and safety stock management of Third Party Material;

(v) manage issues related to Services and / or Additional Services;

(vi) maintain a collaborative and constructive relationship (at operational level);

(vii) potentially propose any Improvement to the Executive Collaboration Leadership;

(viii) closely monitor all transfer activities according to **Sections 14.7** and **14.8**.

7.5. Joint Working Team shall conduct its discussion in good faith with a view to operating to the mutual benefit of the Parties.

7.6. Joint Working Team shall meet as often as any of Joint Working Team Members may reasonably request so, but in any event no less than [***] per [***] in a face-to-face setting with logistics of the meeting to be decided by Joint Working Team Members. Other Joint Working Team meetings can be held face-to-face or by teleconference based on Joint Working Team Members decision.

7.7. In addition to any other topics to be discussed in the agenda of the relevant meeting, the following matters shall be invariably discussed during Joint Working Team meetings:

(i) team member updates;

(ii) performance review (services, quality, relationship, financials);

(iii) risk evaluation and associated risk mitigation projects;

(iv) review status of past meeting action items.

7.8. Joint Working Team Members may invite individuals with special skills to attend such meetings where it is considered to be relevant and appropriate. Individuals belonging to a third party have to be mutually agreed. These invited individuals do not have voting powers.

7.9. The quorum for the validity of Joint Working Team meetings shall be [***] Joint Working Team Members, [***].

7.10. All decisions of Joint Working Team shall be made in good faith in the best interests of this Agreement. In the event that the Joint Working Team is unable to reach a decision on any matter after no more than [***] good faith attempts to resolve such disagreement in a commercially reasonable fashion, then such matter should be immediately escalated, and not later than [***] Business Day after official closure of Joint Working Team's last attempt, to and decided by Executive Collaboration Leadership in a timely manner.

7.11. Joint Working Team shall take minutes of its meetings and resolutions, which shall be promptly circulated to the Parties after each meeting for review and agreement.

8. Forecast and Purchase Orders

8.1. The Parties hereby establish a forecast procedure as follows.

8.2. Customer will provide a good faith rolling forecast covering the current plus next [***] no later than the [***] Business Day of each calendar [***], specifying the Product, the ordered quantity, number of batches and the

expected Delivery Date ("Forecast"). AENOVA will confirm Forecast to Customer within [***] Business Days after the receipt of such a Forecast and provide firm production schedule. The current [***] plus the first [***] of Forecast shall be firm demand ("Binding Period") to both Parties as to the quantity of Product, number of batches and Delivery Date. Customer will issue Purchase Orders upon confirmation of Forecast reflecting the quantities of Binding Period, the batch number and requested Delivery Date. AENOVA will confirm Purchase Order and Delivery Date within [***] Business Days of receipt of such Purchase Order.

8.3. In case Purchase Order is changed by Customer and needs to be rescheduled within Binding Period, both Parties agree to find in good faith an alternative Manufacturing schedule for respective Purchase Order.

8.4. For orders cancelled at least [***] calendar days prior to confirmed Delivery Date, a cancellation penalty of [***]% of the order cost will be due. For orders cancelled at least [***] days prior to the confirmed Delivery Date, a cancellation penalty of [***]% of the order cost will be due. Orders with less than [***] days to confirmed Delivery Date are non-cancellable.

9. Delivery

9.1. Customer shall deliver all FOC Materials with a notice time of at least [***] Business Days prior to the intended delivery date to AENOVA. FOC material shall not be delivered later than [***] Business Days prior to Delivery Date.

9.2. Any delivery of Product by AENOVA to Customer or to a Third Party named by Customer will be based on [***]; [***] (Incoterms 2010). AENOVA will pack the Product in the manner appropriate for transport in line with [***] requirements and the Quality Agreement or mutually agreed shipping procedures. In case Customer has special requirements for transport packing, Customer shall inform AENOVA about such requirements in a timely manner. If agreed between the Parties such special packing requirements shall be documented in writing in the shipping procedures.

9.3. In urgent cases, Customer may request in writing to AENOVA for:

(i) Quarantined Shipment; or

(ii) Production using quarantined materials covered by appropriate quality systems.

Quarantined Production and/or appropriately pre-final dispositioned Product may be moved within the supply chain to prepare for and/or perform further processing to maintain critical production schedules when:

(iii) Controls are established and documented to ensure final distribution of product only occurs when final disposition of product is completed by the responsible party;

(iv) There are no product impacting investigations open for associated material.

Customer assumes all risks, responsibilities and costs associated with a Quarantined Shipment or Provisional Production, unless the reason for the non-compliance of the Product is caused by AENOVA.

9.4. Within [***] Business Days following notification of Final Release, AENOVA and Customer shall agree if AENOVA shall either (a) place Product with a common carrier for delivery to Customer or a Third Party as directed by Customer, or (b) store applicable Product at Facility or other mutually agreed location according to **Schedule F**.

10. Fees

10.1. Customer will pay to AENOVA Service Fee according to **Schedule B** and / or fee for Additional Services following the acceptance of an Offer.

10.2. Service Fee and fee for Additional Services do not [***]. If AENOVA's Services or Additional Services are [***], Customer will be charged for [***] incurred in addition.

10.3. Service Fee will be paid upon Final Release of the respective batch of Product.

10.4. The fees for Additional Services will be paid according to the payment schedule contained in any approved AENOVA's Offer.

10.5. All Payments must be made in [***] and are payable within [***] days from date of invoice or a designated date where the payment will fall due.

10.6. AENOVA may adjust Service Fees [***] on the [***] of [***] of each [***]. Any increase will be calculated with an average value based on [***]% ([***] percent) of the [***] published by the [***] and [***]% ([***] percent) of the [***]. Annual increases will be limited to this [***] or [***]%, whichever amount is the lesser. AENOVA shall provide Customer with all the official referenced sources justifying any adjustment in accordance with this clause with a [***] Business Day notice.

11. Third Party Material

11.1. With regard to specific materials agreed in writing ("Critical Materials"), AENOVA shall be entitled to procure such quantities of Critical Materials required for Manufacture of the quantities of Product corresponding to Customer's requirement for Product for the next [***] according to Rolling Forecast at Customer's risk. Customer shall bear the risk and costs arising from a change of Specifications affecting such Critical Materials, including

expenditures for the destruction and disposal of unusable Materials within the [***] period.

11.2. All Services requiring materials which are purchased, procured, stored and tested by AENOVA shall be at AENOVA's own expense and are subject to correct and punctual supply of AENOVA's respective suppliers.

11.3. AENOVA will promptly inform Customer if it encounters supply problems, including delays and / or delivery of non-conforming Third Party Material with respect to any supply of purchased material for Manufacturing of Product and AENOVA must take reasonable measures to correct such problems and the Customer may in their discretion provide assistance in agreement with AENOVA. AENOVA should ensure sufficient safety stocks available of any such Third Party Material based on best market practice and on AENOVA's experience with its suppliers and their respective contractual agreements. The definition of such safety stock levels should be reviewed periodically and mutually agreed by Joint Working Team.

12. Special Costs

All costs concerning the further use or importation by Customer into a country of Product are to be borne by Customer, especially administration fees connected with the marketing of Product, even if the respective administrative authority should charge AENOVA directly. In such case, Customer ensures that the respective amounts are received by AENOVA on AENOVA bank account within [***] calendar days. Customer will inform AENOVA about any administrative requirement applicable to AENOVA of any country Customer is marketing Product as soon as possible.

13. Financial Audits

In case of Customer's doubts of AENOVA's compliance with respect to FOC Material and Third Party Material inventory management, AENOVA shall make available to Customer or to a certified public accountant ("CPA") acceptable to Customer, upon Customer's reasonable request and with an appropriate period of notice during the regular office hours during Term (or after Term for activities started during Term but with effects after Term), books, records and other documentation relevant to the Services. For the avoidance of doubt, Customer shall bear the cost of the CPA.

14. Term and Termination

14.1. This Agreement is effective as of the last date of signature ("Effective Date") and will expire (if not terminated earlier in accordance with the Agreement's provisions) 3 (three) years thereafter ("Initial Term"). This Agreement will be automatically extended for indefinite period following Initial Term unless Customer terminates it serving written notice to AENOVA by and not later

than 60 days before end of Initial Term. Following Initial Term, Each Party may withdraw from this Agreement at will (without cause) with a pre-notice of 12 (twelve) months at any time.

14.2. This Agreement may be terminated by a Party serving written notice of such termination to the other Party if this latter breaches a material provision of this Agreement including, but not limited to: **Sections 2** (Scope of this Agreement and Schedules), **3** (Customer Responsibilities), **4** (AENOVA Responsibilities), **5** (Order Processing), **6** (Additional Services), **7** (Forecast and Purchase Order), **9** (Delivery), **10** (Fees), **13** (Financial Audit), **15** (Results), **16** (Intellectual Property), **17** (Defective Product), **18** (Indemnification and Limitation of Liability), **19** (Insurance), **20** (Confidentiality) as well as any delay for reasons attributable to AENOVA in fulfilling Customer's orders, which would lead to a Product stock-out and such breach remains uncured for [***] days following the breaching Party's receipt of written notice of such breach from the non-breaching party.

14.3. Each Party shall be entitled to terminate this Agreement with immediate effect if:

(i) any requirement / obligation mentioned in **Schedule D** is violated / breached by the respective other Party and / or its Affiliates;

(ii) a Material Change in Control and Business Model of the respective other Party, in the event that this latter is sold or disposed to, acquired by or merged with a direct competitor of the Party. A direct competitor is defined as an undertaking that manufactures and /or commercializes virtually identical or similar products / services within the same relevant product market(s). Either Party shall notify to the other Party in writing without undue delay if it undergoes a Material Change in Control and Business Model;

(iii) the respective other Party infringes Party's Intellectual Property Rights;

(iv) the development program of Product is ceased (e.g. failure of meeting clinical end points or filing not approved by the Health Authorities).

14.4. Customer shall be entitled to terminate this Agreement with immediate effect if AENOVA loses the right to operate under this Agreement following any decision from the competent authorities and / or revocation of the necessary approvals / regulatory permits (including FDA taking control of AENOVA following a consent decree).

14.5. Unless otherwise agreed in writing termination or expiration of this Agreement for any reason shall not relieve either Party or its Affiliates from their obligations under this Agreement until the date of such termination or expiration or to perform such obligations as described in **Schedule E**) that

will survive for [***] years after the expiration or termination of this Agreement.

14.6. Customer may terminate this Agreement at any time if AENOVA is unable to deliver Services and / or Additional Services. In the event of Force Majeure, Customer may terminate this Agreement if such Force Majeure lasts for a period greater than [***] consecutive calendar months.

14.7. In any event of termination (including termination at will as per **Section 14.1**) of this Agreement triggered by any of the Parties or resulting from a Force Majeure and upon written notice by Customer ("Transfer Request"), AENOVA will start immediately to make available the manufacturing technology from AENOVA to Customer or a Third Party designated by Customer and provide reasonable technical assistance to Customer or such Third Party to operate the manufacturing process developed under the Master Services Agreement (dated XVCVX) and this Agreement in order to enable the Customer or such third party to continue the manufacturing and supply of Products ("Manufacturing Process"). AENOVA shall make reasonable efforts to complete Manufacturing Process transfer within [***].

14.8. AENOVA shall initiate Manufacturing Process transfer within [***] days after written notice from Customer requesting such initiation ("Initiation Notice"), which Initiation Notice may be made by Customer within [***] after the date of Transfer Request. Costs associated with Transfer Request will be borne by Customer unless this Agreement is terminated by Customer pursuant to **Section 14.4**. or by AENOVA pursuant to **Section 14.1**. In case of termination of this Agreement resulting from Force Majeure, Manufacturing Process transfer costs will be equally borne by the Parties.

15. Results

15.1. Neither Party shall, as a result of this Agreement, acquire any right, title, or interest in any intellectual property that the other Party owns or controls as of the Effective Date of this Agreement, or that the other Party obtains ownership or control of separately and apart from the performance of the Services under this Agreement ("Background Intellectual Property").

15.2. Customer shall own exclusively all rights, titles, and interests in any and all intellectual property with regard to the Product that AENOVA conceives, invents, reduces to practice, develops or makes, solely or jointly with Customer, in the course of performance of the Services or as a result of using Customer's Background Intellectual Property.

15.3. Notwithstanding the foregoing, AENOVA shall own all rights, titles and interests in any intellectual property regarding Know-How that AENOVA develops, conceives, invents, reduces to practice or makes in the course of

performance of the Services that (i) relates to AENOVA Background Intellectual Property; (ii) AENOVA's Know-How, (iii) which is severable from Product, and (iii) does not reveal or disclose any Confidential Information of Customer.

16. Intellectual Property

16.1. Customer represents that Manufacture, supply, marketing or any other use by Customer, AENOVA or any Third Party of Products or of Intellectual Property provided by Customer under this Agreement does not violate Intellectual Property of Third Parties. Customer shall be responsible and liable for any damage arising from the violation of Intellectual Property of Third Parties through any use of Products or Intellectual Property provided by Customer under this Agreement. Customer shall bear all judicial and extrajudicial costs and damages in connection with the violation of Intellectual Property.

16.2. For any inventions both parties shall cooperate in good faith to allocate the rights and the costs which are associated with the possible protection of the inventions.

16.3. If the performance of Services and / or Additional Services requires the use of Intellectual Property Rights of AENOVA, AENOVA hereby grants to Customer the necessary rights of use to these Intellectual Property Rights solely for the marketing, distribution and sale of the Products. In addition, AENOVA grants to Customer the necessary rights of use to these Intellectual Property Rights for the manufacture of Products by Customer itself. Such licenses are granted on a worldwide basis, non-exclusively and royalty-free.

16.4. If the performance of this Agreement requires the use of Intellectual Property Rights of Customer or of Third Parties, Customer hereby grants to or procures for AENOVA the necessary rights of use to these Intellectual Property Rights solely for the performance of Services and / or Additional Services on a worldwide basis, non-exclusively and free of fees.

16.5. All documents which AENOVA receives from Customer for the fulfilment of Services remain the property of Customer.

16.6. AENOVA may in each case archive a copy of all documents and data produced at or in connection with Services in copy, and will not use this archive copy for any purposes other than to abide by the relevant commercial and tax law provisions or to the extent to which these documents and this data are suitable as proof of a circumstance on the basis of which an otherwise mandatory existing liability of AENOVA could be excluded.

16.7. Notwithstanding anything to the contrary in this Agreement, AENOVA shall not be required to destroy any computer files stored securely by AENOVA that are created during automatic system back-up.

16.8. Each Party shall be obliged to acquire the inventions and rights on the inventions made under this Agreement of its employees, consultants, agents and representatives to the extent necessary to secure the other Party's rights set out in this **Section 16**. The other Party shall, as the case may be, reimburse any necessary expenses associated with such acquisitions of rights.

17. Defective Product

17.1. Customer shall examine Product Manufactured and delivered by or on behalf of AENOVA for compliance with the Specifications, intactness, shortage, identity or any defect without undue delay. Should any of the Products fail to meet Specifications, or in the event of any other claim, Customer shall inform AENOVA in writing without undue delay, latest within [***] Business Days after observation of the defect. Hidden Defects can be claimed in writing within [***] Business Days after being detected by Customer. If Customer fails to notify the defect within such period, Customer shall be deemed to have accepted the consignment.

17.2. In the event Customer notifies AENOVA within the period mentioned in **Section 17.1** that any of the Products does not conform with Specifications or is otherwise defective and AENOVA agrees with it, AENOVA shall conduct its own evaluation within the time frame define in Quality Agreement. AENOVA will then repeat Service free of charge, if Customer agrees to that. This is Customer's sole and exclusive remedy. If AENOVA fails to remedy, AENOVA will reimburse Customer for the damages caused by the default up to the limits of liabilities as described in **Section 18.** If AENOVA pays the compensation, AENOVA is no longer obliged to perform the respective concerned Service.

17.3. In the event AENOVA disagrees with the results obtained by Customer the issue shall be submitted to an independent testing laboratory, whose decision shall be binding on both Parties. The costs of such test shall be borne by the Party found to be at fault.

18. Indemnification and Limitation of Liability

18.1. Subject to this Agreement, AENOVA shall indemnify, defend and hold harmless Customer and its Affiliates from and against any and all claims, losses, damages and liabilities which are subject to compensation according to applicable law (collectively "Claims"; singularly "Claim") to the

extent arising out of or resulting from (i) any negligent or willful breach of this Agreement by AENOVA; (ii) the supply of any non-conforming Product arising out of AENOVA's negligence or willful misconduct when Manufacturing Product; in each case except to the extent arising out of Customer's Liability and Indemnification according to **Section 18.2**. Customer shall promptly inform AENOVA of any Claim and shall reasonably cooperate with AENOVA in the defense of such Claims, and shall permit AENOVA to control the defense and settlement of such Claims.

18.2. Subject to this Agreement, Customer shall indemnify, defend and hold harmless AENOVA and its Affiliates from and against any and all Claims to the extent arising out of or resulting from (i) any negligent or willful breach of this Agreement by Customer; (ii) the distribution, marketing, sale, import, and any other use by Customer or any Third Party of Product, except to the extent arising out of AENOVA's Liability and Indemnification according to **Section 18.1**. AENOVA shall promptly inform Customer of any Claim and shall reasonably cooperate with Customer in the defense of such Claims, and shall permit Customer to control the defense and settlement of such Claims.

18.3. All indemnification claims in respect of any person seeking indemnification (collectively the "Indemnitees" and each an "Indemnitee") under this **Section 18.3** shall be made by the corresponding Party (the "Indemnified Party"). The Indemnified Party shall give to the other Party (the "Indemnifying Party") prompt written notice ("Indemnification Claim Notice") of any losses or the discovery of any fact upon which such Indemnified Party intends to base an indemnification request. Each Indemnification Claim Notice must contain a description of the Claim and the nature and the amount of incurred loss and / or requested indemnification (to the extent that the nature and the amount are known at such time). Together with Indemnification Claim Notice, the Indemnified Party shall furnish promptly to the Indemnifying Party copies of all the notices and documents (including court papers) received by any Indemnitee in connection with Third Party Claim. The Indemnifying Party shall not be obligated to indemnify the Indemnified Party to the extent any admission or statement made by the Indemnified Party materially prejudices the defence of such Third Party Claim. Where required the Indemnifying Party shall promptly send a copy of Indemnification Claim Notice to its relevant insurers and shall permit them to exercise rights of subrogation.

18.4. At its option the Indemnifying Party may assume control of the defence of any Third Party Claim by giving written notice to the Indemnified Party within [***] Business Days after the Indemnifying Party's receipt of an Indemnification Claim Notice.

18.5. If the Indemnifying Party chooses not to take control of the defence or prosecute any Third Party Claim, the Indemnified Party shall retain control of the defence thereof, but no Indemnified Party or Indemnitee shall admit any liability with respect to, or settle, compromise or discharge, any such Third Party Claim without the prior written consent of the Indemnifying Party, which consent shall not be unreasonably withheld or delayed.

18.6. If AENOVA's cooperation is required in administrative procedures, especially in procedures of admission, customs or of importation, Customer indemnifies AENOVA from any liability which may arise out of this cooperation. That applies, in particular, in cases, where AENOVA, on Customer's request, makes statements or applications at or towards governmental authorities or where AENOVA participates in making those statements or applications.

19. Insurance

19.1. Either Party shall, at its sole cost and expense, obtain and maintain in force for entire Term an adequate and suitable insurance in the minimum amounts set forth below with a reputable insurance company to cover its liability under this Agreement.

19.2. [***] insurance, with [***] limits of [***] for each claim with respect to [***] and / or [***] and [***].

19.3. Upon execution of this Agreement, each Party shall furnish to the other party a written statement by the insurer evidencing such coverages referred herein that must remain in place for the entire duration of this Agreement and for [***] years after termination triggered in compliance with **Section 14** of this Agreement. For the avoidance of doubt, each Party is allowed to change the insurer during the validity term of this clause provided that all the conditions described in this **Section 19** are properly met.

20. Confidentiality

20.1. Each of the Parties will keep Confidential Information of the respective other Party secret. Parties will use Confidential Information only for the performance of Services / Additional Services.

20.2. Each Party shall limit the disclosure of the other Party's Confidential Information to Affiliates, officers or employees, and, in case of AENOVA, to the employees of AENOVA, who reasonably require the same in performance of activities related to this Agreement in order to perform the Services / Additional Services and who are obligated to treat the same as confidential in the same manner and to the same extent as provided herein.

The receiving Party will use its reasonable efforts to ensure that any Affiliate, employee or officer to which it discloses Confidential Information will retain such information in strict confidence.

20.3. The receiving Party may disclose Confidential Information to a governmental, administrative or other regulatory body or during judicial process to the extent required by mandatory law. In case of such disclosure, the receiving Party shall provide the disclosing Party – as far as legally possible - with written notice of such request or requirement so that the disclosing Party may seek a protective order or other appropriate remedy. If the receiving Party is unable to inform the disclosing Party before the information is disclosed pursuant to this paragraph, it shall to the extent permitted by law inform the disclosing Party of the full circumstances of disclosure and the Confidential Information which has been disclosed immediately after the disclosure. The receiving Party agrees further to provide immediately notice to the disclosing Party in the case of any unauthorized use of Confidential Information.

20.4. The provisions of this **Section 20** do not apply to information which receiving Party proves that:

(i) the receiving Party already knew, the prior knowledge of which it can document by prior written records;

(ii) is or becomes public knowledge other than through the receiving Party's breach of this promise of confidentiality;

(iii) the receiving Party receives in good faith from a third party not in violation of an obligation of confidentiality or

(iv) the receiving Party independently develops, discovers or arrives at without use of or reference to the Confidential Information.

20.5. For the avoidance of doubt, no provision in this Agreement shall restrict each Party's right to disclose the existence of a business relationship between the Parties to potential customers.

21. Force Majeure

21.1. Neither Party is liable to the other Party for failure or delay to the extent and for so long as such failure or delay results from causes beyond the reasonable control of such Party, including natural disasters, embargoes, wars, acts of war (whether war is declared or not), terrorist acts, insurrections, riots, civil commotion, omissions or delays in acting by any administrative authority or other party.

21.2. In the event of occurrence of Force Majeure, each Party will use their commercially reasonable efforts to mitigate the adverse consequences.

22. Miscellaneous

22.1. No change of this Agreement is valid unless it is in writing and signed by the Parties. This applies also to the foregoing sentence.

22.2. In case one of the clauses is invalid or unenforceable, the other clauses remain unaffected by this. The Parties shall negotiate in good faith if they wish to replace such invalid or unenforceable clause.

22.3. Any notice or request required or permitted to be given under or in connection with this Agreement or the subject matter hereof shall be given by prepaid registered or certified first class airmail, e-mail or telefax to the recipient at its address set forth on the first page of this Agreement or to such other address as may have therefore been furnished in writing by the recipient to the sending Party. Any such aforementioned notice or request concerning this Agreement shall be effective upon receipt by the Party to which it is addressed.

22.4. Neither Party may assign or transfer this Agreement or any rights or obligations hereunder, by operation or law or otherwise, without the prior written consent of the other Party, except that a Party may make such an assignment or transfer, by operation of law or otherwise, without the other Party's consent to its Affiliate(s) or to an entity that acquires all or substantially all the business of such Party, whether in a merger, consolidation, reorganization, acquisition, sale or otherwise. Notwithstanding anything to the contrary contained herein, in the event of an assignment to an Affiliate pursuant to this **Section 22.4**, the assigning Party consents, acknowledges, covenants and guarantees that it shall remain jointly and severally liable, along with the assignee, to the non – assigning Party for all the obligations contained herein. This Agreement shall be binding on the successors and permitted assigns of the assigning Party, and the name of a Party appearing herein shall be deemed to include the name(s) of such Party's successors and permitted assigns to the extent necessary to carry out the intent of this Agreement. Any assignment or attempted assignment by either Party in violation of this **Section 22.4**, shall be null and void and of no legal effect.

22.5. This Agreement and any potential subsequent amendment to it, may be executed in two or more counterparts, each of which shall be deemed an original and all of which shall constitute together the same instrument. In the event that any signature is delivered by facsimile transmission or by e-mail delivery of a .pdf format data file, such signature shall create a valid and

binding obligation of the party executing (or on whose behalf such signature is executed) with the same force and effect as if such facsimile or ".pdf" signature page where an original thereof.

22.6. This Agreement is governed by the laws of Switzerland. Any controversy, claim or dispute arising out of or relating to this Agreement, any of its Schedule, and / or Offer or the breach thereof shall be settled, if possible, through good faith negotiation between the Parties. Such good faith negotiations shall commence promptly upon a Party's receipt of notice of any claim or dispute from the other Party and continue for a period of [***]. If such efforts are not successful, such controversy, claim or dispute relating to, arising out of, or in any way connected with this Agreement or any term or condition hereof, or the performance by either Party of its obligations hereunder, whether before or after termination of this Agreement, except as otherwise expressly provided in this Agreement, shall be exclusively settled by the competent court in Basel, Switzerland.

IN WITNESS WHEREOF, this Agreement is executed as of the Agreement Effective Date on behalf of the parties by their duly authorized representatives.

[*Signatures on the following page*]

Aenova Haupt Pharma Wolfratshausen GmbH Date: 12.03.2019 Signature: /s/ [***] Name: [***] Position: Managing Director, Haupt Pharma Wolfratshausen, Member of the Aenova Group		If second signature is required: Date: 12.03.2019 Signature: /s/ [***] Name: [***] Position: Head of Customer Service
Ultragenyx Pharmaceutical Inc. Date: 08 April 2019 Signature: /s/ Dennis Huang Name: Dennis Huang Position: Chief Tech Ops Officer		If second signature is required: Date: _____ Signature: _____ Name: _____ Position: _____

SCHEDULE A

Capital Investment Summary

[***]

SCHEDULE B

Service Fee

[***]

Schedule C

Description of Services and Additional Services

[***]

SCHEDULE D

Quality Agreement

Current version of the Quality Agreement executed separately by the Parties

SCHEDULE E

Compliance

1. Compliance

For AENOVA, it is a matter of course that group members of AENOVA comply with the law and any and all other relevant provisions applicable in the countries where they operate. AENOVA expects the same from its business partners.

2. Anti-Corruption

Neither Party shall perform any actions that are prohibited by local and other anti-corruption laws that may be applicable to one or both Parties to the Agreement. Without limiting the foregoing, neither Party shall make any payments, or offer or transfer anything of value, to any government official or government employee, to any political party official or candidate for political office or to any other Third Party related to this Agreement in a manner that would violate Anti-Corruption Laws.

3. Export

Each Party hereby acknowledges that this Agreement is or might be subject to one or more export control laws, regulations or the like, and agrees that it will not transfer, export or re-export any such item, including any documentation, information or product that incorporates, is derived from or otherwise reveals such, without complying with all applicable export control laws, regulations and like, including obtaining and / or cooperating with the other Party in securing all appropriate licenses and authorizations.

Customer specifically certifies that it will not transfer, export, or re-export any item under this Agreement to any country or entity subject to export control restrictions and / or embargoes under any applicable laws, regulations and the like.

4. Dealing with Internal Knowledge, Confidentiality

In principle, company and operational secrets must be treated with confidentiality. This shall also apply to any other information (such as customer information) whose confidentiality is in the interest of AENOVA's customers.

5. Data Privacy

Both Parties must comply with the applicable statutory and operational principles regarding the protection of data regarding employees, customers,

and investors in particular related, but not limited to, to the European General Data Protection Regulation of April 27, 2016 (Regulation (EU) 2016/679) and local applicable supplementary laws. In order to protect personal data either Party must observe the necessary diligence in the context of the assigned task.

6. Documentation of Business Transactions

The documentation of any and all business transactions must be complete, transparent, and in compliance with the statutory provisions as well as with any provisions and processes.

7. Social Responsibility

AENOVA respects the dignity of every human being and is committed to the compliance with and the protection of human rights.

AENOVA does not tolerate any kind of child labour as well as any exploitation of children and adolescents. Minimum age for the admission to employment must not be under the age for the fulfilment of compulsory education and in no case under 15 (fifteen) years.

AENOVA disapproves of any form of forced labour.

8. No Discrimination

AENOVA creates a working atmosphere characterized by respectful cooperation and to strictly oppose to any kind of discrimination on grounds of race or ethnic origin, gender, religion or philosophy of life, disability, age, or sexual identity.

9. EHS (Environmental, Health and Safety)

It is AENOVA's policy to operate in a safe and responsible manner with respect to the environment and health of our employees, our customers and the communities where we operate.

AENOVA will not compromise environmental, health or safety values for other interests; value human life above all else and manage risks accordingly.

AENOVA pursues and continually improves an EHS system and processes to achieve an EHS incident-free environment.

AENOVA complies with applicable laws and set standards and for suppliers.

AENOVA uses its EHS knowledge to enhance the safety and well-being of the communities.

SCHEDULE F

Storage Terms

1. Storage Terms

AENOVA will store Product for Customer due at Facility under the temperature conditions as defined in Specifications and / or according to Customer's requirement. Product will remain sole and exclusive property of Customer and will stored by AENOVA following the applicable GMP regulations and in accordance with the common standards for the storage of pharmaceutical goods.

In deviation of the provisions in **Section 19** of the Agreement, AENOVA will maintain an insurance for the storage site in order to cover the elemental risk for the storage of the Product. Therefore, Customer shall inform AENOVA in writing timely ahead of the first Product storage about the insurance value of Product. Upon request by Customer, AENOVA will provide evidence upon such insurance.

Upon request by Customer, AENOVA will dispatch Product ready to be picked up to a carrier designated by Customer.

2. Limitation of Liability

AENOVA ´s liabilities for the storage services as detailed in this **Schedule F** shall be limited to negligence or willful misconduct. With the exception of cases of willful misconduct, AENOVA shall not be liable to Customer for any indirect, punitive or consequential damages or loss of profit, whether based on contract, tort or rising under other applicable laws. With the exception of cases of willful misconduct, the Parties' respective total liability under this **Schedule F** shall in no event exceed an amount equal to [***].

AENOVA DOES NOT MAKE OR HAS MADE ANY OTHER REPRESENTATION, WARRANTY, COVENANT OR AGREEMENT (WHETHER EXPRESS OR IMPLIED).

Exhibit 10.43

ULTRAGENYX PHARMACEUTICAL INC.
EMPLOYMENT INDUCEMENT PLAN

1. DEFINED TERMS

Exhibit A, which is incorporated by reference, defines the terms used in the Plan and sets forth certain operational rules related to those terms.

2. PURPOSE

The Plan has been established to advance the interests of the Company by providing for the grant to Participants of Stock-based and other incentive Awards as inducement awards for employment with the Company pursuant to Nasdaq Listing Rule 5635(c)(4) (or any successor rule or similar rule of any stock exchange on which the Stock is listed)

3. ADMINISTRATION

The Administrator has discretionary authority, subject only to the express provisions of the Plan, to interpret the Plan; determine eligibility for and grant Awards; determine, modify or waive the terms and conditions of any Award; prescribe forms, rules and procedures relating to the Plan; and otherwise do all things necessary or appropriate to carry out the purposes of the Plan. Determinations of the Administrator made under the Plan will be conclusive and will bind all parties.

4. LIMITS ON AWARDS UNDER THE PLAN

(a) **Number of Shares**. The maximum number of shares of Stock that may be delivered in satisfaction of Awards under the Plan is 500,000. For purposes of this Section 4(a), the aggregate number of shares available for issuance under this Plan at any time shall not be reduced by (i) shares subject to Awards that have been terminated, expired unexercised, forfeited or settled in cash, (ii) shares subject to Awards that have been retained or withheld by the Company in payment or satisfaction of the exercise price, purchase price or tax withholding obligation of an Award, or (iii) shares subject to Awards that otherwise do not result in the issuance of shares in connection with payment or settlement thereof. In addition, shares that have been delivered (either actually or by attestation) to the Company in payment or satisfaction of the exercise price, purchase price or tax withholding obligation of an Award shall be available for issuance under this Plan.

(b) **Type of Shares**. Stock delivered by the Company under the Plan may be authorized but unissued Stock or previously issued Stock acquired by the Company. No fractional shares of Stock will be delivered under the Plan.

5. ELIGIBILITY AND PARTICIPATION

The Administrator will select Participants from Eligible Persons.

6. RULES APPLICABLE TO AWARDS

(a) All Awards.

(1) Award Provisions. The Administrator will determine the terms of all Awards, subject to the limitations provided herein. By accepting (or, under such rules as the Administrator may prescribe, being deemed to have accepted) an Award, the Participant will be deemed to have agreed to the terms of the Award and the Plan. Notwithstanding any provision of this Plan to the contrary, awards of an acquired company that are converted, replaced or adjusted in connection with the acquisition may contain terms and conditions that are inconsistent with the terms and conditions specified herein, as determined by the Administrator.

(2) Term of Plan. No Awards may be made after ten years from February 3, 2021, but previously granted Awards may continue beyond that date in accordance with their terms.

(3) Transferability. Except as the Administrator otherwise expressly provides in accordance with the second sentence of this Section 6(a)(3), Awards may not be transferred other than by will or by the laws of descent and distribution. During a Participant's lifetime, except as the Administrator otherwise expressly, SARs and Stock Options may be exercised only by the Participant. The Administrator may permit the gratuitous transfer (*i.e.*, transfer not for value) of Awards to any transferee eligible to be covered by the provisions of Form S-8 (under the Securities Act), subject to such limitations as the Administrator may impose.

(4) Vesting, etc. The Administrator will determine the time or times at which an Award will vest or become exercisable and the terms on which a Stock Option or SAR will remain exercisable. Without limiting the foregoing, the Administrator may at any time accelerate the vesting or exercisability of an Award, regardless of any adverse or potentially adverse tax or other consequences resulting from such acceleration. Unless the Administrator expressly provides otherwise, however, the following rules will apply if a Participant's Employment ceases:

(A) Immediately upon the cessation of the Participant's Employment and except as provided in (B) and (C) below, each Stock Option and SAR that is then held by the Participant or by the Participant's permitted transferees, if any, will cease to be exercisable and will terminate and all other Awards that are then held by the Participant or by the Participant's permitted transferees, if any, to the extent not already vested will be forfeited.

(B) Subject to (C) and (D) below, all Stock Options and SARs held by the Participant or the Participant's permitted transferees, if any, immediately prior to the cessation of the Participant's Employment, to the extent then exercisable, will remain exercisable for the lesser of (i) a period of three months or (ii) the period ending on the latest date on which such Stock Option or SAR could have been exercised without regard to this Section 6(a)(4), and will thereupon immediately terminate.

(C) All Stock Options and SARs held by a Participant or the Participant's permitted transferees, if any, immediately prior to the Participant's death, to the extent then exercisable, will remain exercisable for the lesser of (i) the one year period

ending with the first anniversary of the Participant's death or (ii) the period ending on the latest date on which such Stock Option or SAR could have been exercised without regard to this Section 6(a)(4), and will thereupon immediately terminate.

(D) All Stock Options and SARs (whether or not exercisable) held by a Participant or the Participant's permitted transferees, if any, immediately prior to the cessation of the Participant's Employment will immediately terminate upon such cessation of Employment if the termination is for Cause or occurs in circumstances that in the sole determination of the Administrator would have constituted grounds for the Participant's Employment to be terminated for Cause.

(5) **Additional Restrictions**. The Administrator may cancel, rescind, withhold or otherwise limit or restrict any Award at any time if the Participant is not in compliance with all applicable provisions of the Award agreement and the Plan, or if the Participant breaches any agreement with the Company or any Affiliate with respect to confidentiality. Without limiting the generality of the foregoing, the Administrator may recover Awards made under the Plan and payments under or gain in respect of any Award to the extent required to comply with Company policy, with Section 10D of the Exchange Act or any stock exchange or similar rule adopted under said Section.

(6) **Taxes**. The delivery, vesting and retention of Stock, cash or other property under an Award are conditioned upon full satisfaction by the Participant of all tax withholding requirements with respect to the Award. The Administrator will prescribe such rules for the withholding of taxes as it deems necessary. The Administrator may, but need not, hold back shares of Stock from an Award or permit a Participant to tender previously owned shares of Stock in satisfaction of tax withholding requirements.

(7) **Dividend Equivalents, Etc**. The Administrator may provide for the payment of amounts (on terms and subject to conditions established by the Administrator) in lieu of cash dividends or other cash distributions with respect to Stock subject to an Award whether or not the holder of such Award is otherwise entitled to share in the actual dividend or distribution in respect of such Award. Any entitlement to dividend equivalents or similar entitlements will be established and administered either consistent with an exemption from, or in compliance with, the requirements of Section 409A. Dividends or dividend equivalent amounts payable in respect of Awards that are subject to restrictions may be subject to such limits or restrictions as the Administrator may impose.

(8) **Rights Limited**. Nothing in the Plan will be construed as giving any person the right to continued employment or service with the Company or any Affiliate, or any rights as a stockholder except as to shares of Stock actually issued under the Plan. The loss of existing or potential profit in Awards will not constitute an element of damages in the event of termination of Employment for any reason, even if the termination is in violation of an obligation of the Company or any Affiliate to the Participant.

(9) **Coordination with Other Plans**. Awards under the Plan may be granted in tandem with other Awards under the Plan or awards made under other compensatory plans or programs of the Company or any Affiliate.

(10) **Section 409A**. Each Award will contain such terms as the Administrator determines, and will be construed and administered, such that the Award either qualifies for an exemption from the requirements of Section 409A or satisfies such requirements.

(11) **Fair Market Value**. In determining the fair market value of any share of Stock under the Plan, the Administrator will make the determination in good faith consistent with the rules of Section 409A to the extent applicable.

(b) **Stock Options and SARs**.

(1) **Time and Manner of Exercise**. Unless the Administrator expressly provides otherwise, no Stock Option or SAR will be deemed to have been exercised until the Administrator receives a notice of exercise (in form acceptable to the Administrator), which may be an electronic notice, signed (including electronic signature in form acceptable to the Administrator) by the appropriate person and accompanied by any payment required under the Award. A Stock Option or SAR exercised by any person other than the Participant will not be deemed to have been exercised until the Administrator has received such evidence as it may require that the person exercising the Award has the right to do so.

(2) **Exercise Price**. The exercise price (or the base value from which appreciation is to be measured) of each Award requiring exercise will be no less than 100% of the fair market value of the Stock subject to the Award, determined as of the date of grant, or such higher amount as the Administrator may determine in connection with the grant. Fair market value will be determined by the Administrator consistent with the applicable requirements of Section 409A.

(3) **Payment of Exercise Price**. Where the exercise of an Award is to be accompanied by payment, payment of the exercise price will be by cash or check acceptable to the Administrator or by such other legally permissible means, if any, as may be acceptable to the Administrator.

(4) **Maximum Term**. Stock Options and SARs will have a maximum term not to exceed 10 years from the date of grant; provided, however, that, if a Participant still holding an outstanding but unexercised Stock Option or SAR 10 years from the date of grant (or, in the case of a Stock Option or SAR with a maximum term of less than 10 years, such maximum term) is prohibited by applicable law or a written policy of the Company applicable to similarly situated employees from engaging in any open-market sales of Stock, and if at such time the Stock is publicly traded (as determined by the Administrator), the maximum term of such Award will instead be deemed to expire on the 30th day following the date the Participant is no longer prohibited from engaging in such open market sales.

(5) **No Repricing without Stockholder Approval**. Other than in connection with a change in the Company's capitalization (as described in Section 7(b)), the Company shall not, without stockholder approval, reduce the exercise price of a Stock Option or SAR and, at any time when the exercise price of a Stock Option or SAR is above the fair market value of a share of Stock, the Company shall not, without stockholder approval (except in the case of a Covered Transaction), cancel and re-grant or exchange such Stock Option or SAR for cash or a new Award.

7. EFFECT OF CERTAIN TRANSACTIONS

(a) **Mergers, *etc***. Except as otherwise provided in an Award agreement, the following provisions will apply in the event of a Covered Transaction:

(1) **Assumption or Substitution**. If the Covered Transaction is one in which there is an acquiring or surviving entity, the Administrator may (but, for the avoidance of doubt, need not) provide (i) for the assumption or continuation of some or all outstanding Awards or any portion thereof or (ii) for the grant of new awards in substitution therefor by the acquiror or survivor or an affiliate of the acquiror or survivor.

(2) **Cash-Out of Awards**. Subject to Section 7(a)(5) below the Administrator may (but, for the avoidance of doubt, need not) provide for payment (a "cash-out"), with respect to some or all Awards or any portion thereof, equal in the case of each affected Award or portion thereof to the excess, if any, of (A) the fair market value of one share of Stock (as determined by the Administrator in its reasonable discretion) times the number of shares of Stock subject to the Award or such portion, over (B) the aggregate exercise or purchase price, if any, under the Award or such portion (in the case of an SAR, the aggregate base value above which appreciation is measured), in each case on such payment terms (which need not be the same as the terms of payment to holders of Stock) and other terms, and subject to such conditions, as the Administrator determines.

(3) **Acceleration of Certain Awards**. Subject to Section 7(a)(5) below, the Administrator may (but, for the avoidance of doubt, need not) provide that any Award requiring exercise will become exercisable, in full or in part and/or that the delivery of any shares of Stock remaining deliverable under any outstanding Award of Stock Units (including Restricted Stock Units and Performance Awards to the extent consisting of Stock Units) will be accelerated in full or in part, in each case on a basis that gives the holder of the Award a reasonable opportunity, as determined by the Administrator, following exercise of the Award or the delivery of the shares, as the case may be, to participate as a stockholder in the Covered Transaction.

(4) **Termination of Awards Upon Consummation of Covered Transaction**. Except as the Administrator may otherwise determine in any case, each Award will automatically terminate (and in the case of outstanding shares of Restricted Stock, will automatically be forfeited) upon consummation of the Covered Transaction, other than Awards assumed or continued pursuant to Section 7(a)(1) above.

(5) **Additional Limitations**. Any share of Stock and any cash or other property delivered pursuant to Section 7(a)(2) or Section 7(a)(3) above with respect to an Award may, in the discretion of the Administrator, contain such restrictions, if any, as the Administrator deems appropriate to reflect any performance or other vesting conditions to which the Award was subject and that did not lapse (and were not satisfied) in connection with the Covered Transaction. For purposes of the immediately preceding sentence, a cash-out under Section 7(a)(2) above or acceleration under Section 7(a)(3) above will not, in and of itself, be treated as the lapsing (or satisfaction) of a performance or other vesting condition. In the case of Restricted Stock that does not vest and is not forfeited in connection with the Covered Transaction, the Administrator may require that any amounts delivered, exchanged or otherwise paid in respect of such Stock in

connection with the Covered Transaction be placed in escrow or otherwise made subject to such restrictions as the Administrator deems appropriate to carry out the intent of the Plan.

(b) Changes in and Distributions With Respect to Stock.

(1) Basic Adjustment Provisions. In the event of a stock dividend, stock split or combination of shares (including a reverse stock split), recapitalization or other change in the Company's capital structure that constitutes an equity restructuring within the meaning of FASB ASC 718, the Administrator will make appropriate adjustments to the maximum number of shares specified in Section 4(a) that may be delivered under the Plan, and will also make appropriate adjustments to the number and kind of shares of stock or securities subject to Awards then outstanding or subsequently granted, any exercise prices relating to Awards and any other provision of Awards affected by such change.

(2) Certain Other Adjustments. The Administrator may also make adjustments of the type described in Section 7(b)(1) above to take into account distributions to stockholders other than those provided for in Section 7(a) and 7(b)(1), or any other event, if the Administrator determines that adjustments are appropriate to avoid distortion in the operation of the Plan, having due regard for the requirements of Section 409A, where applicable.

(3) Continuing Application of Plan Terms. References in the Plan to shares of Stock will be construed to include any stock or securities resulting from an adjustment pursuant to this Section 7.

8. LEGAL CONDITIONS ON DELIVERY OF STOCK

The Company will not be obligated to deliver any shares of Stock pursuant to the Plan or to remove any restriction from shares of Stock previously delivered under the Plan until: (i) the Company is satisfied that all legal matters in connection with the issuance and delivery of such shares have been addressed and resolved; (ii) if the outstanding Stock is at the time of delivery listed on any stock exchange or national market system, the shares to be delivered have been listed or authorized to be listed on such exchange or system upon official notice of issuance; and (iii) all conditions of the Award have been satisfied or waived. The Company may require, as a condition to exercise of the Award, such representations or agreements as counsel for the Company may consider appropriate to avoid violation of the Securities Act or any applicable state or non-U.S. securities law. Any Stock required to be issued to Participants under the Plan will be evidenced in such manner as the Administrator may deem appropriate, including book-entry registration or delivery of stock certificates. In the event that the Administrator determines that Stock certificates will be issued to Participants under the Plan, the Administrator may require that certificates evidencing Stock issued under the Plan bear an appropriate legend reflecting any restriction on transfer applicable to such Stock, and the Company may hold the certificates pending lapse of the applicable restrictions.

9. AMENDMENT AND TERMINATION

The Administrator may at any time or times amend the Plan or any outstanding Award for any purpose which may at the time be permitted by law, and may at any time terminate the Plan as to any future grants of Awards; provided, that except as otherwise expressly provided in the

Plan the Administrator may not, without the Participant's consent, alter the terms of an Award so as to affect materially and adversely the Participant's rights under the Award, unless the Administrator expressly reserved the right to do so at the time the Award was granted. Any amendments to the Plan will be conditioned upon stockholder approval only to the extent, if any, such approval is required by law (including the Code and applicable stock exchange requirements), as determined by the Administrator.

10. OTHER COMPENSATION ARRANGEMENTS

The existence of the Plan or the grant of any Award will not in any way affect the Company's right to Award a person bonuses or other compensation in addition to Awards under the Plan.

11. MISCELLANEOUS

(a) **Waiver of Jury Trial**. By accepting an Award under the Plan and to the extent permitted under applicable law, each Participant waives any right to a trial by jury in any action, proceeding or counterclaim concerning any rights under the Plan and any Award, or under any amendment, waiver, consent, instrument, document or other agreement delivered or which in the future may be delivered in connection therewith, and agrees that any such action, proceedings or counterclaim will be tried before a court and not before a jury. By accepting an Award under the Plan, each Participant certifies that no officer, representative, or attorney of the Company has represented, expressly or otherwise, that the Company would not, in the event of any action, proceeding or counterclaim, seek to enforce the foregoing waivers. Notwithstanding anything to the contrary in the Plan, nothing herein is to be construed as limiting the ability of the Company and a Participant to agree to submit disputes arising under the terms of the Plan or any Award made hereunder to binding arbitration or as limiting the ability of the Company to require any eligible individual to agree to submit such disputes to binding arbitration as a condition of receiving an Award hereunder.

(b) **Limitation of Liability**. Notwithstanding anything to the contrary in the Plan, neither the Company, nor any Affiliate, nor the Administrator, nor any person acting on behalf of the Company, any Affiliate, or the Administrator, will be liable to any Participant or to the estate or beneficiary of any Participant or to any other holder of an Award by reason of any acceleration of income, or any additional tax (including any interest and penalties), asserted by reason of the failure of an Award to satisfy the requirements of Section 409A or by reason of Section 4999 of the Code, or otherwise asserted with respect to the Award; provided, that nothing in this Section 11(b) will limit the ability of the Administrator or the Company, in its discretion, to provide by separate express written agreement with a Participant for any payment in connection with any such acceleration of income or additional tax.

12. ESTABLISHMENT OF SUB-PLANS

The Administrator may from time to time establish one or more sub-plans under the Plan for purposes of satisfying applicable blue sky, securities or tax laws of various jurisdictions. The Administrator will establish such sub-plans by adopting supplements to the Plan setting forth (i) such limitations on the Administrator's discretion under the Plan as it deems necessary or desirable

and (ii) such additional terms and conditions not otherwise inconsistent with the Plan as it deems necessary or desirable. All supplements so established will be deemed to be part of the Plan, but each supplement will apply only to Participants within the affected jurisdiction (as determined by the Administrator).

13. GOVERNING LAW

(a) **Certain Requirements of Corporate Law**. Awards will be granted and administered consistent with the requirements of applicable Delaware law relating to the issuance of Stock and the consideration to be received therefor, and with the applicable requirements of the stock exchanges or other trading systems on which the Stock is listed or entered for trading, in each case as determined by the Administrator.

(b) **Other Matters**. Except as otherwise provided by the express terms of an Award agreement, under a sub-plan described in Section 12 or as provided in Section 13(a) above, the provisions of the Plan and of Awards under the Plan and all claims or disputes arising out of or based upon the Plan or any Award under the Plan or relating to the subject matter hereof or thereof will be governed by and construed in accordance with the domestic substantive laws of the State of Delaware without giving effect to any choice or conflict of laws provision or rule that would cause the application of the domestic substantive laws of any other jurisdiction.

(c) **Jurisdiction**. By accepting an Award, each Participant will be deemed to (i) have submitted irrevocably and unconditionally to the jurisdiction of the federal and state courts located within the geographic boundaries of the United States District Court for the Northern District of California for the purpose of any suit, action or other proceeding arising out of or based upon the Plan or any Award; (ii) agree not to commence any suit, action or other proceeding arising out of or based upon the Plan or an Award, except in the federal and state courts located within the geographic boundaries of the United States District Court for the Northern District of California; and (iii) waive, and agree not to assert, by way of motion as a defense or otherwise, in any such suit, action or proceeding, any claim that it is not subject personally to the jurisdiction of the above-named courts that its property is exempt or immune from attachment or execution, that the suit, action or proceeding is brought in an inconvenient forum, that the venue of the suit, action or proceeding is improper or that the Plan or an Award or the subject matter thereof may not be enforced in or by such court.

EXHIBIT A

Definition of Terms

The following terms, when used in the Plan, will have the meanings and be subject to the provisions set forth below:

"**Administrator**": The Compensation Committee, except that the Compensation Committee may delegate (i) to one or more of its members (or one or more other members of the Board (including the full Board)) such of its duties, powers and responsibilities as it may determine; (ii) to one or more officers of the Company the power to grant Awards to the extent permitted by Section 157(c) of the Delaware General Corporation Law; and (iii) to such Employees or other persons as it determines such ministerial tasks as it deems appropriate; provided, however, that such delegation does not (A) violate state or corporate law or (B) result in the loss of any exemption under Rule 16b-3 promulgated under the Exchange Act for Awards granted to Participants subject to Section 16 of the Exchange Act. In the event of any delegation described in the preceding sentence, the term "Administrator" will include the person or persons so delegated to the extent of such delegation.

"**Affiliate**": Any corporation or other entity that stands in a relationship to the Company that would result in the Company and such corporation or other entity being treated as one employer under Section 414(b) and Section 414(c) of the Code.

"Award": Any or a combination of the following: (i) Stock Options, (ii) SARs, (iii) Restricted Stock, (iv) Unrestricted Stock, (v) Stock Units, including Restricted Stock Units, (vi) Performance Awards, (vii) Cash Awards or (viii) awards (other than Awards described in (i) through (vii) above) that are convertible into or otherwise based on Stock.

"**Board**": The Board of Directors of the Company.

"**Cash Award**": An Award denominated in cash.

"**Cause**": In the case of any Participant who is party to an employment or severance-benefit agreement that contains a definition of "Cause," the definition set forth in such agreement will apply with respect to such Participant under the Plan. In the case of any other Participant, "Cause" will mean, as determined by the Administrator in its reasonable judgment, (i) a substantial failure of the Participant to perform the Participant's duties and responsibilities to the Company or subsidiaries or substantial negligence in the performance of such duties and responsibilities; (ii) the commission by the Participant of a felony or a crime involving moral turpitude; (iii) the commission by the Participant of theft, fraud, embezzlement, material breach of trust or any material act of dishonesty involving the Company or any of its subsidiaries; (iv) a significant violation by the Participant of the code of conduct of the Company or its subsidiaries of any material policy of the Company or its subsidiaries, or of any statutory or common law duty of loyalty to the Company or its subsidiaries; (v) material breach of any of the terms of the Plan or any Award made under the Plan, or of the terms of any other agreement between the Company or subsidiaries and the Participant; or (vi) other conduct by the Participant that could be expected to be harmful to the business, interests or reputation of the Company.

"**Code**": The U.S. Internal Revenue Code of 1986, as from time to time amended and in effect, or any successor statute as from time to time in effect.

"**Company**": Ultragenyx Pharmaceutical Inc.

"**Compensation Committee**": The Compensation Committee of the Board.

"**Covered Transaction**": Any of (i) a consolidation, merger, or similar transaction or series of related transactions, including a sale or other disposition of stock, in which the Company is not the surviving corporation or which results in the acquisition of all or substantially all of the Company's then outstanding common stock by a single person or entity or by a group of persons and/or entities acting in concert, (ii) a sale or transfer of all or substantially all the Company's assets, or (iii) a dissolution or liquidation of the Company. Where a Covered Transaction involves a tender offer that is reasonably expected to be followed by a merger described in clause (i) (as determined by the Administrator), the Covered Transaction will be deemed to have occurred upon consummation of the tender offer.

"**Eligible Person**" means any Employee who is eligible to receive employment inducement grants under the Nasdaq Listing Rule 5635(c)(4) (or any successor rule or similar rule of any stock exchange on which the Stock is listed).

"**Employee**": Any person who is employed by the Company or an Affiliate.

"**Employment**": A Participant's employment or other service relationship with the Company and the Affiliates, which may include service as a director, consultant or independent contractor. Employment will be deemed to continue, unless the Administrator expressly provides otherwise, so long as the Participant is employed by, or otherwise is providing services in a capacity described in Section 5 to the Company or an Affiliate. If a Participant's employment or other service relationship is with an Affiliate and that entity ceases to be an Affiliate, the Participant's Employment will be deemed to have terminated when the entity ceases to be an Affiliate unless the Participant transfers Employment to the Company or its remaining Affiliates. Notwithstanding the foregoing and the definition of "Affiliate" above, in construing the provisions of any Award relating to the payment of "nonqualified deferred compensation" (subject to Section 409A) upon a termination or cessation of Employment, references to termination or cessation of employment, separation from service, retirement or similar or correlative terms will be construed to require a "separation from service" (as that term is defined in Section 1.409A-1(h) of the Treasury Regulations) from the Company and from all other corporations and trades or businesses, if any, that would be treated as a single "service recipient" with the Company under Section 1.409A-1(h)(3) of the Treasury Regulations. The Company may, but need not, elect in writing, subject to the applicable limitations under Section 409A, any of the special elective rules prescribed in Section 1.409A-1(h) of the Treasury Regulations for purposes of determining whether a "separation from service" has occurred. Any such written election will be deemed a part of the Plan.

"**Exchange Act**": Securities Exchange Act of 1934, as from time to time amended and in effect, or any successor statute as from time to time in effect.

"**Participant**": A person who is granted an Award under the Plan.

"**Performance Award**": An Award subject to Performance Criteria.

"**Performance Criteria**": Specified criteria, other than the mere continuation of Employment or the mere passage of time, the satisfaction of which is a condition for the grant, exercisability, vesting or full enjoyment of an Award. A Performance Criterion and any targets with respect thereto determined by the Administrator need not be based upon an increase, a positive or improved result or avoidance of loss. The Administrator may provide in the case of any Award intended to qualify for such exception that one or more of the Performance Criteria applicable to such Award will be adjusted in an objectively determinable manner to reflect events (for example, but without limitation, acquisitions or dispositions) occurring during the performance period that affect the applicable Performance Criterion or Criteria.

"**Plan**": The Ultragenyx Pharmaceutical Inc. Employment Inducement Plan, as from time to time amended and in effect.

"**Restricted Stock**": Stock subject to restrictions requiring that it be redelivered or offered for sale to the Company if specified conditions are not satisfied.

"**Restricted Stock Unit**": A Stock Unit that is, or as to which the delivery of Stock or cash in lieu of Stock is, subject to the satisfaction of specified performance or other vesting conditions.

"**SAR**": A right entitling the holder upon exercise to receive an amount (payable in cash or in shares of Stock of equivalent value) equal to the excess of the fair market value of the shares of Stock subject to the right over the base value from which appreciation under the SAR is to be measured.

"**Section 409A**": Section 409A of the Code.

"**Securities Act**": U.S. Securities Act of 1933, as from time to time amended and in effect, or any successor statute as from time to time in effect.

"**Stock**": Common stock of the Company, par value $0.001 per share.

"**Stock Option**": An option entitling the holder to acquire shares of Stock upon payment of the exercise price. Each Stock Option granted pursuant to the Plan will be treated as providing by its terms that it is not intended to be an "incentive stock option" within the meaning of Section 422 of the Code.

"**Stock Unit**": An unfunded and unsecured promise, denominated in shares of Stock, to deliver Stock or cash measured by the value of Stock in the future.

"**Unrestricted Stock**": Stock not subject to any restrictions under the terms of the Award.

Name:	[-]
Number of Shares of Stock subject to Stock Option:	[-]
Price Per Share:	$[-]
Date of Grant:	[-]
Vesting Start Date:	[-]

ULTRAGENYX PHARMACEUTICAL INC.
EMPLOYMENT INDUCEMENT PLAN

NON-STATUTORY STOCK OPTION AGREEMENT (EMPLOYEES)

This agreement (this "Agreement") evidences a stock option granted by Ultragenyx Pharmaceutical Inc. (the "Company") to the undersigned (the "Optionee") pursuant to and subject to the terms of the Ultragenyx Pharmaceutical Inc. Employment Inducement Plan (as amended from time to time, the "Plan"), which is incorporated herein by reference.

1. Grant of Stock Option. The Company grants to the Optionee on the date set forth above (the "Date of Grant") an option (the "Stock Option") to purchase, on the terms provided herein and in the Plan, up to the number of shares of Stock set forth above (the "Shares") with an exercise price per Share as set forth above, in each case subject to adjustment pursuant to Section 7(b) of the Plan in respect of transactions occurring after the date hereof.

The Stock Option evidenced by this Agreement is a non-statutory option (that is, an option that does not qualify as an incentive stock option under Section 422 of the Code) and is granted to the Optionee in connection with the Optionee's employment by or service to the Company and its qualifying subsidiaries. For purposes of the immediately preceding sentence, "qualifying subsidiary" means a subsidiary of the Company as to which the Company has a "controlling interest" as described in Treas. Regs. §1.409A-1(b)(5)(iii)(E)(1).

2. Meaning of Certain Terms. Except as otherwise defined herein, all capitalized terms used herein have the same meaning as in the Plan. The following terms have the following meanings:

(a) "Beneficiary" means, in the event of the Optionee's death, the beneficiary named in the written designation (in form acceptable to the Administrator) most recently filed with the Administrator by the Optionee prior to the Optionee's death and not subsequently revoked, or, if there is no such designated beneficiary, the executor or administrator of the Optionee's estate. An effective beneficiary designation will be treated as having been revoked only upon receipt by the Administrator, prior to the Optionee's death, of an instrument of revocation in form acceptable to the Administrator.

(b) "Option Holder" means the Optionee or, if as of the relevant time the Stock Option has passed to a Beneficiary, the Beneficiary.

3. Vesting; Method of Exercise; Treatment of the Stock Option Upon Cessation of Employment.

(a) Vesting. As used herein with respect to the Stock Option or any portion thereof, the term "vest" means to become exercisable and the term "vested" as applied to any outstanding Stock Option means that the Stock Option is then exercisable, subject in each case to the terms of the Plan. Unless earlier terminated, forfeited, relinquished or expired, the Stock Option will vest as to 1/4th of the Shares initially subject to the Stock Option on the first (1st) anniversary of the Date of Grant

(the "Anniversary Date"); thereafter, 1/48th of the Shares initially subject to the Stock Option shall vest on each month as measured by the Anniversary Date. Notwithstanding the foregoing, Shares subject to the Stock Option shall not vest on any vesting date unless the Optionee has remained in continuous Employment from the Date of Grant through such vesting date.

(b) Exercise of the Stock Option. No portion of the Stock Option may be exercised until such portion vests. Each election to exercise any vested portion of the Stock Option will be subject to the terms and conditions of the Plan and shall be in writing, signed by the Option Holder (or in such other form as is acceptable to the Administrator). Each such written exercise election must be received by the Company at its principal office or by such other party as the Administrator may prescribe and be accompanied by payment in full as provided in the Plan. The exercise price may be paid (i) by cash or check acceptable to the Administrator, (ii) to the extent permitted by the Administrator, through a broker-assisted cashless exercise program acceptable to the Administrator, (iii) by such other means, if any, as may be acceptable to the Administrator, or (iv) by any combination of the foregoing permissible forms of payment. In the event that the Stock Option is exercised by a person other than the Optionee, the Company will be under no obligation to deliver shares hereunder unless and until it is satisfied as to the authority of the Option Holder to exercise the Stock Option and compliance with applicable securities laws. The latest date on which the Stock Option or any portion thereof may be exercised will be the 10th anniversary of the Date of Grant (the "Final Exercise Date"); provided, however, if at such time the Optionee is prohibited by applicable law or written Company policy applicable to similarly situated employees from engaging in any open-market sales of Stock, the Final Exercise Date will be automatically extended to thirty (30) days following the date the Optionee is no longer prohibited from engaging in such open-market sales. If the Stock Option is not exercised by the Final Exercise Date the Stock Option or any remaining portion thereof will thereupon immediately terminate.

(c) Treatment of the Stock Option Upon Cessation of Employment. If the Optionee's Employment ceases, the Stock Option, to the extent not already vested will be immediately forfeited, and any vested portion of the Stock Option that is then outstanding will be treated as follows:

(i) Subject to clauses (ii) and (iii) below and Section 4 of this Agreement, the Stock Option, to the extent vested immediately prior to the cessation of the Optionee's Employment, will remain exercisable until the earlier of (A) the date that is three months following the date of such cessation of Employment, or (B) the Final Exercise Date, and except to the extent previously exercised as permitted by this Section 3(c)(i) will thereupon immediately terminate.

(ii) Subject to clauses (iii) below and Section 4 of this Agreement, the Stock Option, to the extent vested immediately prior to the cessation of the Optionee's Employment due to death, will remain exercisable until the earlier of (A) the first anniversary of the Optionee's death or (B) the Final Exercise Date, and except to the extent previously exercised as permitted by this Section 3(c)(ii) will thereupon immediately terminate.

(iii) If the Optionee's Employment is terminated by the Company and its subsidiaries in connection with an act or failure to act constituting Cause (as the Administrator, in its sole discretion, may determine), or such termination occurs in circumstances that in the determination of the Administrator would have entitled the Company and its subsidiaries to terminate the Optionee's Employment for Cause, the Stock Option (whether or not vested) will immediately terminate and be forfeited upon such termination.

4. Forfeiture; Recovery of Compensation.

(a) The Administrator may cancel, rescind, withhold or otherwise limit or restrict the Stock Option at any time if the Optionee is not in compliance with all applicable provisions of this Agreement and the Plan.

(b) By accepting the Stock Option, the Optionee expressly acknowledges and agrees that his or her rights, and those of any permitted transferee of the Stock Option, under the Stock Option to any Stock acquired under the Stock Option or proceeds from the disposition thereof, are subject to Section 6(a)(5) of the Plan (including any successor provision). Nothing in the preceding sentence shall be construed as limiting the general application of Section 8 of this Agreement.

5. Transfer of Stock Option. The Stock Option may not be transferred except as expressly permitted under Section 6(a)(3) of the Plan.

6. Withholding. The exercise of this Stock Option will give rise to "wages" subject to withholding. The Optionee expressly acknowledges and agrees that the Optionee's rights hereunder, including the right to be issued shares upon exercise, are subject to the Optionee promptly paying to the Company in cash (or by such other means as may be acceptable to the Administrator in its discretion) all taxes required to be withheld. No shares will be transferred pursuant to the exercise of this Stock Option unless and until the person exercising this Stock Option has remitted to the Company an amount in cash sufficient to satisfy any federal, state, or local withholding tax requirements, or has made other arrangements satisfactory to the Company with respect to such taxes. The Optionee authorizes the Company and its subsidiaries to withhold such amount from any amounts otherwise owed to the Optionee, but nothing in this sentence shall be construed as relieving the Optionee of any liability for satisfying his or her obligation under the preceding provisions of this Section.

7. Effect on Employment. Neither the grant of the Stock Option, nor the issuance of Shares upon exercise of the Stock Option, will give the Optionee any right to be retained in the employ or service of the Company or any of its Affiliates, affect the right of the Company or any of its Affiliates to discharge or discipline such Optionee at any time, or affect any right of such Optionee to terminate his or her Employment at any time.

8. Provisions of the Plan. This Agreement is subject in its entirety to the provisions of the Plan, which are incorporated herein by reference. A copy of the Plan as in effect on the Date of Grant has been furnished to the Optionee. By exercising all or any part of the Stock Option, the Optionee agrees to be bound by the terms of the Plan and this Agreement. In the event of any conflict between the terms of this Agreement and the Plan, the terms of the Plan shall control.

9. Acknowledgements. The Optionee acknowledges and agrees that (a) this Agreement may be executed in two or more counterparts, each of which shall be an original and all of which together shall constitute one and the same instrument, (b) this agreement may be executed and exchanged using facsimile, portable document format (PDF) or electronic signature, which, in each case, shall constitute an original signature for all purposes hereunder and (c) such signature by the Company will be binding against the Company and will create a legally binding agreement when this Agreement is countersigned by the Optionee.

[The remainder of this page is intentionally left blank]

IN WITNESS WHEREOF, the Company has caused this Agreement to be executed by its duly authorized officer.

ULTRAGENYX PHARMACEUTICAL INC.

By:
Name:
Title:

Dated:

Acknowledged and Agreed:

By:

Name:	[-]
Number of Shares of Stock subject to Stock Option:	[-]
Price Per Share:	$[-]
Date of Grant:	[-]
Vesting Start Date:	[-]

ULTRAGENYX PHARMACEUTICAL INC.
EMPLOYMENT INDUCEMENT PLAN

NON-STATUTORY STOCK OPTION AGREEMENT (EMPLOYEES) (ex-U.S.)

This agreement (this "Agreement") evidences a stock option granted by Ultragenyx Pharmaceutical Inc. (the "Company") to the undersigned (the "Optionee") pursuant to and subject to the terms of the Ultragenyx Pharmaceutical Inc. Employment Inducement Plan (as amended from time to time, the "Plan"), which is incorporated herein by reference.

1. Grant of Stock Option. The Company grants to the Optionee on the date set forth above (the "Date of Grant") an option (the "Stock Option") to purchase, on the terms provided herein and in the Plan, up to the number of shares of Stock set forth above (the "Shares") with an exercise price per Share as set forth above, in each case subject to adjustment pursuant to Section 7(b) of the Plan in respect of transactions occurring after the date hereof.

The Stock Option evidenced by this Agreement is a non-statutory option (that is, an option that does not qualify as an incentive stock option under Section 422 of the Code) and is granted to the Optionee in connection with the Optionee's employment by or service to the Company and its qualifying subsidiaries. For purposes of the immediately preceding sentence, "qualifying subsidiary" means a subsidiary of the Company as to which the Company has a "controlling interest" as described in Treas. Regs. §1.409A-1(b)(5)(iii)(E)(1).

2. Meaning of Certain Terms. Except as otherwise defined herein, all capitalized terms used herein have the same meaning as in the Plan. The following terms have the following meanings:

(a)"Beneficiary" means, in the event of the Optionee's death, the beneficiary named in the written designation (in form acceptable to the Administrator) most recently filed with the Administrator by the Optionee prior to the Optionee's death and not subsequently revoked, or, if there is no such designated beneficiary, the executor or administrator of the Optionee's estate. An effective beneficiary designation will be treated as having been revoked only upon receipt by the Administrator, prior to the Optionee's death, of an instrument of revocation in form acceptable to the Administrator.

(b)"Option Holder" means the Optionee or, if as of the relevant time the Stock Option has passed to a Beneficiary, the Beneficiary.

3. Vesting; Method of Exercise; Treatment of the Stock Option Upon Cessation of Employment.

(a)Vesting. As used herein with respect to the Stock Option or any portion thereof, the term "vest" means to become exercisable and the term "vested" as applied to any outstanding Stock Option means that the Stock Option is then exercisable, subject in each case to the terms of the Plan. Unless earlier terminated, forfeited, relinquished or expired, the Stock Option will vest as to 1/4th of the Shares initially subject to the Stock Option on the first (1st) anniversary of the Date of Grant (the "Anniversary Date"); thereafter, 1/48th of the Shares initially subject to the Stock Option shall vest on each month as measured by the Anniversary Date. Notwithstanding the foregoing, Shares subject to the Stock Option shall not vest on any vesting date unless the Optionee has remained in continuous Employment from the Date of Grant through such vesting date.

(b)Exercise of the Stock Option. No portion of the Stock Option may be exercised until such portion vests. Each election to exercise any vested portion of the Stock Option will be subject to the terms and conditions of the Plan and shall be in writing, signed by the Option Holder (or in such other form as is acceptable to the Administrator). Each such written exercise election must be received by the Company at its principal office or by such other party as the Administrator may prescribe and be accompanied by payment in full as provided in the Plan. The exercise price may be paid (i) by cash or check acceptable to the Administrator, (ii) to the extent permitted by the Administrator, through a broker-assisted cashless exercise program acceptable to the Administrator, (iii) by such other means, if any, as may be acceptable to the Administrator, or (iv) by any combination of the foregoing permissible forms of payment. In the event that the Stock Option is exercised by a person other than the Optionee, the Company will be under no obligation to deliver shares hereunder unless and until it is satisfied as to the authority of the Option Holder to exercise the Stock Option and compliance with applicable securities laws. The latest date on which the Stock Option or any portion thereof may be exercised will be the 10th anniversary of the Date of Grant (the "Final Exercise Date"); provided, however, if at such time the Optionee is prohibited by applicable law or written Company policy applicable to similarly situated employees from engaging in any open-market sales of Stock, the Final Exercise Date will be automatically extended to thirty (30) days following the date the Optionee is no longer prohibited from engaging in such open-market sales. If the Stock Option is not exercised by the Final Exercise Date the Stock Option or any remaining portion thereof will thereupon immediately terminate.

(c)Treatment of the Stock Option Upon Cessation of Employment. If the Optionee's Employment ceases, the Stock Option, to the extent not already vested will be immediately forfeited, and any vested portion of the Stock Option that is then outstanding will be treated as follows:

(i) Subject to clauses (ii) and (iii) below and Section 4 of this Agreement, the Stock Option, to the extent vested immediately prior to the cessation of the Optionee's Employment, will remain exercisable until the earlier of (A) the date that is three months following the date of such cessation of Employment, or (B) the Final Exercise Date, and except to the extent previously exercised as permitted by this Section 3(c)(i) will thereupon immediately terminate.

(ii) Subject to clauses (iii) below and Section 4 of this Agreement, the Stock Option, to the extent vested immediately prior to the cessation of the Optionee's Employment due to death, will remain exercisable until the earlier of (A) the first anniversary of the Optionee's death or (B) the Final Exercise Date, and except to the extent previously exercised as permitted by this Section 3(c)(ii) will thereupon immediately terminate.

(iii) If the Optionee's Employment is terminated by the Company and its subsidiaries in connection with an act or failure to act constituting Cause (as the Administrator, in its sole discretion, may determine), or such termination occurs in circumstances that in the determination of the Administrator would have entitled the Company and its subsidiaries to terminate the Optionee's Employment for Cause, the Stock Option (whether or not vested) will immediately terminate and be forfeited upon such termination.

4. Forfeiture; Recovery of Compensation.

(a)The Administrator may cancel, rescind, withhold or otherwise limit or restrict the Stock Option at any time if the Optionee is not in compliance with all applicable provisions of this Agreement and the Plan.

(b)By accepting the Stock Option, the Optionee expressly acknowledges and agrees that his or her rights, and those of any permitted transferee of the Stock Option, under the Stock Option to any Stock acquired under the Stock Option or proceeds from the disposition thereof, are subject to Section 6(a)(5) of the Plan (including any successor provision). Nothing in the preceding sentence shall be construed as limiting the general application of Section 8 of this Agreement.

5. Transfer of Stock Option. The Stock Option may not be transferred except as expressly permitted under Section 6(a)(3) of the Plan.

6. Withholding. The exercise of this Stock Option will give rise to "wages" subject to withholding. The Optionee expressly acknowledges and agrees that the Optionee's rights hereunder, including the right to be issued shares upon exercise, are subject to the Optionee promptly paying to the Company in cash (or by such other means as may be acceptable to the Administrator in its discretion) all taxes required to be withheld (including, without limitation, any social security, healthcare or mandatory retirement contributions and similar taxes or employee contributions). No shares will be transferred pursuant to the exercise of this Stock Option unless and until the person exercising this Stock Option has remitted to the Company an amount in cash sufficient to satisfy any federal, state, local, or foreign withholding tax requirements, or has made other arrangements satisfactory to the Company with respect to such taxes. The Optionee authorizes the Company and its subsidiaries to withhold such amount from any amounts otherwise owed to the Optionee, but nothing in this sentence shall be construed as relieving the Optionee of any liability for satisfying his or her obligation under the preceding provisions of this Section.

7. Effect on Employment. Neither the grant of the Stock Option, nor the issuance of Shares upon exercise of the Stock Option, will give the Optionee any right to be retained in the employ or service of the Company or any of its Affiliates, affect the right of the Company or any of its Affiliates to discharge or discipline such Optionee at any time, or affect any right of such Optionee to terminate his or her Employment at any time.

8. Data Protection. With his or her participation to the Plan, the Optionee expressly agrees to the collection, process, transfer and storage of his or her personal and professional data by the Company, by any mean whatsoever, to the extent they are strictly necessary for the administration of the Plan. The Company may share the collected information with its subsidiaries or its affiliates, with its trusts, accountants, brokers, third party directors or any other person taking control of the Company or its subsidiaries or business units. The Company's department of human resources is designated as data controller in connection with the Plan. The transfer of the Participant's data outside of the European Union is designed to ensure the implementation of the Plan. All data thus collected shall only be stored for such period of time as strictly necessary to implement the Plan, and in no event shall the Company store these data for more than 3 years after the termination of employment of an Optionee. Pursuant to applicable laws and regulations, the Optionee is granted the right to access, correct and oppose, for legitimate reasons, the collection of his or her personal or professional data in connection with the Plan. The Optionee is hereby informed that the collection and process, as well as the transfer outside of the European Union, of his or her personal or professional data gave rise to the necessary declarations and authorizations, as the case may be, by the national authorities having jurisdiction.

9. Provisions of the Plan. This Agreement is subject in its entirety to the provisions of the Plan, which are incorporated herein by reference. A copy of the Plan as in effect on the Date of Grant has been furnished to the Optionee. By exercising all or any part of the Stock Option, the Optionee agrees to be bound by the terms of the Plan and this Agreement. In the event of any conflict between the terms of this Agreement and the Plan, the terms of the Plan shall control.

10. Acknowledgements. The Optionee acknowledges and agrees that (a) this Agreement may be executed in two or more counterparts, each of which shall be an original and all of which together shall constitute one and the same instrument, (b) this agreement may be executed and exchanged using facsimile, portable document format (PDF) or electronic signature, which, in each case, shall constitute an original signature for all purposes hereunder and (c) such signature by the Company will be binding against the Company and will create a legally binding agreement when this Agreement is countersigned by the Optionee.

[The remainder of this page is intentionally left blank]

IN WITNESS WHEREOF, the Company has caused this Agreement to be executed by its duly authorized officer.

ULTRAGENYX PHARMACEUTICAL INC.

By:
Name:
Title:

Dated:

Acknowledged and Agreed:

By:

Exhibit 10.46

Name:	**[-]**
Number of Restricted Stock Units subject to Award:	**[-]**
Date of Grant:	**[-]**

ULTRAGENYX PHARMACEUTICAL INC.

EMPLOYMENT INDUCEMENT PLAN

RESTRICTED STOCK UNIT AGREEMENT (EMPLOYEES)

This agreement (this "Agreement") evidences an award (the "Award") of restricted stock units (the "Restricted Stock Units") granted by Ultragenyx Pharmaceutical Inc. (the "Company") to the undersigned (the "Grantee") pursuant to and subject to the terms of the Ultragenyx Pharmaceutical Inc. Employment Inducement Plan (as amended from time to time, the "Plan"), which is incorporated herein by reference.

1. Grant of Restricted Stock Units. The Company grants to the Grantee on the date set forth above (the "Date of Grant") an award consisting of the right to receive on the terms provided herein and in the Plan, one share of Stock with respect to each Restricted Stock Unit forming part of the Award, in each case, subject to adjustment pursuant to Section 7(b) of the Plan in respect of transactions occurring after the date hereof.

2. Meaning of Certain Terms. Except as otherwise defined herein, all capitalized terms used herein have the same meaning as in the Plan.

3. Vesting. Unless earlier terminated, forfeited, relinquished or expired, the Restricted Stock Units shall vest as follows: 1/4th of the underlying shares shall vest on the first (1st) anniversary of the Date of Grant (the "Anniversary Date"); thereafter, 25% of the underlying shares shall vest each year as measured from the Anniversary Date.

4. Delivery of Stock. The Company shall deliver to the Grantee as soon as practicable upon the vesting of the Restricted Stock Units or any portion thereof, but in all events no later than March 15th of the year following the year in which such Restricted Stock Units vest, one share of Stock with respect to each such vested Restricted Stock Unit, subject to the terms of the Plan and this Agreement.

5. Dividends; Other Rights. The Award shall not be interpreted to bestow upon the Grantee any equity interest or ownership in the Company or any Affiliate prior to the date on which the Company delivers shares of Stock to the Grantee (if any). The Grantee is not entitled to vote any shares of Stock by reason of the granting of this Award or to receive or be credited with any dividends declared and payable on any share of Stock prior to the date on which any such share is delivered to the Grantee hereunder. The Grantee shall have the rights of a shareholder only as to those shares of Stock, if any, that are actually delivered under this Award.

6. Forfeiture; Recovery of Compensation.

(a) The Administrator may cancel, rescind, withhold or otherwise limit or restrict the Award at any time if the Grantee is not in compliance with all applicable provisions of this Agreement and the Plan.

(b) By accepting the Award the Grantee expressly acknowledges and agrees that his or her rights, and those of any permitted transferee of the Award, under the Award to any Stock acquired under the Award or proceeds from the

disposition thereof, are subject to Section 6(a)(5) of the Plan (including any successor provision). Nothing in the preceding sentence shall be construed as limiting the general application of Section 10 of this Agreement.

7. Nontransferability. Neither the Award nor the Restricted Stock Units may be transferred except as expressly permitted under Section 6(a)(3) of the Plan.

8. Certain Tax Matters.

(a) The Grantee expressly acknowledges and agrees that the Grantee's rights hereunder, including the right to be issued shares of Stock upon the vesting of the Restricted Stock Units (or any portion thereof), are subject to the Grantee's promptly paying, or in respect of any later requirement of withholding being liable promptly to pay at such time as such withholdings are due, to the Company in cash (or by such other means as may be acceptable to the Administrator in its discretion) all taxes required to be withheld, if any (the "Tax Withholding Obligation"). No shares of Stock will be transferred pursuant to the vesting of the Restricted Stock Units (or any portion thereof) unless and until the Grantee or the person then holding the Award has remitted to the Company an amount in cash sufficient to satisfy any federal, state, or local withholding tax requirements then due and has committed (and by accepting this Award the Grantee shall be deemed to have committed) to pay in cash all tax withholdings required at any later time in respect of the transfer of such shares, or has made other arrangements satisfactory to the Company with respect to such taxes. The Grantee also authorizes the Company and its subsidiaries to withhold such amount from any amounts otherwise owed to the Grantee, but nothing in this sentence shall be construed as relieving the Grantee of any liability for satisfying his or her obligations under the preceding provisions of this Section.

(b) The Grantee expressly acknowledges that the Grantee's acceptance of this Agreement constitutes the Grantee's instruction and authorization to the Company and any brokerage firm determined acceptable to the Company for such purpose to sell on the Grantee's behalf a whole number of shares from those shares of Stock issuable to the Grantee as the Company determines to be appropriate to generate cash proceeds sufficient to satisfy the applicable Tax Withholding Obligation, and to transfer the proceeds from the sale of such Stock from the Grantee's securities account established with the brokerage service provider for the settlement of the Grantee's vested Restricted Stock Units to any account held in the name of the Company. Such shares will be sold on the date of vesting or as soon thereafter as practicable. Grantee will be responsible for all brokers' fees and other costs of sale, which fees and costs may be deducted from the proceeds of the foregoing sale of Stock, and Grantee agrees to indemnify and hold the Company and any brokerage firm selling such Stock harmless from any losses, costs, damages, or expenses relating to any such sale. To the extent the proceeds of such sale exceed Grantee's Tax Withholding Obligation, such excess cash will be deposited into the securities account established with the brokerage service provider for the settlement of Grantee's vested Restricted Stock Units. Grantee acknowledges that the Company or its designee is under no obligation to arrange for such sale at any particular price, and that the proceeds of any such sale may not be sufficient to satisfy Grantee's Tax Withholding Obligation. Accordingly, Grantee agrees to pay to the Company as soon as practicable, including through additional payroll withholding, any amount of the Tax Withholding Obligation that is not satisfied by the sale of shares described above. Unless otherwise authorized by the Administrator in its sole discretion, the sale of Stock will be the primary method used by the Company to satisfy the applicable Tax Withholding Obligation.

(c) The Grantee expressly acknowledges that because this Award consists of an unfunded and unsecured promise by the Company to deliver Stock in the future, subject to the terms hereof, it is not possible to make a so-called "83(b) election" with respect to the Award.

9. Effect on Employment. Neither the grant of the Award, nor the issuance of Shares upon vesting of the Award, will give the Grantee any right to be retained in the employ or service of the Company or any of its Affiliates, affect the right of the Company or any of its Affiliates to discharge or discipline such Grantee at any time, or affect any right of such Grantee to terminate his or her Employment at any time.

10. Provisions of the Plan. This Agreement is subject in its entirety to the provisions of the Plan, which are incorporated herein by reference. A copy of the Plan as in effect on the Date of Grant has been furnished to the Grantee. By accepting the Award, the Grantee agrees to be bound by the terms of the Plan and this Agreement. In the event of any conflict between the terms of this Agreement and the Plan, the terms of the Plan shall control.

11. Acknowledgments. The Grantee acknowledges and agrees that (a) this Agreement may be executed in two or more counterparts, each of which shall be an original and all of which together shall constitute one and the same instrument, (b) this agreement may be executed and exchanged using facsimile, portable document format (PDF) or electronic signature, which, in each case, shall constitute an original signature for all purposes hereunder and (c) such signature by the Company will be binding against the Company and will create a legally binding agreement when this Agreement is countersigned by the Grantee.

[The remainder of this page is intentionally left blank.]

IN WITNESS WHEREOF, the Company has caused this Agreement to be executed by its duly authorized officer.

ULTRAGENYX PHARMACEUTICAL INC.

By:
Name:
Title:

Dated:

Acknowledged and Agreed:

By:

Exhibit 10.47

Name:	**[-]**
Number of Restricted Stock Units subject to Award:	**[-]**
Date of Grant:	**[-]**

ULTRAGENYX PHARMACEUTICAL INC.

EMPLOYMENT INDUCEMENT PLAN

RESTRICTED STOCK UNIT AGREEMENT (EMPLOYEES) (ex-U.S.)

This agreement (this "Agreement") evidences an award (the "Award") of restricted stock units (the "Restricted Stock Units") granted by Ultragenyx Pharmaceutical Inc. (the "Company") to the undersigned (the "Grantee") pursuant to and subject to the terms of the Ultragenyx Pharmaceutical Inc. Employment Inducement Plan (as amended from time to time, the "Plan"), which is incorporated herein by reference.

1. Grant of Restricted Stock Units. The Company grants to the Grantee on the date set forth above (the "Date of Grant") an award consisting of the right to receive on the terms provided herein and in the Plan, one share of Stock with respect to each Restricted Stock Unit forming part of the Award, in each case, subject to adjustment pursuant to Section 7(b) of the Plan in respect of transactions occurring after the date hereof.

2. Meaning of Certain Terms. Except as otherwise defined herein, all capitalized terms used herein have the same meaning as in the Plan.

3. Vesting. Unless earlier terminated, forfeited, relinquished or expired, the Restricted Stock Units shall vest as follows: 1/4th of the underlying shares shall vest on the first (1st) anniversary of the Date of Grant (the "Anniversary Date"); thereafter, 25% of the underlying shares shall vest each year as measured from the Anniversary Date.

4. Delivery of Stock. The Company shall deliver to the Grantee as soon as practicable upon the vesting of the Restricted Stock Units or any portion thereof, but in all events no later than March 15th of the year following the year in which such Restricted Stock Units vest, one share of Stock with respect to each such vested Restricted Stock Unit, subject to the terms of the Plan and this Agreement.

5. Dividends; Other Rights. The Award shall not be interpreted to bestow upon the Grantee any equity interest or ownership in the Company or any Affiliate prior to the date on which the Company delivers shares of Stock to the Grantee (if any). The Grantee is not entitled to vote any shares of Stock by reason of the granting of this Award or to receive or be credited with any dividends declared and payable on any share of Stock prior to the date on which any such share is delivered to the Grantee hereunder. The Grantee shall have the rights of a shareholder only as to those shares of Stock, if any, that are actually delivered under this Award.

6. Forfeiture; Recovery of Compensation.

(a) The Administrator may cancel, rescind, withhold or otherwise limit or restrict the Award at any time if the Grantee is not in compliance with all applicable provisions of this Agreement and the Plan.

(b) By accepting the Award the Grantee expressly acknowledges and agrees that his or her rights, and those of any permitted transferee of the Award, under the Award to any Stock acquired under the Award or proceeds from the

disposition thereof, are subject to Section 6(a)(5) of the Plan (including any successor provision). Nothing in the preceding sentence shall be construed as limiting the general application of Section 10 of this Agreement.

7. Nontransferability. Neither the Award nor the Restricted Stock Units may be transferred except as expressly permitted under Section 6(a)(3) of the Plan.

8. Certain Tax Matters.

(a) The Grantee expressly acknowledges and agrees that the Grantee's rights hereunder, including the right to be issued shares of Stock upon the vesting of the Restricted Stock Units (or any portion thereof), are subject to the Grantee's promptly paying, or in respect of any later requirement of withholding being liable promptly to pay at such time as such withholdings are due, to the Company in cash (or by such other means as may be acceptable to the Administrator in its discretion) all taxes required to be withheld, if any (including, without limitation, any social security, healthcare or mandatory retirement contributions and similar taxes or employee contributions). No shares of Stock will be transferred pursuant to the vesting of the Restricted Stock Units (or any portion thereof) unless and until the Grantee or the person then holding the Award has remitted to the Company an amount in cash sufficient to satisfy any federal, state, local, or foreign withholding tax requirements then due and has committed (and by accepting this Award the Grantee shall be deemed to have committed) to pay in cash all tax withholdings required at any later time in respect of the transfer of such shares, or has made other arrangements satisfactory to the Company with respect to such taxes. The Grantee also authorizes the Company and its subsidiaries to withhold such amount from any amounts otherwise owed to the Grantee, but nothing in this sentence shall be construed as relieving the Grantee of any liability for satisfying his or her obligations under the preceding provisions of this Section.

(b) The Grantee expressly acknowledges that because this Award consists of an unfunded and unsecured promise by the Company to deliver Stock in the future, subject to the terms hereof, it is not possible to make a so-called "83(b) election" with respect to the Award.

9. Effect on Employment. Neither the grant of the Award, nor the issuance of Shares upon vesting of the Award, will give the Grantee any right to be retained in the employ or service of the Company or any of its Affiliates, affect the right of the Company or any of its Affiliates to discharge or discipline such Grantee at any time, or affect any right of such Grantee to terminate his or her Employment at any time.

10. Data Protection. With his or her participation to the Plan, the Optionee expressly agrees to the collection, process, transfer and storage of his or her personal and professional data by the Company, by any mean whatsoever, to the extent they are strictly necessary for the administration of the Plan. The Company may share the collected information with its subsidiaries or its affiliates, with its trusts, accountants, brokers, third party directors or any other person taking control of the Company or its subsidiaries or business units. The Company's department of human resources is designated as data controller in connection with the Plan. The transfer of the Participant's data outside of the European Union is designed to ensure the implementation of the Plan. All data thus collected shall only be stored for such period of time as strictly necessary to implement the Plan, and in no event shall the Company store these data for more than 3 years after the termination of employment of an Optionee. Pursuant to applicable laws and regulations, the Optionee is granted the right to access, correct and oppose, for legitimate reasons, the collection of his or her personal or professional data in connection with the Plan. The Optionee is hereby informed that the collection and process, as well as the transfer outside of the European Union, of his or her personal or professional data gave rise to the necessary declarations and authorizations, as the case may be, by the national authorities having jurisdiction.

11. Provisions of the Plan. This Agreement is subject in its entirety to the provisions of the Plan, which are incorporated herein by reference. A copy of the Plan as in effect on the Date of Grant has been furnished to the Grantee. By accepting the Award, the Grantee agrees to be bound by the terms of the Plan and this Agreement. In the event of any conflict between the terms of this Agreement and the Plan, the terms of the Plan shall control.

12. Acknowledgments. The Grantee acknowledges and agrees that (a) this Agreement may be executed in two or more counterparts, each of which shall be an original and all of which together shall constitute one and the same instrument, (b) this agreement may be executed and exchanged using facsimile, portable document format (PDF) or electronic signature, which, in each case, shall constitute an original signature for all purposes hereunder and (c) such signature by the Company will be binding against the Company and will create a legally binding agreement when this Agreement is countersigned by the Grantee.

[The remainder of this page is intentionally left blank.]

IN WITNESS WHEREOF, the Company has caused this Agreement to be executed by its duly authorized officer.

ULTRAGENYX PHARMACEUTICAL INC.

By:
Name:
Title:

Dated:

Acknowledged and Agreed:

By:

LEASE AGREEMENT

THIS LEASE AGREEMENT (this "**Lease**") is made this 15th day of December, 2019, between **ARE-SAN FRANCISCO NO. 17, LLC**, a Delaware limited liability company ("**Landlord**"), and **ULTRAGENYX PHARMACEUTICAL INC.**, a Delaware corporation ("**Tenant**").

Building: 7000 Shoreline Court, South San Francisco, California

Premises: That portion of the second floor of the Building containing approximately 10,781 rentable square feet, as determined by Landlord, as shown on **Exhibit A**.

Project: The real property on which the Building in which the Premises are located, together with all improvements thereon and appurtenances thereto as described on **Exhibit B**.

Base Rent: $5.05 per rentable square foot of the Premises per month, subject to adjustment pursuant to Section 4 hereof.

Rentable Area of Premises: 10,781 sq. ft.

Rentable Area of Project: 139,708 sq. ft. **Tenant's Share of Operating Expenses:** 7.72%

Security Deposit: $108,888.10

Rent Adjustment Percentage: 3.0%

Base Term: Beginning on the Commencement Date and ending 60 months from the first day of the first full month after the Commencement Date (as defined in Section 2) hereof. For clarity, if the Commencement Date occurs on the first day of a month, the expiration of the Base Term shall be measured from that date. If the Commencement Date occurs on a day other than the first day of a month, the expiration of the Base Term shall be measured from the first day of the following month.

Permitted Use: Research and development laboratory, GMP manufacturing, related office and other related uses consistent with the character of the Project and otherwise in compliance with the provisions of Section 7 hereof.

Address for Rent Payment:
P.O. Box 975383
Dallas, TX 75397-5383

Landlord's Notice Address:
26 North Euclid Avenue
Pasadena, CA 91101
Attention: Corporate Secretary

Tenant's Notice Address:
7000 Shoreline Court, Suite 102
South San Francisco, California 94080
Attention: Lease Administrator

The following Exhibits and Addenda are attached hereto and incorporated herein by this reference:

[X] **EXHIBIT A** - PREMISES DESCRIPTION
[X] **EXHIBIT B** - DESCRIPTION OF PROJECT
[X] **EXHIBIT C** - WORK LETTER
[X] **EXHIBIT D** - COMMENCEMENT DATE
[X] **EXHIBIT E** - RULES AND REGULATIONS
[X] **EXHIBIT F** - TENANT'S PERSONAL PROPERTY
[X] **EXHIBIT G** - ROFR SPACE

1. **Lease of Premises**. Upon and subject to all of the terms and conditions hereof, Landlord hereby leases the Premises to Tenant and Tenant hereby leases the Premises from Landlord. The portions of the Project which are for the non-exclusive use of tenants of the Project are collectively referred to herein as the "**Common Areas**." Tenant shall have the non-exclusive right during the Term to use the Common Areas along with others having the right to use the Common Areas. Landlord reserves the right to modify Common Areas, provided that such modifications do not materially adversely affect Tenant's use of the Premises for the Permitted Use. From and after the Commencement Date through the expiration of the Term, Tenant shall have access to the Building and the Premises 24 hours a day, 7 days a week, except in the case of emergencies, as the result of Legal Requirements, the performance by Landlord of any installation, maintenance or repairs, or any other temporary interruptions, and otherwise subject to the terms of this Lease.

2. **Delivery; Acceptance of Premises; Commencement Date**. The "**Commencement Date**" shall be the earlier to occur of (i) April 1, 2020, or (ii) if the Existing Lease (as defined below) terminates prior to March 31, 2020, the day immediately following the date that the Existing Lease terminates. Upon request of Landlord, Tenant shall execute and deliver a written acknowledgment of the Commencement Date and the expiration date of the Term when such are established in the form of the "Acknowledgement of Commencement Date" attached to this Lease as **Exhibit D**; provided, however, Tenant's failure to execute and deliver such acknowledgment shall not affect Landlord's rights hereunder. The "**Term**" of this Lease shall be the Base Term, as defined above on the first page of this Lease and the Extension Term which Tenant may elect pursuant to Section 40 hereof.

Landlord and Tenant acknowledge that Tenant occupied the Premises prior to the Commencement Date pursuant to that certain sub-sublease agreement between Iconic Therapeutics, Inc. ("**Iconic**"), and Tenant (as the same has been or may in the future be amended, the "**Iconic Sub-Sublease**"). The Iconic Sublease is subject to the existing lease between Landlord and the existing tenant of the Premises dated as of September 14, 2010 (as the same has been and may in the future be amended, the "**Existing Lease**").

Except as set forth in the Work Letter or as otherwise expressly set forth in this Lease: (i) Tenant shall accept the Premises in their condition as of the Commencement Date; (ii) Landlord shall have no obligation for any defects in the Premises; and (iii) Tenant's taking possession of the Premises shall be conclusive evidence that Tenant accepts the Premises and that the Premises were in good condition at the time possession was taken. Any occupancy of the Premises by Tenant before the Commencement Date shall be subject to all of the terms and conditions of this Lease, including the obligation to pay Base Rent and Operating Expenses.

For the period of 90 consecutive days after the Commencement Date, Landlord shall, at its sole cost and expense (which shall not constitute an Operating Expense), be responsible for any repairs that are required to be made to the Building Systems (as defined in Section 13) serving the Premises, unless Tenant or any Tenant Party was responsible for the cause of such repair, in which case Tenant shall pay the cost.

Tenant agrees and acknowledges that neither Landlord nor any agent of Landlord has made any representation or warranty with respect to the condition of all or any portion of the Premises or the Project, and/or the suitability of the Premises or the Project for the conduct of Tenant's business, and Tenant waives any implied warranty that the Premises or the Project are suitable for the Permitted Use. This Lease constitutes the complete agreement of Landlord and Tenant with respect to the subject matter hereof and supersedes any and all prior representations, inducements, promises, agreements, understandings and negotiations which are not contained herein. Landlord in executing this Lease does so in reliance upon Tenant's representations, warranties, acknowledgments and agreements contained herein.

3. **Rent**.

(a) **Base Rent**. The first month's Base Rent shall be due and payable on delivery of an executed copy of this Lease to Landlord. Tenant shall pay to Landlord in advance, without demand, abatement, deduction or set-off, monthly installments of Base Rent on or before the first day of each calendar month during the Term hereof, in lawful money of the United States of America, at the office of Landlord for payment of Rent set forth above, or to such other person or at such other place as Landlord may from time to time designate in writing. Payments of Base Rent for any fractional calendar month shall be prorated. The obligation of Tenant to pay Base Rent and other sums to Landlord

and the obligations of Landlord under this Lease are independent obligations. Tenant shall have no right at any time to abate, reduce, or set-off any Rent (as defined in Section 5) due hereunder except for any abatement as may be expressly provided in this Lease.

(b) **Additional Rent**. In addition to Base Rent, Tenant agrees to pay to Landlord as additional rent ("**Additional Rent**"): (i) commencing on the Commencement Date, Tenant's Share of "Operating Expenses" (as defined in Section 5), and (ii) any and all other amounts Tenant assumes or agrees to pay under the provisions of this Lease, including, without limitation, any and all other sums that may become due by reason of any default of Tenant or failure to comply with the agreements, terms, covenants and conditions of this Lease to be performed by Tenant, after any applicable notice and cure period.

4. **Base Rent Adjustments**. Base Rent shall be increased on each annual anniversary of the first day of the first full month during the Term of this Lease (each an "**Adjustment Date**") by multiplying the Base Rent payable immediately before such Adjustment Date by the Rent Adjustment Percentage and adding the resulting amount to the Base Rent payable immediately before such Adjustment Date. Base Rent, as so adjusted, shall thereafter be due as provided herein. Base Rent adjustments for any fractional calendar month shall be prorated.

5. **Operating Expense Payments**. Landlord shall deliver to Tenant a written estimate of Operating Expenses for each calendar year during the Term (the "**Annual Estimate**"), which may be revised by Landlord from time to time during such calendar year. Commencing on the Commencement Date and continuing thereafter on the first day of each month during the Term, Tenant shall pay Landlord an amount equal to 1/12th of Tenant's Share of the Annual Estimate. Payments for any fractional calendar month shall be prorated.

The term "**Operating Expenses**" means all costs and expenses of any kind or description whatsoever incurred or accrued each calendar year by Landlord with respect to the Project (including, without duplication, (v) Taxes (as defined in Section 9), (w) transportation services, (x) the cost of Common Area amenities (including, without limitation, any subsidies which Landlord may provide in connection with any such Common Area amenities) now or hereafter serving the Project, (y) capital repairs, improvements and replacements (not including capital repairs, improvements or replacements made for the sole benefit of another tenant of the Project) amortized over the useful life of such capital repairs, improvements and replacements (as determined by Landlord taking into account all relevant factors including, but not limited, the hours of operation of the Building and its use for laboratory/office purposes), and (z) the costs of Landlord's third party property manager (not to exceed 3% of Base Rent) or, if there is no third party property manager, administration rent in the amount of 3% of Base Rent), excluding only:

(a) the original construction costs of the Project and renovation prior to the date of this Lease and costs of correcting defects in such original construction or renovation;

(b) capital expenditures for expansion or reconfiguration of the Project;

(c) interest, principal or any other payments under any Mortgage (as defined in Section 27) debts of Landlord, financing costs and amortization of funds borrowed by Landlord, whether secured or unsecured and all payments of rent (but not taxes or operating expenses) under any ground lease or other underlying lease of all or any portion of the Project;

(d) depreciation of the Project (except for capital improvements, the cost of which are includable in Operating Expenses (and as amortized pursuant to this Section 5));

(e) advertising, marketing, legal and space planning expenses and leasing commissions and other costs and expenses incurred in procuring and leasing space to tenants for the Project, including any leasing office maintained in the Project, free rent and construction allowances for tenants;

(f) legal and other expenses incurred in the negotiation or enforcement of leases;

(g) completing, fixturing, improving, renovating, painting, redecorating or other work, which Landlord pays for or performs for other tenants within their premises, and costs of correcting defects in such work;

(h) costs to be reimbursed by other tenants of the Project or Taxes to be paid directly by Tenant or other tenants of the Project, whether or not actually paid;

(i) salaries, wages, benefits and other compensation paid to (i) personnel of Landlord or its agents or contractors above the position of the person, regardless of title, who has day-to-day management responsibility for the Project or (ii) officers and employees of Landlord or its affiliates who are not assigned in whole or in part to the operation, management, maintenance or repair of the Project; provided, however, that with respect to any such person who does not devote substantially all of his or her employed time to the Project, the salaries, wages, benefits and other compensation of such person shall be prorated to reflect time spent on matters related to operating, managing, maintaining or repairing the Project in comparison to the time spent on matters unrelated to operating, managing, maintaining or repairing the Project;

(j) general organizational, administrative and overhead costs relating to maintaining Landlord's existence, either as a corporation, partnership, or other entity, including general corporate, legal and accounting expenses;

(k) costs (including attorneys' fees and costs of settlement, judgments and payments in lieu thereof) incurred in connection with disputes with tenants, other occupants, or prospective tenants, and costs and expenses, including legal fees, incurred in connection with negotiations or disputes with employees, consultants, management agents, leasing agents, purchasers or mortgagees of the Building;

(l) costs incurred by Landlord due to the violation by Landlord, its employees, agents or contractors or any tenant of the terms and conditions of any lease of space in the Project or any Legal Requirement (as defined in Section 7);

(m) penalties, fines or interest incurred as a result of Landlord's inability or failure to make payment of Taxes and/or to file any tax or informational returns when due, or from Landlord's failure to make any payment of Taxes required to be made by Landlord hereunder before delinquency;

(n) overhead and profit increment paid to Landlord or to subsidiaries or affiliates of Landlord for goods and/or services in or to the Project to the extent the same exceeds the costs of such goods and/or services rendered by unaffiliated third parties on a competitive basis;

(o) costs of Landlord's charitable or political contributions, or of fine art maintained at the Project;

(p) costs in connection with services (including electricity), items or other benefits of a type which are not standard for the Project and which are not available to Tenant without specific charges therefor, but which are provided to another tenant or occupant of the Project, whether or not such other tenant or occupant is specifically charged therefor by Landlord;

(q) costs incurred in the sale or refinancing of the Project;

(r) net income taxes of Landlord or the owner of any interest in the Project, franchise, capital stock, gift, estate or inheritance taxes or any federal, state or local documentary taxes imposed against the Project or any portion thereof or interest therein;

(s) costs arising from the gross negligence, intentional misconduct or fraud of Landlord or Landlord's officers, directors, employees, managers or agents;

(t) property management fees except as expressly set forth above;

(u) any costs incurred to remove, study, test or remediate, or otherwise related to the presence of Hazardous Materials in or about the Building or the Project for which Tenant is not responsible under this Lease;

(v) the cost of installing or upgrading any utility metering for any part of the Project;

(w) any expenses otherwise includable within Operating Expenses to the extent actually reimbursed by insurance policies required to be maintained by Landlord in accordance with Section 17; and

(x) any expenses otherwise includable within Operating Expenses to the extent actually reimbursed by persons other than tenants of the Project under leases for space in the Project.

Within 90 days after the end of each calendar year (or such longer period as may be reasonably required), Landlord shall furnish to Tenant a statement (an "**Annual Statement**") showing in reasonable detail: (a) the total and Tenant's Share of actual Operating Expenses for the previous calendar year, and (b) the total of Tenant's payments in respect of Operating Expenses for such year. If Tenant's Share of actual Operating Expenses for such year exceeds Tenant's payments of Operating Expenses for such year, the excess shall be due and payable by Tenant as Rent within 30 days after delivery of such Annual Statement to Tenant. If Tenant's payments of Operating Expenses for such year exceed Tenant's Share of actual Operating Expenses for such year Landlord shall pay the excess to Tenant within 30 days after delivery of such Annual Statement, except that after the expiration, or earlier termination of the Term or if Tenant is delinquent in its obligation to pay Rent, Landlord shall pay the excess to Tenant after deducting all other amounts due Landlord. Landlord's and Tenant's obligations to pay any overpayments or deficiencies due pursuant to this paragraph shall survive the expiration or earlier termination of this Lease; provided, however, that following the date that is 18 months after expiration or earlier termination of this Lease, neither party shall be responsible to pay overpayments or deficiencies not reflected in the Annual Statement for the final calendar year of the Term, except in connection with Taxes for which Tenant is responsible under this Lease and/or any costs or credits for which Landlord is billed or credited after the expiration of such 18 month period.

The Annual Statement shall be final and binding upon Tenant unless Tenant, within 60 days after Tenant's receipt thereof, shall contest any item therein by giving written notice to Landlord, specifying each item contested and the reason therefor. Operating Expenses for the calendar years in which Tenant's obligation to share therein begins and ends shall be prorated. Notwithstanding anything set forth herein to the contrary, if the Project is not at least 95% occupied on average during any year of the Term, Tenant's Share of Operating Expenses for such year shall be computed as though the Project had been 95% occupied on average during such year. Landlord shall not be entitled to collect Operating Expenses from the tenants of the Project in excess of 100% of the total Operating Expenses actually incurred or accrued by Landlord nor shall Landlord be entitled to make any profit from Landlord's collection of Operating Expenses.

"**Tenant's Share**" shall be the percentage set forth on the first page of this Lease as Tenant's Share as reasonably adjusted by Landlord for changes in the physical size of the Premises or the Project occurring thereafter. Landlord may equitably increase Tenant's Share for any item of expense or cost reimbursable by Tenant that relates to a repair, replacement, or service that benefits only the Premises or only a portion of the Project that includes the Premises or that varies with occupancy or use. Base Rent, Tenant's Share of Operating Expenses and all other amounts payable by Tenant to Landlord hereunder are collectively referred to herein as "**Rent**."

6. **Security Deposit**. Tenant shall deposit with Landlord, on or before the Commencement Date, a security deposit (the "**Security Deposit**") for the performance of all of Tenant's obligations hereunder in the amount set forth on page 1 of this Lease, which Security Deposit shall be in the form of an unconditional and irrevocable letter of credit (the "**Letter of Credit**"): (i) in form and substance reasonably satisfactory to Landlord, (ii) naming Landlord as beneficiary, (iii) expressly allowing Landlord to draw upon it at any time from time to time by delivering to the issuer notice that Landlord is entitled to draw thereunder, (iv) issued by Silicon Valley Bank or another FDIC-insured financial institution satisfactory to Landlord, and (v) redeemable by presentation of a sight draft in the State of California. If Tenant does not provide Landlord with a substitute Letter of Credit complying with all of the requirements hereof at least 10 days before the stated expiration date of any then current Letter of Credit, Landlord shall have the right to draw the full amount of the current Letter of Credit and hold the funds drawn in cash without obligation for interest thereon as the Security Deposit. The Security Deposit shall be held by Landlord as security for the performance of Tenant's obligations under this Lease. The Security Deposit is not an advance rental deposit or a measure of Landlord's damages in case of Tenant's default. Upon each occurrence of a Default (as defined in Section 20), Landlord may use all or any part of the Security Deposit to pay delinquent payments due under this Lease, future

rent damages under California Civil Code Section 1951.2, and the cost of any damage, injury, expense or liability caused by such Default, without prejudice to any other remedy provided herein or provided by law. Landlord's right to use the Security Deposit under this Section 6 includes the right to use the Security Deposit to pay future rent damages following the termination of this Lease pursuant to Section 21(c) below. Upon any use of all or any portion of the Security Deposit, Tenant shall pay Landlord on demand the amount that will restore the Security Deposit to the amount set forth on Page 1 of this Lease. Tenant hereby waives the provisions of any law, now or hereafter in force, including, without limitation, California Civil Code Section 1950.7, which provide that Landlord may claim from a security deposit only those sums reasonably necessary to remedy defaults in the payment of Rent, to repair damage caused by Tenant or to clean the Premises, it being agreed that Landlord may, in addition, claim those sums reasonably necessary to compensate Landlord for any other loss or damage, foreseeable or unforeseeable, caused by the act or omission of Tenant or any officer, employee, agent or invitee of Tenant. Upon bankruptcy or other debtor-creditor proceedings against Tenant, the Security Deposit shall be deemed to be applied first to the payment of Rent and other charges due Landlord for periods prior to the filing of such proceedings. If Tenant shall fully perform every provision of this Lease to be performed by Tenant, the Security Deposit, or any balance thereof (i.e., after deducting therefrom all amounts to which Landlord is entitled under the provisions of this Lease), shall be returned to Tenant (or, at Landlord's option, to the last assignee of Tenant's interest hereunder) within 90 days after the expiration or earlier termination of this Lease.

If Landlord transfers its interest in the Project or this Lease, Landlord shall either (a) transfer any Security Deposit then held by Landlord to a person or entity assuming Landlord's obligations under this Section 6, or (b) return to Tenant any Security Deposit then held by Landlord and remaining after the deductions permitted herein. Upon such transfer to such transferee or the return of the Security Deposit to Tenant, Landlord shall have no further obligation with respect to the Security Deposit, and Tenant's right to the return of the Security Deposit shall apply solely against Landlord's transferee. The Security Deposit is not an advance rental deposit or a measure of Landlord's damages in case of Tenant's default. Landlord's obligation respecting the Security Deposit is that of a debtor, not a trustee, and no interest shall accrue thereon.

7. **Use**. The Premises shall be used solely for the Permitted Use set forth in the basic lease provisions on page 1 of this Lease, and in compliance with all laws, orders, judgments, ordinances, regulations, codes, directives, permits, licenses, covenants and restrictions now or hereafter applicable to the Premises, and to the use and occupancy thereof, including, without limitation, the Americans With Disabilities Act, 42 U.S.C. § 12101, et seq. (together with the regulations promulgated pursuant thereto, "**ADA**") (collectively, "**Legal Requirements**" and each, a "**Legal Requirement**"). Tenant shall, upon 5 days' written notice from Landlord, discontinue any use of the Premises which is declared by any Governmental Authority (as defined in Section 9) having jurisdiction to be a violation of a Legal Requirement. Tenant will not use or permit the Premises to be used for any purpose or in any manner that would void Tenant's or Landlord's insurance, increase the insurance risk, or cause the disallowance of any sprinkler or other credits. The use that Tenant has disclosed to Landlord that Tenant will be making of the Premises as of the Commencement Date will not result in the voidance of or an increased insurance risk with respect to the insurance currently being maintained by Landlord. Tenant shall not permit any part of the Premises to be used as a "place of public accommodation", as defined in the ADA or any similar legal requirement. Tenant shall reimburse Landlord promptly upon demand for any additional premium charged for any such insurance policy by reason of Tenant's failure to comply with the provisions of this Section or otherwise caused by Tenant's use and/or occupancy of the Premises. Tenant will use the Premises in a careful, safe and proper manner and will not commit or permit waste, overload the floor or structure of the Premises, subject the Premises to use that would damage the Premises or obstruct or interfere with the rights of Landlord or other tenants or occupants of the Project, including conducting or giving notice of any auction, liquidation, or going out of business sale on the Premises, or using or allowing the Premises to be used for any unlawful purpose. Tenant shall cause any equipment or machinery to be installed in the Premises so as to reasonably prevent sounds or vibrations from the Premises from extending into Common Areas, or other space in the Project. Tenant shall not place any machinery or equipment that would overload the floor in or upon the Premises or transport or move such items through the Common Areas of the Project or in the Project elevators without the prior written consent of Landlord, which consent shall not be unreasonably withheld, conditioned or delayed. Except as may be provided under the Work Letter, Tenant shall not, without the prior written consent of Landlord, use the Premises in any manner which will require ventilation, air exchange, heating, gas, steam, electricity or water beyond the existing capacity of the Project as proportionately allocated to the Premises based upon Tenant's Share as usually furnished for the Permitted Use.

Landlord shall be responsible for the compliance of the Common Areas of the Project with Legal Requirements, including the ADA, as of the date of this Lease. Following the Commencement Date, Landlord shall, as an Operating Expense (to the extent such Legal Requirement is generally applicable to similar buildings in the area in which the Project is located) and at Tenant's expense (to the extent such Legal Requirement is triggered by reason of Tenant's, as compared to other tenants of the Project, specific use of the Premises or Tenant's alterations) make any alterations or modifications to the Common Areas or the exterior of the Building that are required by Legal Requirements. Except as provided in the two immediately preceding sentences, Tenant, at its sole expense, shall make any alterations or modifications to the interior of the Premises that are required by Legal Requirements (including, without limitation, compliance of the Premises with the ADA) related to Tenant's use or occupancy of the Premises or Tenant's Alterations. Notwithstanding any other provision herein to the contrary, Tenant shall be responsible for any and all demands, claims, liabilities, losses, costs, expenses, actions, causes of action, damages or judgments, and all reasonable expenses incurred in investigating or resisting the same (including, without limitation, reasonable attorneys' fees, charges and disbursements and costs of suit) (collectively, "**Claims**") arising out of or in connection with Legal Requirements related to Tenant's use or occupancy of the Premises or Tenant's Alterations, and Tenant shall indemnify, defend, hold and save Landlord harmless from and against any and all Claims arising out of or in connection with any failure of the Premises to comply with any Legal Requirement related to Tenant's use or occupancy of the Premises or Tenant's Alterations.

Tenant acknowledges that Landlord may, but shall not be obligated to, seek to obtain Leadership in Energy and Environmental Design (LEED), WELL Building Standard, or other similar "green" certification with respect to the Project and/or the Premises, and Tenant agrees to reasonably cooperate with Landlord, and to provide such information and/or documentation as Landlord may reasonably request, in connection therewith.

8. **Holding Over**. If, with Landlord's express written consent, Tenant retains possession of the Premises after the termination of the Term, (i) unless otherwise agreed in such written consent, such possession shall be subject to immediate termination by Landlord at any time, (ii) all of the other terms and provisions of this Lease (including, without limitation, the adjustment of Base Rent pursuant to Section 4 hereof) shall remain in full force and effect (excluding any expansion or renewal option or other similar right or option) during such holdover period, (iii) Tenant shall continue to pay Base Rent in the amount payable upon the date of the expiration or earlier termination of this Lease or such other amount as Landlord may indicate, in Landlord's sole and absolute discretion, in such written consent, and (iv) all other payments shall continue under the terms of this Lease. If Tenant remains in possession of the Premises after the expiration or earlier termination of the Term without the express written consent of Landlord, (A) Tenant shall become a tenant at sufferance upon the terms of this Lease except that (i) for the first 30 days of such holdover, the monthly rental shall be equal to 125% of Rent in effect during the last 30 days of the Term, and (ii) for any period of holdover in excess of 30 days, the monthly rental shall be equal to 150% of Rent in effect during the last 30 days of the Term, and (B) Tenant shall be responsible for all damages suffered by Landlord resulting from or occasioned by Tenant's holding over, including consequential damages. No holding over by Tenant, whether with or without consent of Landlord, shall operate to extend this Lease except as otherwise expressly provided, and this Section 8 shall not be construed as consent for Tenant to retain possession of the Premises. Acceptance by Landlord of Rent after the expiration of the Term or earlier termination of this Lease shall not result in a renewal or reinstatement of this Lease.

9. **Taxes**. Landlord shall pay, as part of Operating Expenses, all taxes, levies, fees, assessments and governmental charges of any kind, existing as of the Commencement Date or thereafter enacted (collectively referred to as "**Taxes**"), imposed by any federal, state, regional, municipal, local or other governmental authority or agency, including, without limitation, quasi-public agencies (collectively, "**Governmental Authority**") during the Term, including, without limitation, all Taxes: (i) imposed on or measured by or based, in whole or in part, on rent payable to (or gross receipts received by) Landlord under this Lease and/or from the rental by Landlord of the Project or any portion thereof, or (ii) based on the square footage, assessed value or other measure or evaluation of any kind of the Premises or the Project, or (iii) assessed or imposed by or on the operation or maintenance of any portion of the Premises or the Project, including parking, or (iv) assessed or imposed by, or at the direction of, or resulting from Legal Requirements, or interpretations thereof, promulgated by any Governmental Authority, or (v) imposed as a license or other fee, charge, tax, or assessment on Landlord's business or occupation of leasing space in the Project. Landlord may contest by appropriate legal proceedings the amount, validity, or application of any Taxes or liens securing Taxes. Taxes shall not include any net income taxes imposed on Landlord except to the extent such net

income taxes are in substitution for any Taxes payable hereunder. If any such Tax is levied or assessed directly against Tenant, then Tenant shall be responsible for and shall pay the same at such times and in such manner as the taxing authority shall require. Tenant shall pay, prior to delinquency, any and all Taxes levied or assessed against any personal property or trade fixtures placed by Tenant in the Premises, whether levied or assessed against Landlord or Tenant. If any Taxes on Tenant's personal property or trade fixtures are levied against Landlord or Landlord's property, or if the assessed valuation of the Project is increased by a value attributable to improvements within or Alterations (as defined in Section 12) to the Premises, whether owned by Landlord or Tenant and whether or not affixed to the real property so as to become a part thereof, higher than the base valuation on which Landlord from time-to-time allocates Taxes to all tenants in the Project, Landlord shall have the right, but not the obligation, to pay such Taxes. Landlord's reasonable determination of any excess assessed valuation shall be binding and conclusive, absent manifest error. The amount of any such payment by Landlord shall constitute Additional Rent due from Tenant to Landlord within 10 days after Landlord's delivery of demand therefor.

10. **Parking**. Subject to all matters of record, Force Majeure, a Taking (as defined in Section 19 below) and the exercise by Landlord of its rights hereunder, Tenant shall have the right, at no additional cost during the Base Term, in common with other tenants of the Project pro rata in accordance with the rentable area of the Premises and the rentable areas of the Project occupied by such other tenants, to park in those areas designated for non-reserved parking, subject in each case to Landlord's rules and regulations. Tenant's pro rata share of parking shall be equal to 2.8 parking spaces per 1,000 rentable square feet of the Premises. Landlord may allocate parking spaces among Tenant and other tenants in the Project pro rata as described above if Landlord determines that such parking facilities are becoming crowded. Landlord shall not be responsible for enforcing Tenant's parking rights against any third parties, including other tenants of the Project.

11. **Utilities, Services**. Landlord shall provide, subject to the terms of this Section 11, water, electricity, heat, light, power, sewer, and other utilities (including gas and fire sprinklers to the extent the Project is plumbed for such services), refuse and trash collection and janitorial services (collectively, "**Utilities**"). Landlord shall pay, as Operating Expenses or subject to Tenant's reimbursement obligation, for all Utilities used on the Premises, all maintenance charges for Utilities, and any storm sewer charges or other similar charges for Utilities imposed by any Governmental Authority or Utility provider, and any taxes, penalties, surcharges or similar charges thereon. Landlord may cause, at Tenant's expense, any Utilities to be separately metered or charged directly to Tenant by the provider. Tenant shall pay directly to the Utility provider, prior to delinquency, any separately metered Utilities and services which may be furnished to Tenant or the Premises during the Term. Tenant shall pay, as part of Operating Expenses, its share of all charges for jointly metered Utilities based upon consumption, as reasonably determined by Landlord. No interruption or failure of Utilities, from any cause whatsoever other than Landlord's willful misconduct, shall result in eviction or constructive eviction of Tenant, termination of this Lease or, except as provided in the immediately following paragraph, the abatement of Rent. Tenant agrees to limit use of water and sewer with respect to Common Areas to normal restroom use.

Notwithstanding anything to the contrary set forth herein, if (i) a stoppage of an Essential Service (as defined below) to the Premises shall occur and such stoppage is due solely to the gross negligence or willful misconduct of Landlord and not due in any part to any act or omission on the part of Tenant or any Tenant Party or any matter beyond Landlord's reasonable control (any such stoppage of an Essential Service being hereinafter referred to as a "**Service Interruption**"), and (ii) such Service Interruption continues for more than 5 consecutive days after Landlord shall have received written notice thereof from Tenant, and (iii) as a result of such Service Interruption, the conduct of Tenant's normal operations in the Premises are materially and adversely affected, then there shall be an abatement of one day's Base Rent for each day during which such Service Interruption continues after such 5 day period; provided, however, that if any part of the Premises is reasonably useable for Tenant's normal business operations or if Tenant conducts all or any part of its operations in any portion of the Premises notwithstanding such Service Interruption, then the amount of each daily abatement of Base Rent shall only be proportionate to the nature and extent of the interruption of Tenant's normal operations or ability to use the Premises. The rights granted to Tenant under this paragraph shall be Tenant's sole and exclusive remedy resulting from a failure of Landlord to provide services, and Landlord shall not otherwise be liable for any loss or damage suffered or sustained by Tenant resulting from any failure or cessation of services. For purposes hereof, the term "**Essential Services**" shall mean the following services: access to the Premises, HVAC service, water, sewer and electricity, but in each case only to the extent that Landlord

has an obligation to provide same to Tenant under this Lease. The provisions of this paragraph shall not apply to any sublessee of Tenant.

Landlord's sole obligation for either providing emergency generators or providing emergency back-up power to Tenant shall be: (i) to provide emergency generators with not less than the capacity of the emergency generators located in the Building as of the Commencement Date, and (ii) to contract with a third party to maintain the emergency generators as per the manufacturer's standard maintenance guidelines. Except as otherwise provided in the immediately preceding sentence, Landlord shall have no obligation to provide Tenant with operational emergency generators or back-up power or to supervise, oversee or confirm that the third party maintaining the emergency generators is maintaining the generators as per the manufacturer's standard guidelines or otherwise. Landlord shall, upon written request from Tenant (not more frequently than once per calendar year), make available for Tenant's inspection the maintenance contract and maintenance records for the emergency generators for the 12 month period immediately preceding Landlord's receipt of Tenant's written request. During any period of replacement, repair or maintenance of the emergency generators when the emergency generators are not operational, including any delays thereto due to the inability to obtain parts or replacement equipment, Landlord shall have no obligation to provide Tenant with an alternative back-up generator or generators or alternative sources of back-up power. Tenant expressly acknowledges and agrees that Landlord does not guaranty that such emergency generators will be operational at all times or that emergency power will be available to the Premises when needed.

Tenant agrees to provide Landlord with access to Tenant's water and/or energy usage data on a monthly basis, either by providing Tenant's applicable utility login credentials to Landlord's Measurabl online portal, or by another delivery method reasonably agreed to by Landlord and Tenant. The costs and expenses incurred by Landlord in connection with receiving and analyzing such water and/or energy usage data (including, without limitation, as may be required pursuant to applicable Legal Requirements) shall be included as part of Operating Expenses.

12. **Alterations and Tenant's Property**. Any alterations, additions, or improvements made to the Premises by or on behalf of Tenant, including additional locks or bolts of any kind or nature upon any doors or windows in the Premises, but excluding installation, removal or realignment of furniture systems (other than removal of furniture systems owned or paid for by Landlord) not involving any modifications to the structure or connections (other than by ordinary plugs or jacks) to Building Systems (as defined in Section 13) ("**Alterations**") shall be subject to Landlord's prior written consent, which may be given or withheld in Landlord's sole discretion if any such Alteration affects the structure or Building Systems and shall not be otherwise unreasonably withheld. If Landlord approves any Alterations, Landlord may impose such reasonable conditions on Tenant in connection with the commencement, performance and completion of such Alterations as Landlord may deem appropriate in Landlord's reasonable discretion. Any request for approval shall be in writing, delivered not less than 15 business days in advance of any proposed construction, and accompanied by plans, specifications, bid proposals, work contracts and such other information concerning the nature and cost of the alterations as may be reasonably requested by Landlord, including the identities and mailing addresses of all persons performing work or supplying materials. Landlord's right to review plans and specifications and to monitor construction shall be solely for its own benefit, and Landlord shall have no duty to ensure that such plans and specifications or construction comply with applicable Legal Requirements. Tenant shall cause, at its sole cost and expense, all Alterations to comply with insurance requirements and with Legal Requirements and shall implement at its sole cost and expense any alteration or modification required by Legal Requirements as a result of any Alterations. With respect to Alterations costing in excess of $50,000.00, Tenant shall pay to Landlord, as Additional Rent, on demand an amount equal to 3% of all charges incurred by Tenant or its contractors or agents in connection with any Alteration to cover Landlord's overhead and expenses for plan review, coordination, scheduling and supervision. Before Tenant begins any Alteration, Landlord may post on and about the Premises notices of non-responsibility pursuant to applicable law. Tenant shall reimburse Landlord for, and indemnify and hold Landlord harmless from, any expense incurred by Landlord by reason of faulty work done by Tenant or its contractors, delays caused by such work, or inadequate cleanup.

Tenant shall furnish security or make other arrangements satisfactory to Landlord to assure payment for the completion of all Alterations work free and clear of liens, and shall provide (and cause each contractor or subcontractor to provide) certificates of insurance for workers' compensation and other coverage in amounts and from an insurance company satisfactory to Landlord protecting Landlord against liability for personal injury or property damage during construction. Upon completion of any Alterations, Tenant shall deliver to Landlord: (i) sworn statements setting forth

the names of all contractors and subcontractors who did the work and final lien waivers from all such contractors and subcontractors; and (ii) "as built" plans for any such Alteration.

Except for Removable Installations (as hereinafter defined), all Installations (as hereinafter defined) shall be and shall remain the property of Landlord during the Term and following the expiration or earlier termination of the Term, shall not be removed by Tenant at any time during the Term, and shall remain upon and be surrendered with the Premises as a part thereof. Notwithstanding the foregoing, Landlord may, at the time its approval of any such Installation is requested, notify Tenant that Landlord requires that Tenant remove such Installation upon the expiration or earlier termination of the Term, in which event Tenant shall remove such Installation in accordance with the immediately succeeding sentence. Upon the expiration or earlier termination of the Term, Tenant shall remove (i) all wires, cables or similar equipment which Tenant has installed in the Premises or in the risers or plenums of the Building, (ii) any Installations for which Landlord has given Tenant notice of removal in accordance with the immediately preceding sentence, and (iii) all of Tenant's Property (as hereinafter defined), and Tenant shall restore and repair any damage caused by or occasioned as a result of such removal, including, without limitation, capping off all such connections behind the walls of the Premises and repairing any holes. During any restoration period beyond the expiration or earlier termination of the Term, Tenant shall pay Rent to Landlord as provided herein as if said space were otherwise occupied by Tenant. If Landlord is requested by Tenant or any lender, lessor or other person or entity claiming an interest in any of Tenant's Property to waive any lien Landlord may have against any of Tenant's Property, and Landlord consents to such waiver, then Landlord shall be entitled to be paid as administrative rent a fee of $1,000 per occurrence for its time and effort in preparing and negotiating such a waiver of lien.

For purposes of this Lease, (x) "**Removable Installations**" means any items listed on **Exhibit F** attached hereto and any items agreed by Landlord in writing to be included on **Exhibit F** in the future, (y) "**Tenant's Property**" means Removable Installations and, other than Installations, any personal property or equipment of Tenant that may be removed without material damage to the Premises, and (z) "**Installations**" means all property of any kind paid for with the TI Fund, all Alterations, all fixtures, and all partitions, hardware, built-in machinery, built-in casework and cabinets and other similar additions, equipment, property and improvements built into the Premises so as to become an integral part of the Premises, including, without limitation, fume hoods which penetrate the roof or plenum area, built-in cold rooms, built-in warm rooms, walk-in cold rooms, walk-in warm rooms, deionized water systems, glass washing equipment, autoclaves, chillers, built-in plumbing, electrical and mechanical equipment and systems, and any power generator and transfer switch.

13. **Landlord's Repairs**. Landlord, as an Operating Expense (except to the extent the cost thereof is excluded from Operating Expenses pursuant to Section 5 hereof), shall maintain all of the structural, exterior, parking and other Common Areas of the Project, including HVAC, plumbing, fire sprinklers, elevators and all other building systems serving the Premises and other portions of the Project ("**Building Systems**"), in good repair, reasonable wear and tear and uninsured losses and damages caused by Tenant, or by any of Tenant, or by any of Tenant's assignees, sublessees, licensees, agents, servants, employees, invitees and contractors (or any of Tenant's assignees, sublessees and/or licensees respective agents, servants, employees, invitees and contractors) (collectively, "**Tenant Parties**") excluded. Landlord shall be responsible for contracting for pest control services with respect to the Common Areas of the Project, if determined reasonably necessary by Landlord. Subject to the provisions of the penultimate paragraph of Section 17, losses and damages caused by Tenant or any Tenant Party shall be repaired by Landlord, to the extent not covered by insurance, at Tenant's sole cost and expense. Landlord reserves the right to stop Building Systems services when necessary (i) by reason of accident or emergency, or (ii) for planned repairs, alterations or improvements, which are, in the judgment of Landlord, desirable or necessary to be made, until said repairs, alterations or improvements shall have been completed. Landlord shall have no responsibility or liability for failure to supply Building Systems services during any such period of interruption; provided, however, that Landlord shall, except in case of emergency, make a commercially reasonable effort to give Tenant 2 business days' advance notice of any planned stoppage of Building Systems services for routine maintenance, repairs, alterations or improvements. Tenant shall promptly give Landlord written notice of any repair required by Landlord pursuant to this Section, after which Landlord shall make a commercially reasonable effort to effect such repair. Landlord shall not be liable for any failure to make any repairs or to perform any maintenance unless such failure shall persist for an unreasonable time after Tenant's written notice of the need for such repairs or maintenance. Tenant waives its rights under any state or local law to terminate this Lease or, except as otherwise expressly set forth in Section 31, to make such repairs at Landlord's expense and agrees that the parties' respective rights with respect to such matters shall be solely as set forth herein.

Repairs required as the result of fire, earthquake, flood, vandalism, war, or similar cause of damage or destruction shall be controlled by Section 18.

14. **Tenant's Repairs**. Subject to Section 13 hereof, Tenant, at its expense, shall repair, replace and maintain in good condition all portions of the Premises, including, without limitation, entries, doors, ceilings, interior windows, interior walls, and the interior side of demising walls. Such repair and replacement may include capital expenditures and repairs whose benefit may extend beyond the Term. Should Tenant fail to make any such repair or replacement or fail to maintain the Premises, Landlord shall give Tenant notice of such failure. If Tenant fails to commence cure of such failure within 10 business days of Landlord's notice, and thereafter diligently prosecute such cure to completion, Landlord may perform such work and shall be reimbursed by Tenant within 30 days after demand therefor; provided, however, that if such failure by Tenant creates or could create an emergency, Landlord may immediately commence cure of such failure and shall thereafter be entitled to recover the costs of such cure from Tenant. Subject to Sections 17 and 18, Tenant shall bear the full uninsured cost of any repair or replacement to any part of the Project that results from damage caused by Tenant or any Tenant Party and any repair that benefits only the Premises.

15. **Mechanic's Liens**. Tenant shall discharge, by bond or otherwise, any mechanic's lien filed against the Premises or against the Project for work claimed to have been done for, or materials claimed to have been furnished to, Tenant within 10 business days after Tenant's receipt of notice of the filing thereof, at Tenant's sole cost and shall otherwise keep the Premises and the Project free from any liens arising out of work performed, materials furnished or obligations incurred by Tenant. Should Tenant fail to discharge any lien described herein, Landlord shall have the right, but not the obligation, to pay such claim or post a bond or otherwise provide security to eliminate the lien as a claim against title to the Project and the cost thereof shall be immediately due from Tenant as Additional Rent. If Tenant shall lease or finance the acquisition of office equipment, furnishings, or other personal property of a removable nature utilized by Tenant in the operation of Tenant's business, Tenant warrants that any Uniform Commercial Code Financing Statement filed as a matter of public record by any lessor or creditor of Tenant will upon its face or by exhibit thereto indicate that such Financing Statement is applicable only to removable personal property of Tenant located within the Premises. In no event shall the address of the Project be furnished on the statement without qualifying language as to applicability of the lien only to removable personal property, located in an identified suite held by Tenant.

16. **Indemnification**. Tenant hereby indemnifies and agrees to defend, save and hold Landlord, its officers, directors, employees, managers, agents, sub-agents and constituent entities (collectively, "**Landlord Indemnified Parties**") harmless from and against any and all Claims for injury or death to persons or damage to property occurring within or about the Premises or the Project arising directly or indirectly out of use or occupancy of the Premises or the Project (including, without limitation, any act, omission or neglect by Tenant or any Tenant's Parties in or about the Premises or at the Project) or the a breach or default by Tenant in the performance of any of its obligations hereunder, except to the extent caused by the willful misconduct or gross negligence of Landlord Indemnified Parties. Landlord shall not be liable to Tenant for, and Tenant assumes all risk of damage to, personal property (including, without limitation, loss of records kept within the Premises). Tenant further waives any and all Claims for injury to Tenant's business or loss of income relating to any such damage or destruction of personal property (including, without limitation, any loss of records). Landlord Indemnified Parties shall not be liable for any damages arising from any act, omission or neglect of any tenant in the Project or of any other third party or Tenant Parties.

17. **Insurance**. Landlord shall maintain all risk property and, if applicable, sprinkler damage insurance covering the full replacement cost of the Project. Landlord shall further procure and maintain commercial general liability insurance with a single loss limit of not less than $2,000,000 for bodily injury and property damage with respect to the Project. Landlord may, but is not obligated to, maintain such other insurance and additional coverages as it may deem necessary, including, but not limited to, flood, environmental hazard and earthquake, loss or failure of building equipment, errors and omissions, rental loss during the period of repair or rebuilding, workers' compensation insurance and fidelity bonds for employees employed to perform services and insurance for any improvements installed by Tenant or which are in addition to the standard improvements customarily furnished by Landlord without regard to whether or not such are made a part of the Project. All such insurance shall be included as part of the Operating Expenses. The Project may be included in a blanket policy (in which case the cost of such insurance

allocable to the Project will be determined by Landlord based upon the insurer's cost calculations). Tenant shall also reimburse Landlord for any increased premiums or additional insurance resulting from Tenant's particular use of the Premises.

Tenant, at its sole cost and expense, shall maintain during the Term: all risk property insurance with business interruption and extra expense coverage, covering the full replacement cost of all property and improvements installed or placed in the Premises by Tenant at Tenant's expense; workers' compensation insurance with no less than the minimum limits required by law; employer's liability insurance with employers liability limits of $1,000,000 bodily injury by accident – each accident, $1,000,000 bodily injury by disease – policy limit, and $1,000,000 bodily injury by disease – each employee; and commercial general liability insurance, with a minimum limit of not less than $2,000,000 per occurrence for bodily injury and property damage with respect to the Premises. The commercial general liability insurance maintained by Tenant shall name Alexandria Real Estate Equities, Inc., and Landlord, its officers, directors, employees, managers, agents, sub-agents and constituent entities (collectively, "**Landlord Insured Parties**"), as additional insureds; insure on an occurrence and not a claims-made basis; be issued by insurance companies which have a rating of not less than policyholder rating of A and financial category rating of at least Class X in "Best's Insurance Guide"; not contain a hostile fire exclusion; contain a contractual liability endorsement; and provide primary coverage to Landlord Insured Parties (any policy issued to Landlord Insured Parties providing duplicate or similar coverage shall be deemed excess over Tenant's policies, regardless of limits). Tenant shall (i) provide Landlord with 30 days' advance written notice of cancellation of such commercial general liability policy, and (ii) require Tenant's insurer to endeavor to provide 10 days' advance written notice of cancellation of such commercial general liability policy. Copies of such policies (if requested by Landlord), or certificates of insurance showing the limits of coverage required hereunder and showing Landlord as an additional insured, along with reasonable evidence of the payment of premiums for the applicable period, shall be delivered to Landlord by Tenant prior to (i) the earlier to occur of (x) the Commencement Date, or (y) the date that Tenant accesses the Premises under this Lease, and (ii) each renewal of said insurance. Tenant's policy may be a "blanket policy" with an aggregate per location endorsement which specifically provides that the amount of insurance shall not be prejudiced by other losses covered by the policy. Tenant shall, prior to the expiration of such policies, furnish Landlord with renewal certificates.

In each instance where insurance is to name Landlord as an additional insured, Tenant shall upon written request of Landlord also designate and furnish certificates so evidencing Landlord as additional insured to: (i) any lender of Landlord holding a security interest in the Project or any portion thereof, (ii) the landlord under any lease wherein Landlord is tenant of the real property on which the Project is located, if the interest of Landlord is or shall become that of a tenant under a ground or other underlying lease rather than that of a fee owner, and/or (iii) any management company retained by Landlord to manage the Project.

The property insurance obtained by Landlord and Tenant shall include a waiver of subrogation by the insurers and all rights based upon an assignment from its insured, against Landlord or Tenant, and their respective officers, directors, employees, managers, agents, invitees and contractors ("**Related Parties**"), in connection with any loss or damage thereby insured against. Neither party nor its respective Related Parties shall be liable to the other for loss or damage caused by any risk insured against under property insurance required to be maintained hereunder, and each party waives any claims against the other party, and its respective Related Parties, for such loss or damage. The failure of a party to insure its property shall not void this waiver. Landlord and its respective Related Parties shall not be liable for, and Tenant hereby waives all claims against such parties for, business interruption and losses occasioned thereby sustained by Tenant or any person claiming through Tenant resulting from any accident or occurrence in or upon the Premises or the Project from any cause whatsoever. If the foregoing waivers shall contravene any law with respect to exculpatory agreements, the liability of Landlord or Tenant shall be deemed not released but shall be secondary to the other's insurer.

Landlord may require insurance policy limits to be raised to conform with requirements of Landlord's lender and/or to bring coverage limits to levels then being generally required of new tenants within the Project.

18. **Restoration**. If, at any time during the Term, the Project or the Premises are damaged or destroyed by a fire or other insured casualty, Landlord shall notify Tenant within 45 days after discovery of such damage as to the amount of time Landlord reasonably estimates it will take to restore the Project or the Premises, as applicable (the "**Restoration Period**"). If the Restoration Period is estimated to exceed 12 months (the "**Maximum Restoration**

Period"), Landlord may, in such notice, elect to terminate this Lease as of the date that is 60 days after the date of discovery of such damage or destruction; provided, however, that notwithstanding Landlord's election to restore, Tenant may elect to terminate this Lease by written notice to Landlord delivered within 5 business days of receipt of a notice from Landlord estimating a Restoration Period for the Premises longer than the Maximum Restoration Period. Unless either Landlord or Tenant so elects to terminate this Lease, Landlord shall, subject to receipt of sufficient insurance proceeds (with any deductible to be treated as a current Operating Expense), promptly restore the Premises (excluding the improvements installed by Tenant or by Landlord and paid for by Tenant), subject to delays arising from the collection of insurance proceeds, from Force Majeure events or as needed to obtain any license, clearance or other authorization of any kind required to enter into and restore the Premises issued by any Governmental Authority having jurisdiction over the use, storage, handling, treatment, generation, release, disposal, removal or remediation of Hazardous Materials (as defined in Section 30) in, on or about the Premises (collectively referred to herein as "**Hazardous Materials Clearances**"); provided, however, that if repair or restoration of the Premises is not substantially complete as of the end of the Maximum Restoration Period or, if longer, the Restoration Period, Landlord may, in its sole and absolute discretion, elect not to proceed with such repair and restoration, or Tenant may by written notice to Landlord delivered within 5 business days of the expiration of the Maximum Restoration Period or, if longer, the Restoration Period, elect to terminate this Lease, in which event Landlord shall be relieved of its obligation to make such repairs or restoration and this Lease shall terminate as of the date that is 75 days after the later of: (i) discovery of such damage or destruction, or (ii) the date all required Hazardous Materials Clearances are obtained, but Landlord shall retain any Rent paid and the right to any Rent payable by Tenant prior to such election by Landlord or Tenant.

Tenant, at its expense, shall promptly perform, subject to delays arising from the collection of insurance proceeds, from Force Majeure (as defined in Section 34) events or to obtain Hazardous Material Clearances, any repairs or restoration Tenant wishes to have performed that are not required to be done by Landlord and shall promptly re-enter the Premises and commence doing business in accordance with this Lease. Notwithstanding the foregoing, either Landlord or Tenant may terminate this Lease upon written notice to the other if the Premises are damaged during the last year of the Term and Landlord reasonably estimates that it will take more than 2 months to repair such damage; provided, however, that such notice is delivered within 10 business days after the date that Landlord provides Tenant with written notice of the estimated Restoration Period. Notwithstanding anything to the contrary contained herein, Landlord shall also have the right to terminate this Lease if insurance proceeds are not available for such restoration. Rent shall be abated from the date all required Hazardous Material Clearances are obtained until the Premises are repaired and restored, in the proportion which the area of the Premises, if any, which is not usable by Tenant bears to the total area of the Premises, unless Landlord provides Tenant with other space during the period of repair that is suitable (as reasonably determined by Tenant) for the temporary conduct of Tenant's business for the Permitted Use. In the event that no Hazardous Material Clearances are required to be obtained by Tenant with respect to the Premises, rent abatement shall commence on the date of discovery of the damage or destruction. Such abatement shall be the sole remedy of Tenant, and except as provided in this Section 18, Tenant waives any right to terminate this Lease by reason of damage or casualty loss.

The provisions of this Lease, including this Section 18, constitute an express agreement between Landlord and Tenant with respect to any and all damage to, or destruction of, all or any part of the Premises, or any other portion of the Project, and any statute or regulation which is now or may hereafter be in effect shall have no application to this Lease or any damage or destruction to all or any part of the Premises or any other portion of the Project, the parties hereto expressly agreeing that this Section 18 sets forth their entire understanding and agreement with respect to such matters.

19. **Condemnation**. If the whole or any material part of the Premises or the Project is taken for any public or quasi-public use under governmental law, ordinance, or regulation, or by right of eminent domain, or by private purchase in lieu thereof (a "**Taking**" or "**Taken**"), and the Taking would in Landlord's reasonable judgment, either prevent or materially interfere with Tenant's use of the Premises or materially interfere with or impair Landlord's ownership or operation of the Project, then upon written notice by Landlord this Lease shall terminate and Rent shall be apportioned as of said date. If part of the Premises shall be Taken, and this Lease is not terminated as provided above, Landlord shall promptly restore the Premises and the Project as nearly as is commercially reasonable under the circumstances to their condition prior to such partial Taking and the rentable square footage of the Building, the rentable square footage of the Premises, Tenant's Share of Operating Expenses and the Rent payable hereunder

during the unexpired Term shall be reduced to such extent as may be fair and reasonable under the circumstances. Upon any such Taking, Landlord shall be entitled to receive the entire price or award from any such Taking without any payment to Tenant, and Tenant hereby assigns to Landlord Tenant's interest, if any, in such award. Tenant shall have the right, to the extent that same shall not diminish Landlord's award, to make a separate claim against the condemning authority (but not Landlord) for such compensation as may be separately awarded or recoverable by Tenant for moving expenses and damage to Tenant's trade fixtures, if a separate award for such items is made to Tenant. Tenant hereby waives any and all rights it might otherwise have pursuant to any provision of state law to terminate this Lease upon a partial Taking of the Premises or the Project.

20. **Events of Default**. Each of the following events shall be a default ("**Default**") by Tenant under this Lease:

(a) **Payment Defaults**. Tenant shall fail to pay any installment of Rent or any other payment hereunder when due; provided, however, that Landlord will give Tenant notice and an opportunity to cure any failure to pay Rent within 5 days of any such notice not more than once in any 12 month period and Tenant agrees that such notice shall be in lieu of and not in addition to, or shall be deemed to be, any notice required by law.

(b) **Insurance**. Any insurance required to be maintained by Tenant pursuant to this Lease shall be canceled or terminated or shall expire or shall be reduced or materially changed, or Landlord shall receive a notice of nonrenewal of any such insurance and Tenant shall fail to obtain replacement insurance before the expiration of the current coverage.

(c) **Abandonment**. Tenant shall abandon the Premises. Tenant shall not be deemed to have abandoned the Premises if Tenant provides Landlord with reasonable advance notice prior to vacating and, at the time of vacating the Premises, (i) Tenant completes Tenant's obligations under the Decommissioning and HazMat Closure Plan in compliance with Section 28, (ii) Tenant has obtained the release of the Premises of all Hazardous Materials Clearances and the Premises are free from any residual impact from the Tenant HazMat Operations and provides reasonably detailed documentation to Landlord confirming such matters, (iii) Tenant has made reasonable arrangements with Landlord for the security of the Premises for the balance of the Term, and (iv) Tenant continues during the balance of the Term to satisfy and perform all of Tenant's obligations under this Lease as they come due.

(d) **Improper Transfer**. Tenant shall assign, sublease or otherwise transfer or attempt to transfer all or any portion of Tenant's interest in this Lease or the Premises except as expressly permitted herein, or Tenant's interest in this Lease shall be attached, executed upon, or otherwise judicially seized and such action is not released within 90 days of the action.

(e) **Liens**. Tenant shall fail to discharge or otherwise obtain the release of any lien placed upon the Premises in violation of this Lease within 10 business days after Tenant's receipt of notice any such lien is filed against the Premises.

(f) **Insolvency Events**. Tenant or any guarantor or surety of Tenant's obligations hereunder shall: (A) make a general assignment for the benefit of creditors; (B) commence any case, proceeding or other action seeking to have an order for relief entered on its behalf as a debtor or to adjudicate it a bankrupt or insolvent, or seeking reorganization, arrangement, adjustment, liquidation, dissolution or composition of it or its debts or seeking appointment of a receiver, trustee, custodian or other similar official for it or for all or of any substantial part of its property (collectively a "**Proceeding for Relief**"); (C) become the subject of any Proceeding for Relief which is not dismissed within 90 days of its filing or entry; or (D) die or suffer a legal disability (if Tenant, guarantor, or surety is an individual) or be dissolved or otherwise fail to maintain its legal existence (if Tenant, guarantor or surety is a corporation, partnership or other entity).

(g) **Estoppel Certificate or Subordination Agreement**. Tenant fails to execute any document required from Tenant under Sections 23 or 27 within 5 business days after a second notice requesting such document.

(h) **Other Defaults**. Tenant shall fail to comply with any provision of this Lease other than those specifically referred to in this Section 20, and, except as otherwise expressly provided herein, such failure shall continue for a period of 30 days after written notice thereof from Landlord to Tenant.

Any notice given under Section 20(h) hereof shall: (i) specify the alleged default, (ii) demand that Tenant cure such default, (iii) be in lieu of, and not in addition to, or shall be deemed to be, any notice required under any provision of applicable law, and (iv) not be deemed a forfeiture or a termination of this Lease unless Landlord elects otherwise in such notice; provided that if the nature of Tenant's default pursuant to Section 20(h) is such that it cannot be cured by the payment of money and reasonably requires more than 30 days to cure, then Tenant shall not be deemed to be in default if Tenant commences such cure within said 30 day period and thereafter diligently prosecutes the same to completion; provided, however, that such cure shall be completed no later than 60 days from the date of Landlord's notice.

21. **Landlord's Remedies**.

(a) **Payment By Landlord; Interest**. Upon a Default by Tenant hereunder, Landlord may, without waiving or releasing any obligation of Tenant hereunder, make such payment or perform such act. All sums so paid or incurred by Landlord, together with interest thereon, from the date such sums were paid or incurred, at the annual rate equal to 12% per annum or the highest rate permitted by law (the "**Default Rate**"), whichever is less, shall be payable to Landlord on demand as Additional Rent. Nothing herein shall be construed to create or impose a duty on Landlord to mitigate any damages resulting from Tenant's Default hereunder.

(b) **Late Payment Rent**. Late payment by Tenant to Landlord of Rent and other sums due will cause Landlord to incur costs not contemplated by this Lease, the exact amount of which will be extremely difficult and impracticable to ascertain. Such costs include, but are not limited to, processing and accounting charges and late charges which may be imposed on Landlord under any Mortgage covering the Premises. Therefore, if any installment of Rent due from Tenant is not received by Landlord within 5 days after the date such payment is due, Tenant shall pay to Landlord an additional sum equal to 6% of the overdue Rent as a late charge. Notwithstanding the foregoing, before assessing a late charge the first time in any calendar year, Landlord shall provide Tenant written notice of the delinquency and will waive the right if Tenant pays such delinquency within 5 business days thereafter. The parties agree that this late charge represents a fair and reasonable estimate of the costs Landlord will incur by reason of late payment by Tenant. In addition to the late charge, Rent not paid when due shall bear interest at the Default Rate from the 5th day after the date due until paid.

(c) **Remedies**. Upon the occurrence of a Default, Landlord, at its option, without further notice or demand to Tenant, shall have in addition to all other rights and remedies provided in this Lease, at law or in equity, the option to pursue any one or more of the following remedies, each and all of which shall be cumulative and nonexclusive, without any notice or demand whatsoever.

(i) Terminate this Lease, or at Landlord's option, Tenant's right to possession only, in which event Tenant shall immediately surrender the Premises to Landlord, and if Tenant fails to do so, Landlord may, without prejudice to any other remedy which it may have for possession or arrearages in rent, enter upon and take possession of the Premises and expel or remove Tenant and any other person who may be occupying the Premises or any part thereof, without being liable for prosecution or any claim for damages therefor;

(ii) Upon any termination of this Lease, whether pursuant to the foregoing Section 21(c)(i) or otherwise, Landlord may recover from Tenant the following:

(A) The worth at the time of award of any unpaid rent which has been earned at the time of such termination; plus

(B) The worth at the time of award of the amount by which the unpaid rent which would have been earned after termination until the time of award exceeds the amount of such rental loss that Tenant proves could have been reasonably avoided; plus

(C) The worth at the time of award of the amount by which the unpaid rent for the balance of the Term after the time of award exceeds the amount of such rental loss that Tenant proves could have been reasonably avoided; plus

(D) Any other amount necessary to compensate Landlord for all the detriment proximately caused by Tenant's failure to perform its obligations under this Lease or which in the ordinary course of things would be likely to result therefrom, specifically including, but not limited to, brokerage commissions and advertising expenses incurred, expenses of remodeling the Premises or any portion thereof for a new tenant, whether for the same or a different use, and any special concessions made to obtain a new tenant; and

(E) At Landlord's election, such other amounts in addition to or in lieu of the foregoing as may be permitted from time to time by applicable law.

The term "**rent**" as used in this Section 21 shall be deemed to be and to mean all sums of every nature required to be paid by Tenant pursuant to the terms of this Lease, whether to Landlord or to others. As used in Sections 21(c)(ii)(A) and (B), above, the "**worth at the time of award**" shall be computed by allowing interest at the Default Rate. As used in Section 21(c)(ii)(C) above, the "**worth at the time of award**" shall be computed by discounting such amount at the discount rate of the Federal Reserve Bank of San Francisco at the time of award plus 1%.

(iii) Landlord may continue this Lease in effect after Tenant's Default and recover rent as it becomes due (Landlord and Tenant hereby agreeing that Tenant has the right to sublet or assign hereunder, subject only to reasonable limitations). Accordingly, if Landlord does not elect to terminate this Lease following a Default by Tenant, Landlord may, from time to time, without terminating this Lease, enforce all of its rights and remedies hereunder, including the right to recover all Rent as it becomes due.

(iv) Whether or not Landlord elects to terminate this Lease following a Default by Tenant, Landlord shall have the right to terminate any and all subleases, licenses, concessions or other consensual arrangements for possession entered into by Tenant and affecting the Premises or may, in Landlord's sole discretion, succeed to Tenant's interest in such subleases, licenses, concessions or arrangements. Upon Landlord's election to succeed to Tenant's interest in any such subleases, licenses, concessions or arrangements, Tenant shall, as of the date of notice by Landlord of such election, have no further right to or interest in the rent or other consideration receivable thereunder.

(d) **Effect of Exercise**. Exercise by Landlord of any remedies hereunder or otherwise available shall not be deemed to be an acceptance of surrender of the Premises and/or a termination of this Lease by Landlord, it being understood that such surrender and/or termination can be effected only by the express written agreement of Landlord and Tenant. Any law, usage, or custom to the contrary notwithstanding, Landlord shall have the right at all times to enforce the provisions of this Lease in strict accordance with the terms hereof; and the failure of Landlord at any time to enforce its rights under this Lease strictly in accordance with same shall not be construed as having created a custom in any way or manner contrary to the specific terms, provisions, and covenants of this Lease or as having modified the same and shall not be deemed a waiver of Landlord's right to enforce one or more of its rights in connection with any subsequent default. A receipt by Landlord of Rent or other payment with knowledge of the breach of any covenant hereof shall not be deemed a waiver of such breach, and no waiver by Landlord of any provision of this Lease shall be deemed to have been made unless expressed in writing and signed by Landlord. To the greatest extent permitted by law, Tenant waives all right of redemption in case Tenant shall be dispossessed by a judgment or by warrant of any court or judge. Any reletting of the Premises or any portion thereof shall be on such terms and conditions as Landlord in its sole discretion may determine. Landlord shall not be liable for, nor shall Tenant's obligations hereunder be diminished because of, Landlord's failure to relet the Premises or collect rent due in respect of such reletting or otherwise to mitigate any damages arising by reason of Tenant's Default.

22. **Assignment and Subletting**.

(a) **General Prohibition**. Without Landlord's prior written consent subject to and on the conditions described in this Section 22, Tenant shall not, directly or indirectly, voluntarily or by operation of law, assign this

Lease or sublease the Premises or any part thereof or mortgage, pledge, or hypothecate its leasehold interest or grant any concession or license within the Premises, and any attempt to do any of the foregoing shall be void and of no effect. If Tenant is a corporation, partnership or limited liability company, the shares or other ownership interests thereof which are not actively traded upon a stock exchange or in the over-the-counter market, a transfer or series of transfers whereby 50% or more of the issued and outstanding shares or other ownership interests of such corporation are, or voting control is, transferred (but excepting transfers upon deaths of individual owners) from a person or persons or entity or entities which were owners thereof at time of execution of this Lease to persons or entities who were not owners of shares or other ownership interests of the corporation, partnership or limited liability company at time of execution of this Lease, shall be deemed an assignment of this Lease requiring the consent of Landlord as provided in this Section 22. Notwithstanding the foregoing, Tenant shall have the right to obtain financing from institutional investors (including venture capital funding and corporate partners) which regularly invest in biotechnology companies or undergo a public offering which results in a change in control of Tenant without such change of control constituting an assignment under this Section 22 requiring Landlord consent, provided that (i) Tenant notifies Landlord in writing of the financing at least 5 business days prior to the closing of the financing, and (ii) provided that in no event shall such financing result in a change in use of the Premises from the use contemplated by Tenant at the commencement of the Term.

(b) **Permitted Transfers**. If Tenant desires to assign, sublease, hypothecate or otherwise transfer this Lease or sublet the Premises other than pursuant to a Permitted Assignment (as defined below), then at least 15 business days, but not more than 45 business days, before the date Tenant desires the assignment or sublease to be effective (the "**Assignment Date**"), Tenant shall give Landlord a notice (the "**Assignment Notice**") containing such information about the proposed assignee or sublessee, including the proposed use of the Premises and any Hazardous Materials proposed to be used, stored handled, treated, generated in or released or disposed of from the Premises, the Assignment Date, any relationship between Tenant and the proposed assignee or sublessee, and all material terms and conditions of the proposed assignment or sublease, including a copy of any proposed assignment or sublease in its final form, and such other information as Landlord may deem reasonably necessary or appropriate to its consideration whether to grant its consent. Landlord may, by giving written notice to Tenant within 15 business days after receipt of the Assignment Notice: (i) grant such consent (provided that Landlord shall further have the right to review and approve or disapprove, in Landlord's reasonable discretion, the proposed form of sublease prior to the effective date of any such subletting), (ii) refuse such consent, in its reasonable discretion; or (iii) with respect to any assignment of this Lease or any sublease that would result in more than 50% of the Premises being subleased for substantially the remainder of the Term, terminate this Lease with respect to the space described in the Assignment Notice as of the Assignment Date (an "**Assignment Termination**"). Among other reasons, it shall be reasonable for Landlord to withhold its consent in any of these instances: (1) the proposed assignee or subtenant is a governmental agency; (2) in Landlord's reasonable judgment, the use of the Premises by the proposed assignee or subtenant would entail any alterations that would lessen the value of the leasehold improvements in the Premises, or would require increased services by Landlord; (3) in Landlord's reasonable judgment, the proposed assignee or subtenant is engaged in areas of scientific research or other business concerns that are controversial; (4) in Landlord's reasonable judgment, the proposed assignee or subtenant lacks the creditworthiness to support the financial obligations it will incur under the proposed assignment or sublease; (5) in Landlord's reasonable judgment, the character, reputation, or business of the proposed assignee or subtenant is inconsistent with the desired tenant-mix or the quality of other tenancies in the Project or is inconsistent with the type and quality of the nature of the Building; (6) Landlord has received from any prior landlord to the proposed assignee or subtenant a negative report concerning such prior landlord's experience with the proposed assignee or subtenant; (7) Landlord has experienced previous defaults by or is in litigation with the proposed assignee or subtenant; (8) the use of the Premises by the proposed assignee or subtenant will violate any applicable Legal Requirement; (9) the proposed assignee or subtenant, or any entity that, directly or indirectly, controls, is controlled by, or is under common control with the proposed assignee or subtenant, is then an occupant of the Project (for whom alternate space in the Building is then-currently available that meets such party's needs); (10) the proposed assignee or subtenant is an entity with whom Landlord is then-currently negotiating to lease space in the Project; or (11) the assignment or sublease is prohibited by Landlord's lender. If Landlord delivers notice of its election to exercise an Assignment Termination, Tenant shall have the right to withdraw such Assignment Notice by written notice to Landlord of such election within 5 business days after Landlord's notice electing to exercise the Assignment Termination. If Tenant withdraws such Assignment Notice, this Lease shall continue in full force and effect. If Tenant does not withdraw such Assignment Notice, this Lease, and the term and estate herein granted, shall terminate as of the Assignment Date with respect to the space described in such Assignment Notice. No failure of Landlord to exercise

any such option to terminate this Lease, or to deliver a timely notice in response to the Assignment Notice, shall be deemed to be Landlord's consent to the proposed assignment, sublease or other transfer. Tenant shall pay to Landlord a fee equal to Two Thousand Dollars ($2,000) in connection with its consideration of any Assignment Notice and/or its preparation or review of any consent documents. Notwithstanding the foregoing, Landlord's consent to an assignment of this Lease or a subletting of any portion of the Premises to any entity controlling, controlled by or under common control with Tenant (a "**Control Permitted Assignment**") shall not be required, provided that Landlord shall have the right to reasonably approve the form of any such sublease or assignment. In addition, Tenant shall have the right to assign this Lease, upon 30 days prior written notice to Landlord ((x) unless Tenant is prohibited from providing such notice by applicable Legal Requirements in which case Tenant shall notify Landlord promptly thereafter, and (y) if the transaction is subject to confidentiality requirements, Tenant's advance notification shall be subject to Landlord's execution of a non-disclosure agreement reasonably acceptable to Landlord and Tenant) but without obtaining Landlord's prior written consent, to a corporation or other entity which is a successor-in-interest to Tenant, by way of merger, consolidation or corporate reorganization, or by the purchase of all or substantially all of the assets, stock or other ownership interests of Tenant provided that (i) such merger or consolidation, or such acquisition or assumption, as the case may be, is for a good business purpose and not principally for the purpose of transferring this Lease, and (ii) the net worth (as determined in accordance with generally accepted accounting principles ("**GAAP**")) of the assignee is not less than the greater of the net worth (as determined in accordance with GAAP) of Tenant as of (A) the Commencement Date, or (B) as of the date of Tenant's most current quarterly or annual financial statements, and (iii) such assignee shall, to the extent that the surviving entity is not Ultragenyx Pharmaceutical Inc., a Delaware corporation, such assignee shall agree in writing to assume all of the terms, covenants and conditions of this Lease (a "**Corporate Permitted Assignment**"). Control Permitted Assignments and Corporate Permitted Assignments are hereinafter referred to as "**Permitted Assignments**." The rights provided to Tenant herein with respect to a Corporate Permitted Assignment shall be personal to Ultragenyx Pharmaceutical Inc., a Delaware corporation, in connection with this Lease only and shall not inure to the benefit of any assignee, sublessee or other transferee of Ultragenyx Pharmaceutical Inc.'s interest in this Lease, other than in connection with a Permitted Assignment.

(c) **Additional Conditions**. As a condition to any such assignment or subletting, whether or not Landlord's consent is required, Landlord may require:

(i) that any assignee or subtenant agree, in writing at the time of such assignment or subletting, that if Landlord gives such party notice that Tenant is in default under this Lease, such party shall thereafter make all payments otherwise due Tenant directly to Landlord, which payments will be received by Landlord without any liability except to credit such payment against those due under this Lease, and any such third party shall agree to attorn to Landlord or its successors and assigns should this Lease be terminated for any reason; provided, however, in no event shall Landlord or its successors or assigns be obligated to accept such attornment; and

(ii) A list of Hazardous Materials, certified by the proposed assignee or sublessee to be true and correct, which the proposed assignee or sublessee intends to use, store, handle, treat, generate in or release or dispose of from the Premises, together with copies of all documents relating to such use, storage, handling, treatment, generation, release or disposal of Hazardous Materials by the proposed assignee or subtenant in the Premises or on the Project, prior to the proposed assignment or subletting, including, without limitation: permits; approvals; reports and correspondence; storage and management plans; plans relating to the installation of any storage tanks to be installed in or under the Project (provided, said installation of tanks shall only be permitted after Landlord has given its written consent to do so, which consent may be withheld in Landlord's sole and absolute discretion); and all closure plans or any other documents required by any and all federal, state and local Governmental Authorities for any storage tanks installed in, on or under the Project for the closure of any such tanks. Neither Tenant nor any such proposed assignee or subtenant is required, however, to provide Landlord with any portion(s) of the such documents containing information of a proprietary nature which, in and of themselves, do not contain a reference to any Hazardous Materials or hazardous activities.

(d) **No Release of Tenant, Sharing of Excess Rents**. Notwithstanding any assignment or subletting, Tenant and any guarantor or surety of Tenant's obligations under this Lease shall at all times remain fully and primarily responsible and liable for the payment of Rent and for compliance with all of Tenant's other obligations under this

Lease. Except in connection with Permitted Assignments, if the Rent due and payable by a sublessee or assignee (or a combination of the rental payable under such sublease or assignment plus any bonus or other consideration therefor or incident thereto in any form) exceeds the sum of the rental payable under this Lease, (excluding however, any Rent payable under this Section) and actual and reasonable brokerage fees, legal costs and any design or construction fees directly related to and required pursuant to the terms of any such sublease) ("**Excess Rent**"), then Tenant shall be bound and obligated to pay Landlord as Additional Rent hereunder 50% of such Excess Rent within 10 business days following receipt thereof by Tenant. If Tenant shall sublet the Premises or any part thereof, Tenant hereby immediately and irrevocably assigns to Landlord, as security for Tenant's obligations under this Lease, all rent from any such subletting, and Landlord as assignee and as attorney-in-fact for Tenant, or a receiver for Tenant appointed on Landlord's application, may collect such rent and apply it toward Tenant's obligations under this Lease; except that, until the occurrence of a Default, Tenant shall have the right to collect such rent.

(e) **No Waiver**. The consent by Landlord to an assignment or subletting shall not relieve Tenant or any assignees of this Lease or any sublessees of the Premises from obtaining the consent of Landlord to any further assignment or subletting nor shall it release Tenant or any assignee or sublessee of Tenant from full and primary liability under this Lease. The acceptance of Rent hereunder, or the acceptance of performance of any other term, covenant, or condition thereof, from any other person or entity shall not be deemed to be a waiver of any of the provisions of this Lease or a consent to any subletting, assignment or other transfer of the Premises.

(f) **Prior Conduct of Proposed Transferee**. Notwithstanding any other provision of this Section 22, if (i) the proposed assignee or sublessee of Tenant has been required by any prior landlord, lender or Governmental Authority to take remedial action in connection with Hazardous Materials contaminating a property, where the contamination resulted from such party's action or use of the property in question, (ii) the proposed assignee or sublessee is subject to an enforcement order issued by any Governmental Authority in connection with the use, storage, handling, treatment, generation, release or disposal of Hazardous Materials (including, without limitation, any order related to the failure to make a required reporting to any Governmental Authority), or (iii) because of the existence of a pre-existing environmental condition in the vicinity of or underlying the Project, the risk that Landlord would be targeted as a responsible party in connection with the remediation of such pre-existing environmental condition would be materially increased or exacerbated by the proposed use of Hazardous Materials by such proposed assignee or sublessee, Landlord shall have the absolute right to refuse to consent to any assignment or subletting to any such party.

23. **Estoppel Certificate**. Tenant shall, within 15 business days of written notice from Landlord, execute, acknowledge and deliver a statement in writing in any form reasonably requested by a proposed lender or purchaser, (i) certifying that this Lease is unmodified and in full force and effect (or, if modified, stating the nature of such modification and certifying that this Lease as so modified is in full force and effect) and the dates to which the rental and other charges are paid in advance, if any, (ii) acknowledging that, to Tenant's actual knowledge, there are not any uncured defaults on the part of Landlord hereunder, or specifying such defaults if any are claimed, and (iii) setting forth such further information with respect to the status of this Lease or the Premises as may be reasonably requested thereon. Any such statement may be relied upon by any prospective purchaser or encumbrancer of all or any portion of the real property of which the Premises are a part. Tenant's failure to deliver such statement within 5 business days after a second notice requesting such document shall be conclusive upon Tenant that this Lease is in full force and effect and without modification except as may be represented by Landlord in any certificate prepared by Landlord and delivered to Tenant for execution.

24. **Quiet Enjoyment**. So long as Tenant is not in Default under this Lease, Tenant shall, subject to the terms of this Lease, at all times during the Term, have peaceful and quiet enjoyment of the Premises against any person claiming by, through or under Landlord.

25. **Prorations**. All prorations required or permitted to be made hereunder shall be made on the basis of a 360 day year and 30 day months.

26. **Rules and Regulations**. Tenant shall, at all times during the Term and any extension thereof, comply with all reasonable rules and regulations at any time or from time to time established by Landlord covering use of the Premises and the Project. The current rules and regulations are attached hereto as **Exhibit E**. If there is any conflict between said rules and regulations and other provisions of this Lease, the terms and provisions of this

Lease shall control. Landlord shall not have any liability or obligation for the breach of any rules or regulations by other tenants in the Project and shall not enforce such rules and regulations in a discriminatory manner.

27. **Subordination**. This Lease and Tenant's interest and rights hereunder are hereby made and shall be subject and subordinate at all times to the lien of any Mortgage now existing or hereafter created on or against the Project or the Premises, and all amendments, restatements, renewals, modifications, consolidations, refinancing, assignments and extensions thereof, without the necessity of any further instrument or act on the part of Tenant; provided, however that so long as there is no Default hereunder, Tenant's right to possession of the Premises shall not be disturbed by the Holder of any such Mortgage. Tenant agrees, at the election of the Holder of any such Mortgage, to attorn to any such Holder. Tenant agrees upon demand to execute, acknowledge and deliver such instruments, confirming such subordination, and such instruments of attornment as shall be requested by any such Holder, provided any such instruments contain appropriate non-disturbance provisions assuring Tenant's quiet enjoyment of the Premises as set forth in Section 24 hereof. Notwithstanding the foregoing, any such Holder may at any time subordinate its Mortgage to this Lease, without Tenant's consent, by notice in writing to Tenant, and thereupon this Lease shall be deemed prior to such Mortgage without regard to their respective dates of execution, delivery or recording and in that event such Holder shall have the same rights with respect to this Lease as though this Lease had been executed prior to the execution, delivery and recording of such Mortgage and had been assigned to such Holder. The term "**Mortgage**" whenever used in this Lease shall be deemed to include deeds of trust, security assignments and any other encumbrances, and any reference to the "**Holder**" of a Mortgage shall be deemed to include the beneficiary under a deed of trust. As of the date of this Lease, there is no existing Mortgage encumbering the Project.

28. **Surrender**. Upon the expiration of the Term or earlier termination of Tenant's right of possession, Tenant shall surrender the Premises to Landlord in the same condition as received, subject to any Alterations or Installations permitted by Landlord to remain in the Premises, free of Hazardous Materials brought upon, kept, used, stored, handled, treated, generated in, or released or disposed of from, the Premises by any person other than a Landlord Party (collectively, "**Tenant HazMat Operations**") and released of all Hazardous Materials Clearances, broom clean, ordinary wear and tear and casualty loss and condemnation covered by Sections 18 and 19 excepted. At least 3 months prior to the surrender of the Premises or such earlier date as Tenant may elect to cease operations at the Premises, Tenant shall deliver to Landlord a narrative description of the actions proposed (or required by any Governmental Authority) to be taken by Tenant in order to surrender the Premises (including any Installations permitted by Landlord to remain in the Premises) at the expiration or earlier termination of the Term, free from any residual impact from the Tenant HazMat Operations and otherwise released for unrestricted use and occupancy (the "**Decommissioning and HazMat Closure Plan**"). Such Decommissioning and HazMat Closure Plan shall be accompanied by a current listing of (i) all Hazardous Materials licenses and permits held by or on behalf of any Tenant Party with respect to the Premises, and (ii) all Hazardous Materials used, stored, handled, treated, generated, released or disposed of from the Premises, and shall be subject to the review and approval of Landlord's environmental consultant. In connection with the review and approval of the Decommissioning and HazMat Closure Plan, upon the request of Landlord, Tenant shall deliver to Landlord or its consultant such additional non-proprietary information concerning Tenant HazMat Operations as Landlord shall request. On or before such surrender, Tenant shall deliver to Landlord evidence that the approved Decommissioning and HazMat Closure Plan shall have been satisfactorily completed and Landlord shall have the right, subject to reimbursement at Tenant's expense as set forth below, to cause Landlord's environmental consultant to inspect the Premises and perform such additional procedures as may be deemed reasonably necessary to confirm that the Premises are, as of the effective date of such surrender or early termination of this Lease, free from any residual impact from Tenant HazMat Operations. Tenant shall reimburse Landlord, as Additional Rent, for the actual out-of-pocket expense incurred by Landlord for Landlord's environmental consultant to review and approve the Decommissioning and HazMat Closure Plan and to visit the Premises and verify satisfactory completion of the same, which cost shall not exceed $2,500. Landlord shall have the unrestricted right to deliver such Decommissioning and HazMat Closure Plan and any report by Landlord's environmental consultant with respect to the surrender of the Premises to third parties.

If Tenant shall fail to prepare or submit a Decommissioning and HazMat Closure Plan approved by Landlord, or if Tenant shall fail to complete the approved Decommissioning and HazMat Closure Plan, or if such Decommissioning and HazMat Closure Plan, whether or not approved by Landlord, shall fail to adequately address any residual effect of Tenant HazMat Operations in, on or about the Premises, Landlord shall have the right to take such actions as Landlord may deem reasonable or appropriate to assure that the Premises and the Project are

surrendered free from any residual impact from Tenant HazMat Operations, the cost of which actions shall be reimbursed by Tenant as Additional Rent, without regard to the limitation set forth in the first paragraph of this Section 28.

Tenant shall immediately return to Landlord all keys and/or access cards to parking, the Project, restrooms or all or any portion of the Premises furnished to or otherwise procured by Tenant. If any such access card or key is lost, Tenant shall pay to Landlord, at Landlord's election, either the cost of replacing such lost access card or key or the cost of reprogramming the access security system in which such access card was used or changing the lock or locks opened by such lost key. Any Tenant's Property, Alterations and property not so removed by Tenant as permitted or required herein shall be deemed abandoned and may be stored, removed, and disposed of by Landlord at Tenant's expense, and Tenant waives all claims against Landlord for any damages resulting from Landlord's retention and/or disposition of such property. All obligations of Tenant hereunder not fully performed as of the termination of the Term, including the obligations of Tenant under Section 30 hereof, shall survive the expiration or earlier termination of the Term, including, without limitation, indemnity obligations, payment obligations with respect to Rent and obligations concerning the condition and repair of the Premises.

29. **Waiver of Jury Trial**. TO THE EXTENT PERMITTED BY LAW, TENANT AND LANDLORD WAIVE ANY RIGHT TO TRIAL BY JURY OR TO HAVE A JURY PARTICIPATE IN RESOLVING ANY DISPUTE, WHETHER SOUNDING IN CONTRACT, TORT, OR OTHERWISE, BETWEEN LANDLORD AND TENANT ARISING OUT OF THIS LEASE OR ANY OTHER INSTRUMENT, DOCUMENT, OR AGREEMENT EXECUTED OR DELIVERED IN CONNECTION HEREWITH OR THE TRANSACTIONS RELATED HERETO.

30. **Environmental Requirements**.

(a) **Prohibition/Compliance/Indemnity**. Tenant shall not cause or permit any Hazardous Materials (as hereinafter defined) to be brought upon, kept, used, stored, handled, treated, generated in or about, or released or disposed of from, the Premises or the Project in violation of applicable Environmental Requirements (as hereinafter defined) by Tenant or any Tenant Party. If Tenant breaches the obligation stated in the preceding sentence, or if the presence of Hazardous Materials in the Premises during the Term or any other period of occupancy of the Premises by Tenant over results in contamination of the Premises, the Project or any adjacent property or if contamination of the Premises, the Project or any adjacent property by Hazardous Materials brought into, kept, used, stored, handled, treated, generated in or about, or released or disposed of from, the Premises by anyone other than Landlord and Landlord's employees, agents and contractors otherwise occurs during the Term or any other period of occupancy of the Premises by Tenant, Tenant hereby indemnifies and shall defend and hold Landlord, its officers, directors, employees, agents and contractors harmless from any and all actions (including, without limitation, remedial or enforcement actions of any kind, administrative or judicial proceedings, and orders or judgments arising out of or resulting therefrom), costs, claims, damages (including, without limitation, punitive damages and damages based upon diminution in value of the Premises or the Project, or the loss of, or restriction on, use of the Premises or any portion of the Project), expenses (including, without limitation, attorneys', consultants' and experts' fees, court costs and amounts paid in settlement of any claims or actions), fines, forfeitures or other civil, administrative or criminal penalties, injunctive or other relief (whether or not based upon personal injury, property damage, or contamination of, or adverse effects upon, the environment, water tables or natural resources), liabilities or losses (collectively, "**Environmental Claims**") which arise during or after the Term as a result of such contamination. This indemnification of Landlord by Tenant includes, without limitation, costs incurred in connection with any investigation of site conditions or any cleanup, treatment, remedial, removal, or restoration work required by any federal, state or local Governmental Authority because of Hazardous Materials present in the air, soil or ground water above, on, or under the Premises. Without limiting the foregoing, if the presence of any Hazardous Materials on the Premises, the Project or any adjacent property caused or permitted by Tenant or any Tenant Party results in any contamination of the Premises, the Project or any adjacent property, Tenant shall promptly take all actions at its sole expense and in accordance with applicable Environmental Requirements as are necessary to return the Premises, the Project or any adjacent property to the condition existing prior to the time of such contamination, provided that Landlord's approval of such action shall first be obtained, which approval shall not unreasonably be withheld so long as such actions would not potentially have any material adverse long-term or short-term effect on the Premises or the Project. Notwithstanding anything to the contrary contained in Section 28 or this Section 30, Tenant shall not be responsible for, and the indemnification and hold harmless obligation set forth in this paragraph shall not apply to (i)

contamination in the Premises which Tenant can prove existed in the Premises prior to Tenant's occupancy of the Premises, or (ii) the presence of any Hazardous Materials in the Premises which Tenant can prove migrated from outside of the Premises into the Premises, unless in either case, the presence of such Hazardous Materials (x) is the result of a breach by Tenant of any of its obligations under this Lease, or (y) was caused, contributed to or exacerbated by Tenant or any Tenant Party.

(b) **Business**. Landlord acknowledges that it is not the intent of this Section 30 to prohibit Tenant from using the Premises for the Permitted Use. Tenant may operate its business according to prudent industry practices so long as the use or presence of Hazardous Materials is strictly and properly monitored according to all then applicable Environmental Requirements. As a material inducement to Landlord to allow Tenant to use Hazardous Materials in connection with its business, Tenant agrees to deliver to Landlord prior to the Commencement Date a list identifying each type of Hazardous Materials to be brought upon, kept, used, stored, handled, treated, generated on, or released or disposed of from, the Premises and setting forth any and all governmental approvals or permits required in connection with the presence, use, storage, handling, treatment, generation, release or disposal of such Hazardous Materials on or from the Premises ("**Hazardous Materials List**"). Upon Landlord's request, or any time that Tenant is required to deliver a Hazardous Materials List to any Governmental Authority (e.g., the fire department) in connection with Tenant's use or occupancy of the Premises, Tenant shall deliver to Landlord a copy of such Hazardous Materials List. Tenant shall deliver to Landlord true and correct copies of the following documents (the "**Haz Mat Documents**") relating to the use, storage, handling, treatment, generation, release or disposal of Hazardous Materials prior to the Commencement Date, or if unavailable at that time, concurrent with the receipt from or submission to a Governmental Authority: permits; approvals; reports and correspondence; storage and management plans, notice of violations of any Legal Requirements; plans relating to the installation of any storage tanks to be installed in or under the Project (provided, said installation of tanks shall only be permitted after Landlord has given Tenant its written consent to do so, which consent may be withheld in Landlord's sole and absolute discretion); all closure plans or any other documents required by any and all federal, state and local Governmental Authorities for any storage tanks installed in, on or under the Project for the closure of any such tanks; and a Decommissioning and HazMat Closure Plan (to the extent surrender in accordance with Section 28 cannot be accomplished in 3 months). Tenant is not required, however, to provide Landlord with any portion(s) of the Haz Mat Documents containing information of a proprietary nature which, in and of themselves, do not contain a reference to any Hazardous Materials or hazardous activities. It is not the intent of this Section to provide Landlord with information which could be detrimental to Tenant's business should such information become possessed by Tenant's competitors.

(c) **Tenant Representation and Warranty**. Tenant hereby represents and warrants to Landlord that (i) neither Tenant nor any of its legal predecessors has been required by any prior landlord, lender or Governmental Authority at any time to take remedial action in connection with Hazardous Materials contaminating a property which contamination was permitted by Tenant of such predecessor or resulted from Tenant's or such predecessor's action or use of the property in question, and (ii) Tenant is not subject to any enforcement order issued by any Governmental Authority in connection with the use, storage, handling, treatment, generation, release or disposal of Hazardous Materials (including, without limitation, any order related to the failure to make a required reporting to any Governmental Authority). If Landlord determines that this representation and warranty was not true as of the date of this lease, Landlord shall have the right to terminate this Lease in Landlord's sole and absolute discretion.

(d) **Testing**. Landlord shall have the right to conduct annual tests of the Premises to determine whether any contamination of the Premises or the Project has occurred as a result of Tenant's use. Tenant shall be required to pay the cost of such annual test of the Premises; provided, however, that if Tenant conducts its own tests of the Premises using third party contractors and test procedures acceptable to Landlord which tests are certified to Landlord, Landlord shall accept such tests in lieu of the annual tests to be paid for by Tenant. In addition, at any time, and from time to time, prior to the expiration or earlier termination of the Term, Landlord shall have the right to conduct appropriate tests of the Premises and the Project to determine if contamination has occurred as a result of Tenant's use of the Premises. In connection with such testing, upon the request of Landlord, Tenant shall deliver to Landlord or its consultant such non-proprietary information concerning the use of Hazardous Materials in or about the Premises by Tenant or any Tenant Party. If contamination has occurred for which Tenant is liable under this Section 30, Tenant shall pay all costs to conduct such tests. If no such contamination is found, Landlord shall pay the costs of such tests (which shall not constitute an Operating Expense). Landlord shall provide Tenant with a copy of all third party, non-confidential reports and tests of the Premises made by or on behalf of Landlord during the Term without representation

or warranty and subject to a confidentiality agreement. Tenant shall, at its sole cost and expense, promptly and satisfactorily remediate any environmental conditions identified by such testing in accordance with all Environmental Requirements. Landlord's receipt of or satisfaction with any environmental assessment in no way waives any rights which Landlord may have against Tenant.

(e) **Control Areas**. Tenant shall be allowed to utilize up to its pro rata share of the Hazardous Materials inventory within any control area or zone (located within the Premises), as designated by the applicable building code, for chemical use or storage. As used in the preceding sentence, Tenant's pro rata share of any control areas or zones located within the Premises shall be determined based on the rentable square footage that Tenant leases within the applicable control area or zone. For purposes of example only, if a control area or zone contains 10,000 rentable square feet and 2,000 rentable square feet of a tenant's premises are located within such control area or zone (while such premises as a whole contains 5,000 rentable square feet), the applicable tenant's pro rata share of such control area would be 20%.

(f) **Underground Tanks**. If underground or other storage tanks storing Hazardous Materials located on the Premises or the Project are used by Tenant or are hereafter placed on the Premises or the Project by Tenant, Tenant shall install, use, monitor, operate, maintain, upgrade and manage such storage tanks, maintain appropriate records, obtain and maintain appropriate insurance, implement reporting procedures, properly close any underground storage tanks, and take or cause to be taken all other actions necessary or required under applicable state and federal Legal Requirements, as such now exists or may hereafter be adopted or amended in connection with the installation, use, maintenance, management, operation, upgrading and closure of such storage tanks.

(g) **Tenant's Obligations**. Tenant's obligations under this Section 30 shall survive the expiration or earlier termination of this Lease. During any period of time after the expiration or earlier termination of this Lease required by Tenant or Landlord to complete the removal from the Premises of any Hazardous Materials for which Tenant is responsible under this Lease (including, without limitation, the release and termination of any licenses or permits restricting the use of the Premises and the completion of the approved Decommissioning and HazMat Closure Plan), Tenant shall continue to pay the full Rent in accordance with this Lease for any portion of the Premises not relet by Landlord in Landlord's sole discretion, which Rent shall be prorated daily.

(h) **Definitions**. As used herein, the term "**Environmental Requirements**" means all applicable present and future statutes, regulations, ordinances, rules, codes, judgments, orders or other similar enactments of any Governmental Authority regulating or relating to health, safety, or environmental conditions on, under, or about the Premises or the Project, or the environment, including without limitation, the following: the Comprehensive Environmental Response, Compensation and Liability Act; the Resource Conservation and Recovery Act; and all state and local counterparts thereto, and any regulations or policies promulgated or issued thereunder. As used herein, the term "**Hazardous Materials**" means and includes any substance, material, waste, pollutant, or contaminant listed or defined as hazardous or toxic, or regulated by reason of its impact or potential impact on humans, animals and/or the environment under any Environmental Requirements, asbestos and petroleum, including crude oil or any fraction thereof, natural gas liquids, liquefied natural gas, or synthetic gas usable for fuel (or mixtures of natural gas and such synthetic gas). As defined in Environmental Requirements, Tenant is and shall be deemed to be the "**operator**" of Tenant's "**facility**" and the "**owner**" of all Hazardous Materials brought on the Premises by Tenant or any Tenant Party, and the wastes, by-products, or residues generated, resulting, or produced therefrom.

31. **Tenant's Remedies/Limitation of Liability**. Landlord shall not be in default hereunder unless Landlord fails to perform any of its obligations hereunder within 30 days after written notice from Tenant specifying such failure (unless such performance will, due to the nature of the obligation, require a period of time in excess of 30 days, then after such period of time as is reasonably necessary). Upon any default by Landlord, Tenant shall give notice by registered or certified mail to any Holder of a Mortgage covering the Premises and to any landlord of any lease of property in or on which the Premises are located and Tenant shall offer such Holder and/or landlord a reasonable opportunity to cure the default, including time to obtain possession of the Project by power of sale or a judicial action if such should prove necessary to effect a cure; provided Landlord shall have furnished to Tenant in writing the names and addresses of all such persons who are to receive such notices. All obligations of Landlord hereunder shall be construed as covenants, not conditions; and, except as may be otherwise expressly provided in this Lease, Tenant may not terminate this Lease for breach of Landlord's obligations hereunder.

Notwithstanding the foregoing, if any claimed Landlord default hereunder will immediately, materially and adversely affect Tenant's ability to conduct its business in the Premises (a "**Material Landlord Default**"), Tenant shall, as soon as reasonably possible, but in any event within 2 business days of obtaining knowledge of such claimed Material Landlord Default, give Landlord written notice of such claim which notice shall specifically state that a Material Landlord Default exists and telephonic notice to Tenant's principal contact with Landlord. Landlord shall then have 2 business days to commence cure of such claimed Material Landlord Default and shall diligently prosecute such cure to completion. If such claimed Material Landlord Default is not a default by Landlord hereunder, Landlord shall be entitled to recover from Tenant, as Additional Rent, any costs incurred by Landlord in connection with such cure in excess of the costs, if any, that Landlord would otherwise have been liable to pay hereunder. If Landlord fails to commence cure of any claimed Material Landlord Default as provided above, Tenant may commence and prosecute such cure to completion provided that it does not affect any Building Systems affecting other tenants, the Building structure or Common Areas, and shall be entitled to recover the costs of such cure (but not any consequential or other damages) from Landlord by way of reimbursement from Landlord with no right to offset against Rent, to the extent of Landlord's obligation to cure such claimed Material Landlord Default hereunder, subject to the limitations set forth in the immediately preceding sentence of this paragraph and the other provisions of this Lease.

All obligations of Landlord under this Lease will be binding upon Landlord only during the period of its ownership of the Premises and not thereafter. The term "**Landlord**" in this Lease shall mean only the owner for the time being of the Premises. Upon the transfer by such owner of its interest in the Premises, such owner shall thereupon be released and discharged from all obligations of Landlord thereafter accruing, but such obligations shall be binding during the Term upon each new owner for the duration of such owner's ownership.

32. **Inspection and Access**. Landlord and its agents, representatives, and contractors may enter the Premises at any reasonable time to inspect the Premises and to make such repairs as may be required or permitted pursuant to this Lease and for any other business purpose. Landlord and Landlord's representatives may enter the Premises during business hours on not less than 48 hours advance written notice (except in the case of emergencies in which case no such notice shall be required and such entry may be at any time) for the purpose of effecting any such repairs, inspecting the Premises, showing the Premises to prospective purchasers and, during the last 12 months of the Term, to prospective tenants or for any other business purpose. Landlord may grant easements, make public dedications, designate Common Areas and create restrictions on or about the Premises, provided that no such easement, dedication, designation or restriction materially, adversely affects Tenant's use of the Premises for the Permitted Use or Tenant's occupancy of, or access to or from, the Premises, or Tenant's parking rights under Section 10. At Landlord's request, Tenant shall execute such instruments as may be necessary for such easements, dedications or restrictions. Tenant shall at all times, except in the case of emergencies, have the right to escort Landlord or its agents, representatives, contractors or guests while the same are in the Premises, provided such escort does not materially and adversely affect Landlord's access rights hereunder.

33. **Security**. Tenant acknowledges and agrees that security devices and services, if any, while intended to deter crime may not in given instances prevent theft or other criminal acts and that Landlord is not providing any security services with respect to the Premises. Tenant agrees that Landlord shall not be liable to Tenant for, and Tenant waives any claim against Landlord with respect to, any loss by theft or any other damage suffered or incurred by Tenant in connection with any unauthorized entry into the Premises or any other breach of security with respect to the Premises. Tenant shall be solely responsible for the personal safety of Tenant's officers, employees, agents, contractors, guests and invitees while any such person is in, on or about the Premises and/or the Project. Tenant shall at Tenant's cost obtain insurance coverage to the extent Tenant desires protection against such criminal acts.

34. **Force Majeure**. Except for the payment of Rent, neither Landlord nor Tenant shall be held responsible or liable for delays in the performance of its obligations hereunder when caused by, related to, or arising out of acts of God, sinkholes or subsidence, strikes, lockouts, or other labor disputes, embargoes, quarantines, weather, national, regional, or local disasters, calamities, or catastrophes, inability to obtain labor or materials (or reasonable substitutes therefor) at reasonable costs or failure of, or inability to obtain, utilities necessary for performance, governmental restrictions, orders, limitations, regulations, or controls, national emergencies, delay in issuance or revocation of permits, enemy or hostile governmental action, terrorism, insurrection, riots, civil disturbance or commotion, fire or other casualty, and other causes or events beyond their reasonable control ("**Force Majeure**").

35. **Brokers**. Landlord and Tenant each represents and warrants that it has not dealt with any broker, agent or other person (collectively, "**Broker**") in connection with this transaction and that no Broker brought about this transaction, other than Kidder Mathews and Jones Lang LaSalle. Landlord and Tenant each hereby agree to indemnify and hold the other harmless from and against any claims by any Broker, other than Kidder Mathews and Jones Lang LaSalle, claiming a commission or other form of compensation by virtue of having dealt with Tenant or Landlord, as applicable, with regard to this leasing transaction. Landlord shall be responsible for all commissions due to Kidder Mathews and Jones Lang LaSalle arising out of the execution of this Lease in accordance with the terms of a separate written agreements between Landlord, on the one hand, and Kidder Mathews and Jones Lang LaSalle, on the other hand.

36. **Limitation on Landlord's Liability**. NOTWITHSTANDING ANYTHING SET FORTH HEREIN OR IN ANY OTHER AGREEMENT BETWEEN LANDLORD AND TENANT TO THE CONTRARY: (A) LANDLORD SHALL NOT BE LIABLE TO TENANT OR ANY OTHER PERSON FOR (AND TENANT AND EACH SUCH OTHER PERSON ASSUME ALL RISK OF) LOSS, DAMAGE OR INJURY, WHETHER ACTUAL OR CONSEQUENTIAL TO: TENANT'S PERSONAL PROPERTY OF EVERY KIND AND DESCRIPTION, INCLUDING, WITHOUT LIMITATION TRADE FIXTURES, EQUIPMENT, INVENTORY, SCIENTIFIC RESEARCH, SCIENTIFIC EXPERIMENTS, LABORATORY ANIMALS, PRODUCT, SPECIMENS, SAMPLES, AND/OR SCIENTIFIC, BUSINESS, ACCOUNTING AND OTHER RECORDS OF EVERY KIND AND DESCRIPTION KEPT AT THE PREMISES AND ANY AND ALL INCOME DERIVED OR DERIVABLE THEREFROM; (B) THERE SHALL BE NO PERSONAL RECOURSE TO LANDLORD FOR ANY ACT OR OCCURRENCE IN, ON OR ABOUT THE PREMISES OR ARISING IN ANY WAY UNDER THIS LEASE OR ANY OTHER AGREEMENT BETWEEN LANDLORD AND TENANT WITH RESPECT TO THE SUBJECT MATTER HEREOF AND ANY LIABILITY OF LANDLORD HEREUNDER SHALL BE STRICTLY LIMITED SOLELY TO LANDLORD'S INTEREST IN THE PROJECT OR ANY PROCEEDS FROM SALE OR CONDEMNATION THEREOF AND ANY INSURANCE PROCEEDS PAYABLE IN RESPECT OF LANDLORD'S INTEREST IN THE PROJECT OR IN CONNECTION WITH ANY SUCH LOSS; AND (C) IN NO EVENT SHALL ANY PERSONAL LIABILITY BE ASSERTED AGAINST LANDLORD IN CONNECTION WITH THIS LEASE NOR SHALL ANY RECOURSE BE HAD TO ANY OTHER PROPERTY OR ASSETS OF LANDLORD OR ANY OF LANDLORD'S OFFICERS, DIRECTORS, EMPLOYEES, AGENTS OR CONTRACTORS. UNDER NO CIRCUMSTANCES SHALL LANDLORD OR ANY OF LANDLORD'S OFFICERS, DIRECTORS, EMPLOYEES, AGENTS OR CONTRACTORS BE LIABLE FOR INJURY TO TENANT'S BUSINESS OR FOR ANY LOSS OF INCOME OR PROFIT THEREFROM.

37. **Severability**. If any clause or provision of this Lease is illegal, invalid or unenforceable under present or future laws, then and in that event, it is the intention of the parties hereto that the remainder of this Lease shall not be affected thereby. It is also the intention of the parties to this Lease that in lieu of each clause or provision of this Lease that is illegal, invalid or unenforceable, there be added, as a part of this Lease, a clause or provision as similar in effect to such illegal, invalid or unenforceable clause or provision as shall be legal, valid and enforceable.

38. **Signs; Exterior Appearance**. Tenant shall not, without the prior written consent of Landlord, which may be granted or withheld in Landlord's sole discretion: (i) attach any awnings, exterior lights, decorations, balloons, flags, pennants, banners, painting or other projection to any outside wall of the Project, (ii) use any curtains, blinds, shades or screens other than Landlord's standard window coverings, (iii) coat or otherwise sunscreen the interior or exterior of any windows, (iv) place any bottles, parcels, or other articles on the window sills, (v) place any equipment, furniture or other items of personal property on any exterior balcony, or (vi) paint, affix or exhibit on any part of the Premises or the Project any signs, notices, window or door lettering, placards, decorations, or advertising media of any type which can be viewed from the exterior of the Premises. Interior signs on doors and signage on the directory tablet shall be inscribed, painted or affixed for Tenant by Landlord at the sole cost and expense of Tenant, and shall be of a size, color and type acceptable to Landlord. Nothing may be placed on the exterior of corridor walls or corridor doors other than Landlord's standard lettering. The directory tablet shall be provided exclusively for the display of the name and location of tenants.

39. **Right to Expand**.

(a) **Right of First Refusal**. Subject to the rights of existing tenants of the Project and the terms of this Section 39(a), the first time after the date of this Lease through December 31, 2020 (the "**ROFR Expiration Date**"), that Landlord intends to accept a bona fide written proposal or deliver a counter proposal which Landlord would be willing to accept (the "**Pending Deal**") to lease all or a portion the ROFR Space (as hereinafter defined) to a third party, Landlord shall deliver to Tenant written notice (the "**Pending Deal Notice**") of the existence of such Pending Deal, which Pending Deal Notice shall include the material terms of the Pending Deal. For purposes of this Section 39(a), "**ROFR Space**" that certain space on the first floor of the Building containing approximately 14,834 rentable square feet, as more particularly described on **Exhibit G** attached hereto, which is not occupied by a tenant or which is occupied by an existing tenant whose lease is expiring within 9 months or less and such tenant does not wish to renew (whether or not such tenant has a right to renew) its occupancy of such space. For the avoidance of doubt, Tenant shall be required to exercise its right under this Section 39(a) with respect to all of the space described in the Pending Deal Notice, including, at Landlord's option, any space in addition to the ROFR Space that is described in the Pending Deal Notice, which additional space shall be deemed to be included as part of the ROFR Space (the "**Identified Space**"). Within 10 days after Tenant's receipt of the Pending Deal Notice, Tenant shall deliver to Landlord written notice (the "**Acceptance Notice**") if Tenant elects to lease the Identified Space. Tenant's right to receive the Pending Deal Notice and election to lease or not lease the Identified Space pursuant to this Section 39(a) is hereinafter referred to as the "**Right of First Refusal**." If Tenant elects to lease the Identified Space described in the Pending Deal Notice by delivering the Space Acceptance Notice within the required 10 day period, Tenant shall be deemed to agree to expand the Premises to include the Identified Space and to lease the Identified Space on the same general terms and conditions as this Lease except that the terms of this Lease shall be modified to reflect the terms of the Pending Deal Notice for the rental of the Identified Space. If the Identified Space subject to a Pending Deal Notice does not include all of the ROFR Space, Tenant's Right of First Refusal shall continue (through the ROFR Expiration Date) to apply with respect to any remaining portion of the ROFR Space. Tenant acknowledges that the term of this Lease with respect to the Identified Space and the Term of this Lease with respect to the existing Premises may not be co-terminous. Notwithstanding anything to the contrary contained herein, in no event shall the Work Letter apply to the Identified Space. If Tenant fails to deliver an Acceptance Notice to Landlord within the required 10 day period, Tenant shall be deemed to have waived its rights under this Section 39(a) to lease the Identified Space, and Landlord shall have the right to lease the Identified Space to the third party subject to the Pending Deal (or an affiliate of such third party) ("**Pending Deal Party**") on substantially the same business terms and conditions set forth in the Pending Deal Notice. Notwithstanding the foregoing, Tenant's Right of First Refusal shall be restored if Landlord fails to enter into an agreement to lease the Identified Space to the Pending Deal Party within 6 months after Landlord's delivery of the Pending Deal Notice to Tenant; provided, however, that in no event shall Tenant's Right of First Refusal continue beyond the ROFR Expiration Date.

(b) **Amended Lease**. If: (i) Tenant fails to timely deliver an Acceptance Notice, or (ii) after the expiration of a period of 10 days after Landlord's delivery to Tenant of a lease amendment for Tenant's lease of the Identified Space, no lease amendment for the Identified Space acceptable to both parties each in their reasonable discretion, has been executed, Tenant shall be deemed to have waived its right to lease such Identified Space.

(c) **Exceptions**. Notwithstanding the above, the Right of First Refusal shall, at Landlord's option, not be in effect and may not be exercised by Tenant:

(i) during any period of time that Tenant is in Default under any provision of this Lease; or

(ii) if Tenant has been in Default under any provision of this Lease 3 or more times, whether or not the Defaults are cured, during the 12 month period prior to the date on which Tenant seeks to exercise the Right of First Refusal.

(d) **Termination**. The Right of First Refusal shall, at Landlord's option, terminate and be of no further force or effect even after Tenant's due and timely exercise of the Right of First Refusal if, after such exercise, but prior to the commencement date of the lease of the Identified Space, (i) Tenant fails to timely cure any Default by Tenant under this Lease; or (ii) Tenant has Defaulted 3 or more times during the period from the date of the exercise

of the Right of First Refusal to the date of the commencement of the lease of the Identified Space, whether or not such Defaults are cured.

(e) **Subordinate**. Tenant's rights in connection with the Expansion Right are and shall be subject to and subordinate to any expansion rights existing as of the date of this Lease.

(f) **Rights Personal**. The Right of First Refusal is personal to Tenant and is not assignable without Landlord's consent, which may be granted or withheld in Landlord's sole discretion separate and apart from any consent by Landlord to an assignment of Tenant's interest in this Lease, except that they may be assigned in connection with any Permitted Assignment of this Lease.

(g) **No Extensions**. The period of time within which the Right of First Refusal may be exercised shall not be extended or enlarged by reason of Tenant's inability to exercise the Right of First Refusal.

40. **Right to Extend Term**. Tenant shall have the right to extend the Term of this Lease upon the following terms and conditions:

(a) **Extension Rights**. Tenant shall have 1 right (the "**Extension Right**") to extend the term of this Lease for 36 months (the "**Extension Term**") on the same terms and conditions as this Lease (other than with respect to Base Rent and the Work Letter) by giving Landlord written notice (the "**Exercise Notice**") of its election to exercise the Extension Right at least 9 months prior to the expiration of the Base Term of the Lease (the "**Exercise Date**").

Upon the commencement of any Extension Term, Base Rent shall be payable at the Market Rate (as defined below). Base Rent shall thereafter be adjusted on each annual anniversary of the commencement of such Extension Term by a percentage as determined by Landlord and agreed to by Tenant at the time the Market Rate is determined. As used herein, "**Market Rate**" shall mean the rate that comparable landlords of comparable buildings have accepted in current transactions from non-equity (i.e., not being offered equity in the buildings) and nonaffiliated tenants of similar financial strength for space of comparable size, quality (including all Tenant Improvements, Alterations and other improvements) and floor height in Class A laboratory/office buildings in South San Francisco for a comparable term, with the determination of the Market Rate to take into account all relevant factors, including tenant inducements, available amenities (parking costs, leasing commissions, allowances or concessions, if any.

Tenant shall exercise the Extension Right, if at all, as follows: (i) Tenant shall deliver written notice to Landlord (the "**Interest Notice**") not more than 15 months nor less than 12 months prior to the expiration of the Base Term of the Lease stating that Tenant may be interested in exercising its Extension Right; (ii) Landlord shall deliver written notice (the "**Option Rent Notice**") to Tenant within 30 days after Landlord's receipt of the Interest Notice setting forth Landlord's good faith determination of the Market Rate; and (iii) if Tenant wishes to exercise its Extension Right, Tenant shall, on or before the Exercise Date, exercise the Extension Right by delivering an Exercise Notice to Landlord. Concurrently with Tenant's delivery of the Exercise Notice to Landlord, Tenant may object, in writing (the "**Objection Notice**"), to Landlord's determination of the Market Rate set forth in the Option Rent Notice, in which event such Market Rate shall be determined by arbitration pursuant to Section 39(b) below). If Tenant does not deliver an Objection Notice pursuant to the immediately preceding sentence, Tenant shall be deemed to have accepted the Market Rate set forth in the Option Rent Notice. Tenant acknowledges and agrees that, if Tenant has delivered an Exercise Notice to Landlord pursuant to this Section 39(a), Tenant shall have no right thereafter to rescind such Exercise Notice or elect not to extend the term of the Lease for the Extension Term.

(b) **Arbitration**.

(i) Within 10 days of Tenant's notice to Landlord of its election (or deemed election) to arbitrate Market Rate and escalations, each party shall deliver to the other a proposal containing the Market Rate and escalations that the submitting party believes to be correct ("**Extension Proposal**"). If either party fails to timely submit an Extension Proposal, the other party's submitted proposal shall determine the Base Rent and escalations for the Extension Term. If both parties submit Extension Proposals, then Landlord and Tenant shall meet within 7 days after delivery of the last Extension Proposal and make a good faith attempt to mutually appoint a single Arbitrator (and defined below) to determine the Market Rate. If Landlord and

Tenant are unable to agree upon a single Arbitrator, then each shall, by written notice delivered to the other within 10 days after the meeting, select an Arbitrator. If either party fails to timely give notice of its selection for an Arbitrator, the other party's submitted proposal shall determine the Base Rent for the Extension Term. The 2 Arbitrators so appointed shall, within 5 business days after their appointment, appoint a third Arbitrator. If the 2 Arbitrators so selected cannot agree on the selection of the third Arbitrator within the time above specified, then either party, on behalf of both parties, may request such appointment of such third Arbitrator by application to any state court of general jurisdiction in the jurisdiction in which the Premises are located, upon 10 days prior written notice to the other party of such intent.

(ii) The decision of the Arbitrator(s) shall be made within 30 days after the appointment of a single Arbitrator or the third Arbitrator, as applicable. The decision of the single Arbitrator shall be final and binding upon the parties. The average of the two closest Arbitrators in a three Arbitrator panel shall be final and binding upon the parties. Each party shall pay the fees and expenses of the Arbitrator appointed by or on behalf of such party and the fees and expenses of the third Arbitrator shall be borne equally by both parties. If the Market Rate and escalations are not determined by the first day of the Extension Term, then Tenant shall pay Landlord Base Rent in an amount equal to the Base Rent in effect immediately prior to the Extension Term and increased by 3% until such determination is made. After the determination of the Market Rate and escalations, the parties shall make any necessary adjustments to such payments made by Tenant. Landlord and Tenant shall then execute an amendment recognizing the Market Rate and escalations for the Extension Term.

(iii) An "**Arbitrator**" shall be any person appointed by or on behalf of either party or appointed pursuant to the provisions hereof and: (i) shall be (A) a member of the American Institute of Real Estate Appraisers with not less than 10 years of experience in the appraisal of improved office and high tech industrial real estate in the greater San Francisco Bay area, or (B) a licensed commercial real estate broker with not less than 15 years' experience representing landlords and/or tenants in the leasing of high tech or life sciences space in the greater San Francisco Bay area, (ii) devoting substantially all of their time to professional appraisal or brokerage work, as applicable, at the time of appointment and (iii) be in all respects impartial and disinterested.

(c) **Rights Personal**. The Extension Right is personal to Tenant and is not assignable without Landlord's consent, which may be granted or withheld in Landlord's sole discretion separate and apart from any consent by Landlord to an assignment of Tenant's interest in this Lease, except that they may be assigned in connection with any Permitted Assignment of this Lease.

(d) **Exceptions**. Notwithstanding anything set forth above to the contrary, the Extension Right shall, at Landlord's option, not be in effect and Tenant may not exercise the Extension Right:

(i) during any period of time that Tenant is in Default under any provision of this Lease; or

(ii) if Tenant has been in Default under any provision of this Lease 3 or more times, whether or not the Defaults are cured, during the 12 month period immediately prior to the date that Tenant intends to exercise the Extension Right, whether or not the Defaults are cured.

(e) **No Extensions**. The period of time within which the Extension Right may be exercised shall not be extended or enlarged by reason of Tenant's inability to exercise the Extension Right.

(f) **Termination**. The Extension Right shall, at Landlord's option, terminate and be of no further force or effect even after Tenant's due and timely exercise of the Extension Right, if, after such exercise, but prior to the commencement date of the Extension Term, (i) Tenant fails to timely cure any default by Tenant under this Lease; or (ii) Tenant has Defaulted 3 or more times during the period from the date of the exercise of the Extension Right to the date of the commencement of the Extension Term, whether or not such Defaults are cured.

41. **Intentionally Omitted**.

42. **Miscellaneous**.

(a) **Notices**. All notices or other communications between the parties shall be in writing and shall be deemed duly given upon delivery or refusal to accept delivery by the addressee thereof if delivered in person, or upon actual receipt if delivered by reputable overnight guaranty courier, addressed and sent to the parties at their addresses set forth above. Landlord and Tenant may from time to time by written notice to the other designate another address for receipt of future notices.

(b) **Intentionally Omitted**.

(c) **Financial Information**. Tenant shall furnish Landlord with true and complete copies of (i) Tenant's most recent audited annual financial statements within 90 days of the end of each of Tenant's fiscal years during the Term, (ii) Tenant's most recent unaudited quarterly financial statements within 45 days of the end of each of Tenant's first three fiscal quarters of each of Tenant's fiscal years during the Term, and (iii) any other financial information or summaries that Tenant typically provides to its lenders or shareholders. So long as Tenant is a "public company" and its financial information is publicly available, then the foregoing delivery requirements of this Section 42(c) shall not apply. Landlord shall treat Tenant's financial information as confidential information belonging to Tenant and will not disclose the same other than on a need-to-know basis (and with instructions that such information is to be treated as confidential) to Landlord's affiliates, legal, financial or tax advisors, consultants, potential lenders and potential purchasers and as required by Legal Requirements.

(d) **Recordation**. Neither this Lease nor a memorandum of lease shall be filed by or on behalf of Tenant in any public record. Landlord may prepare and file, and upon request by Landlord Tenant will execute, a memorandum of lease.

(e) **Interpretation**. The normal rule of construction to the effect that any ambiguities are to be resolved against the drafting party shall not be employed in the interpretation of this Lease or any exhibits or amendments hereto. Words of any gender used in this Lease shall be held and construed to include any other gender, and words in the singular number shall be held to include the plural, unless the context otherwise requires. The captions inserted in this Lease are for convenience only and in no way define, limit or otherwise describe the scope or intent of this Lease, or any provision hereof, or in any way affect the interpretation of this Lease.

(f) **Not Binding Until Executed**. The submission by Landlord to Tenant of this Lease shall have no binding force or effect, shall not constitute an option for the leasing of the Premises, nor confer any right or impose any obligations upon either party until execution of this Lease by both parties.

(g) **Limitations on Interest**. It is expressly the intent of Landlord and Tenant at all times to comply with applicable law governing the maximum rate or amount of any interest payable on or in connection with this Lease. If applicable law is ever judicially interpreted so as to render usurious any interest called for under this Lease, or contracted for, charged, taken, reserved, or received with respect to this Lease, then it is Landlord's and Tenant's express intent that all excess amounts theretofore collected by Landlord be credited on the applicable obligation (or, if the obligation has been or would thereby be paid in full, refunded to Tenant), and the provisions of this Lease immediately shall be deemed reformed and the amounts thereafter collectible hereunder reduced, without the necessity of the execution of any new document, so as to comply with the applicable law, but so as to permit the recovery of the fullest amount otherwise called for hereunder.

(h) **Choice of Law**. Construction and interpretation of this Lease shall be governed by the internal laws of the state in which the Premises are located, excluding any principles of conflicts of laws.

(i) **Time**. Time is of the essence as to the performance of Tenant's obligations under this Lease.

(j) **OFAC**. Tenant and all beneficial owners of Tenant are currently (a) in compliance with and shall at all times during the Term of this Lease remain in compliance with the regulations of the Office of Foreign Assets Control ("**OFAC**") of the U.S. Department of Treasury and any statute, executive order, or regulation relating thereto (collectively, the "**OFAC Rules**"), (b) not listed on, and shall not during the term of this Lease be listed on, the

Specially Designated Nationals and Blocked Persons List, Foreign Sanctions Evaders List, or the Sectoral Sanctions Identification List, which are all maintained by OFAC and/or on any other similar list maintained by OFAC or other governmental authority pursuant to any authorizing statute, executive order, or regulation, and (c) not a person or entity with whom a U.S. person is prohibited from conducting business under the OFAC Rules.

(k) **Incorporation by Reference**. All exhibits and addenda attached hereto are hereby incorporated into this Lease and made a part hereof. If there is any conflict between such exhibits or addenda and the terms of this Lease, such exhibits or addenda shall control.

(l) **Entire Agreement**. This Lease, including the exhibits attached hereto, constitutes the entire agreement between Landlord and Tenant pertaining to the subject matter hereof and supersedes all prior and contemporaneous agreements, understandings, letters of intent, negotiations and discussions, whether oral or written, of the parties, and there are no warranties, representations or other agreements, express or implied, made to either party by the other party in connection with the subject matter hereof except as specifically set forth herein.

(m) **No Accord and Satisfaction**. No payment by Tenant or receipt by Landlord of a lesser amount than the monthly installment of Base Rent or any Additional Rent will be other than on account of the earliest stipulated Base Rent and Additional Rent, nor will any endorsement or statement on any check or letter accompanying a check for payment of any Base Rent or Additional Rent be an accord and satisfaction. Landlord may accept such check or payment without prejudice to Landlord's right to recover the balance of such Rent or to pursue any other remedy provided in this Lease.

(n) **Hazardous Activities**. Notwithstanding any other provision of this Lease, Landlord, for itself and its employees, agents and contractors, reserves the right to refuse to perform any repairs or services in any portion of the Premises which, pursuant to Tenant's routine safety guidelines, practices or custom or prudent industry practices, require any form of protective clothing or equipment other than safety glasses. In any such case, Tenant shall contract with parties who are acceptable to Landlord, in Landlord's reasonable discretion, for all such repairs and services, and Landlord shall, to the extent required, equitably adjust Tenant's Share of Operating Expenses in respect of such repairs or services to reflect that Landlord is not providing such repairs or services to Tenant.

(o) **EV Charging Stations**. Landlord shall not unreasonably withhold its consent to Tenant's written request to install 1 or more electric vehicle car charging stations ("**EV Stations**") in the parking area serving the Project; provided, however, that Tenant complies with all reasonable requirements, standards, rules and regulations which may be imposed by Landlord, at the time Landlord's consent is granted, in connection with Tenant's installation, maintenance, repair and operation of such EV Stations, which may include, without limitation, the charge to Tenant of a reasonable monthly rental amount for the parking spaces used by Tenant for such EV Stations, Landlord's designation of the location of Tenant's EV Stations, and Tenant's payment of all costs whether incurred by Landlord or Tenant in connection with the installation, maintenance, repair and operation of each Tenant's EV Station(s). Nothing contained in this paragraph is intended to increase the number of parking spaces which Tenant is otherwise entitled to use at the Project under Section 10 of this Lease nor impose any additional obligations on Landlord with respect to Tenant's parking rights at the Project.

(p) **California Accessibility Disclosure**. For purposes of Section 1938(a) of the California Civil Code, Landlord hereby discloses to Tenant, and Tenant hereby acknowledges, that the Project has not undergone inspection by a Certified Access Specialist (CASp). In addition, the following notice is hereby provided pursuant to Section 1938(e) of the California Civil Code: "A Certified Access Specialist (CASp) can inspect the subject premises and determine whether the subject premises comply with all of the applicable construction-related accessibility standards under state law. Although state law does not require a CASp inspection of the subject premises, the commercial property owner or lessor may not prohibit the lessee or tenant from obtaining a CASp inspection of the subject premises for the occupancy or potential occupancy of the lessee or tenant, if requested by the lessee or tenant. The parties shall mutually agree on the arrangements for the time and manner of the CASp inspection, the payment of the fee for the CASp inspection, and the cost of making any repairs necessary to correct violations of construction-related accessibility standards within the premises." In furtherance of and in connection with such notice: (i) Tenant, having read such notice and understanding Tenant's right to request and obtain a CASp inspection, hereby elects not to obtain such CASp inspection and forever waives its rights to obtain a CASp inspection with respect to the Premises, Building

and/or Project to the extent permitted by Legal Requirements; and (ii) if the waiver set forth in clause (i) hereinabove is not enforceable pursuant to Legal Requirements, then Landlord and Tenant hereby agree as follows (which constitutes the mutual agreement of the parties as to the matters described in the last sentence of the foregoing notice): (A) Tenant shall have the one-time right to request for and obtain a CASp inspection, which request must be made, if at all, in a written notice delivered by Tenant to Landlord; (B) any CASp inspection timely requested by Tenant shall be conducted (1) at a time mutually agreed to by Landlord and Tenant, (2) in a professional manner by a CASp designated by Landlord and without any testing that would damage the Premises, Building or Project in any way, and (3) at Tenant's sole cost and expense, including, without limitation, Tenant's payment of the fee for such CASp inspection, the fee for any reports prepared by the CASp in connection with such CASp inspection (collectively, the "**CASp Reports**") and all other costs and expenses in connection therewith; (C) the CASp Reports shall be delivered by the CASp simultaneously to Landlord and Tenant; (D) Tenant, at its sole cost and expense, shall be responsible for making any improvements, alterations, modifications and/or repairs to or within the Premises to correct violations of construction-related accessibility standards including, without limitation, any violations disclosed by such CASp inspection; and (E) if such CASp inspection identifies any improvements, alterations, modifications and/or repairs necessary to correct violations of construction-related accessibility standards relating to those items of the Building and Project located outside the Premises that are Landlord's obligation to repair as set forth in this Lease, then Landlord shall perform such improvements, alterations, modifications and/or repairs as and to the extent required by Legal Requirements to correct such violations, and Tenant shall reimburse Landlord for the cost of such improvements, alterations, modifications and/or repairs within 10 business days after Tenant's receipt of an invoice therefor from Landlord. Nothing contained in this Section 41(p) shall affect the obligations of Landlord or Tenant under the second paragraph of Section 7 above.

(q) **Counterparts**. This Lease may be executed in 2 or more counterparts, each of which shall be deemed an original, but all of which together shall constitute one and the same instrument. Counterparts may be delivered via facsimile, electronic mail (including pdf or any electronic signature process complying with the U.S. federal ESIGN Act of 2000) or other transmission method and any counterpart so delivered shall be deemed to have been duly and validly delivered and be valid and effective for all purposes. Electronic signatures shall be deemed original signatures for purposes of this Lease and all matters related thereto, with such electronic signatures having the same legal effect as original signatures.

(r) **Project Specific Requirements**. Tenant acknowledges that the use and operation of the Project are governed by, among other things, CC&Rs and Environmental CC&Rs, and Tenant acknowledges having reviewed copies of the same. Tenant agrees to comply with all of the terms of the CC&Rs and Environmental CC&Rs which are applicable to tenants of the Project including, without limitation, maintaining the insurance required under the Environmental CC&Rs. As used herein, (i) "**CC&Rs**" mean that certain Amended and Restated Declaration of Covenants, Conditions and Restrictions for Sierra Point recorded in the Official Records of San Mateo County on October 23, 1998, as amended, and (ii) "**Environmental CC&Rs**" mean that certain First Amended and Restated Declaration of Covenants, Conditions and Environmental Restrictions Relating to Environmental Compliance for Sierra Point, recorded in the Official Records of San Mateo County on October 20, 1999 as Instrument No. 1999-176058.

(s) **Non-Recurring Payments**. If a time frame for the payment by Tenant of a non-recurring charge, cost or expense payable by Tenant pursuant to this Lease is not set forth in this Lease, such non-recurring charge, cost or expense shall be due within 30 days after Landlord's delivery to Tenant of written demand therefor.

[Signatures on next page]

IN WITNESS WHEREOF, Landlord and Tenant have executed this Lease as of the day and year first above written.

TENANT:

ULTRAGENYX PHARMACEUTICAL INC.,
a Delaware corporation

By: /s/ Shalini Sharp
Its: Chief Financial Officer

LANDLORD:

ARE-SAN FRANCISCO NO. 17, LLC,
a Delaware limited liability company

By: ALEXANDRIA REAL ESTATE EQUITIES, L.P.,
a Delaware limited partnership,
managing member

By: ARE-QRS CORP.,
a Maryland corporation,
general partner

By: /s/ Kristen Childs
Its: Vice President, RE Legal Affairs

EXHIBIT B TO LEASE

DESCRIPTION OF PROJECT

CITY OF SOUTH SAN FRANCISCO

PARCEL 1:

PARCEL C, AS SHOWN ON THAT CERTAIN MAP ENTITLED, “PARCEL MAP 98-044 LANDS OF SIERRA POINT, LLC, CITY OF SOUTH SAN FRANCISCO”, FILED IN THE OFFICE OF THE COUNTY RECORDER OF SAN MATEO COUNTY, STATE OF CALIFORNIA, ON AUGUST 6, 1999, IN BOOK 71 OF PARCEL MAPS, AT PAGE(S) 71 AND 72.

PARCEL 2:

THOSE CERTAIN ACCESS EASEMENTS AS DESCRIBED IN THE FIRST AMENDMENT TO AMENDED AND RESTATED DECLARATION OF COVENANTS, CONDITIONS AND RESTRICTIONS FOR SIERRA POINT RECORDED AUGUST 6, 1999, AS DOCUMENT NO. 1999-134787, AND RERECORDED OCTOBER 20, 1999, AS DOCUMENT NO. 1999-176057.

ASSESSOR’S PARCEL NO. 015-010-570 JOINT PLANT NO. 015-001-010-02.04A

EXHIBIT C TO LEASE

WORK LETTER

THIS WORK LETTER (this "**Work Letter**") is incorporated into that certain Lease Agreement (the "**Lease**") dated as of December ___, 2019 by and between **ARE-SAN FRANCISCO NO. 17, LLC**, a Delaware limited liability company ("**Landlord**"), and **ULTRAGENYX PHARMACEUTICAL INC.**, a Delaware corporation ("**Tenant**"). Any initially capitalized terms used but not defined herein shall have the meanings given them in the Lease.

1. **General Requirements**.

(a) **Tenant's Authorized Representative**. Tenant designates Joseph Seiwert III ("**Tenant's Representative**") as the only person authorized to act for Tenant pursuant to this Work Letter. Landlord shall not be obligated to respond to or act upon any request, approval, inquiry or other communication ("**Communication**") from or on behalf of Tenant in connection with this Work Letter unless such Communication is in writing from Tenant's Representative. Tenant may change Tenant's Representative at any time upon not less than 5 business days advance written notice to Landlord.

(b) **Landlord's Authorized Representative**. Landlord designates Hong Leahey and Greg Gehlen (either such individual acting alone, "**Landlord's Representative**") as the only persons authorized to act for Landlord pursuant to this Work Letter. Tenant shall not be obligated to respond to or act upon any request, approval, inquiry or other Communication from or on behalf of Landlord in connection with this Work Letter unless such Communication is in writing from Landlord's Representative. Landlord may change either Landlord's Representative at any time upon not less than 5 business days advance written notice to Tenant.

(c) **Architects, Consultants and Contractors**. Landlord and Tenant hereby acknowledge and agree that the architect (the "**TI Architect**") for the Tenant Improvements (as defined in Section 2(a) below), the general contractor and any subcontractors for the Tenant Improvements shall be selected by Tenant, subject to Landlord's approval, which approval shall not be unreasonably withheld, conditioned or delayed. Landlord shall be named a third party beneficiary of any contract entered into by Tenant with the TI Architect, any consultant, any contractor or any subcontractor, and of any warranty made by any contractor or any subcontractor.

2. **Tenant Improvements**.

(a) **Tenant Improvements Defined**. As used herein, "**Tenant Improvements**" shall mean all improvements to the Premises desired by Tenant of a fixed and permanent nature. Other than funding the TI Allowance (as defined below) as provided herein, Landlord shall not have any obligation whatsoever with respect to the finishing of the Premises for Tenant's use and occupancy.

(b) **Tenant's Space Plans**. Tenant shall deliver to Landlord schematic drawings and outline specifications (the "**TI Design Drawings**") detailing Tenant's requirements for the Tenant Improvements. Not more than 10 days thereafter, Landlord shall deliver to Tenant the written objections, questions or comments of Landlord and the TI Architect with regard to the TI Design Drawings. Tenant shall cause the TI Design Drawings to be revised to address such written comments and shall resubmit said drawings to Landlord for approval within 10 days thereafter. Such process shall continue until Landlord has approved the TI Design Drawings.

(c) **Working Drawings**. Not later than 15 business days following the approval of the TI Design Drawings by Landlord, Tenant shall cause the TI Architect to prepare and deliver to Landlord for review and comment construction plans, specifications and drawings for the Tenant Improvements ("**TI Construction Drawings**"), which TI Construction Drawings shall be prepared substantially in accordance with the TI Design Drawings. Tenant shall be solely responsible for ensuring that the TI Construction Drawings reflect Tenant's requirements for the Tenant Improvements. Landlord shall deliver its written comments on the TI Construction Drawings to Tenant not later than 10 business days after Landlord's receipt of the same; provided, however, that Landlord may not disapprove any matter that is consistent with the TI Design Drawings. Tenant and the TI Architect shall consider all such comments

in good faith and shall, within 10 business days after receipt, notify Landlord how Tenant proposes to respond to such comments. Any disputes in connection with such comments shall be resolved in accordance with Section 2(d) hereof. Provided that the design reflected in the TI Construction Drawings is consistent with the TI Design Drawings, Landlord shall approve the TI Construction Drawings submitted by Tenant. Once approved by Landlord, subject to the provisions of Section 4 below, Tenant shall not materially modify the TI Construction Drawings except as may be reasonably required in connection with the issuance of the TI Permit (as defined in Section 3(a) below).

(d) **Approval and Completion**. If any dispute regarding the design of the Tenant Improvements is not settled within 10 business days after notice of such dispute is delivered by one party to the other, Tenant may make the final decision regarding the design of the Tenant Improvements, provided (i) Tenant acts reasonably and such final decision is either consistent with or a compromise between Landlord's and Tenant's positions with respect to such dispute, (ii) that all costs and expenses resulting from any such decision by Tenant shall be payable out of the TI Fund (as defined in Section 5(d) below), and (iii) Tenant's decision will not affect the base Building, structural components of the Building or any Building systems (in which case Landlord shall make the final decision). Any changes to the TI Construction Drawings following Landlord's and Tenant's approval of same requested by Tenant shall be processed as provided in Section 4 hereof.

3. **Performance of the Tenant Improvements**.

(a) **Commencement and Permitting of the Tenant Improvements**. Tenant shall commence construction of the Tenant Improvements upon obtaining and delivering to Landlord a building permit (the "**TI Permit**") authorizing the construction of the Tenant Improvements consistent with the TI Construction Drawings approved by Landlord. The cost of obtaining the TI Permit shall be payable from the TI Fund. Landlord shall assist Tenant in obtaining the TI Permit. Prior to the commencement of the Tenant Improvements, Tenant shall deliver to Landlord a copy of any contract with Tenant's general contractor, the TI Architect and/or Tenant's engineer, and certificates of insurance from any contractor performing any part of the Tenant Improvement evidencing industry standard commercial general liability, automotive liability, "builder's risk", and workers' compensation insurance. Tenant shall cause the general contractor to provide a certificate of insurance naming Landlord, Alexandria Real Estate Equities, Inc., and Landlord's lender (if any) as additional insureds for the general contractor's liability coverages required above.

(b) **Selection of Materials, Etc**. Where more than one type of material or structure is indicated on the TI Construction Drawings approved by Tenant and Landlord, the option will be within Tenant's reasonable discretion if the matter concerns the Tenant Improvements, and within Landlord's sole and absolute subjective discretion if the matter concerns the structural components of the Building or any Building system.

(c) **Tenant Liability**. Tenant shall be responsible for correcting any deficiencies or defects in the Tenant Improvements.

(d) **Substantial Completion**. Tenant shall substantially complete or cause to be substantially completed the Tenant Improvements in a good and workmanlike manner, in accordance with the TI Permit subject, in each case, to Minor Variations and normal "punch list" items of a non-material nature which do not interfere with the use of the Premises ("**Substantial Completion**" or "**Substantially Complete**"). Upon Substantial Completion of the Tenant Improvements, Tenant shall require the TI Architect and the general contractor to execute and deliver, for the benefit of Tenant and Landlord, a Certificate of Substantial Completion in the form of the American Institute of Architects ("**AIA**") document G704. For purposes of this Work Letter, "**Minor Variations**" shall mean any modifications reasonably required: (i) to comply with all applicable Legal Requirements and/or to obtain or to comply with any required permit (including the TI Permit); (ii) to comport with good design, engineering, and construction practices which are not material; or (iii) to make reasonable adjustments for field deviations or conditions encountered during the construction of the Tenant Improvements.

4. **Changes**. Any changes requested by Tenant to the Tenant Improvements after the delivery and approval by Landlord of the TI Design Drawings, shall be requested and instituted in accordance with the provisions of this Section 4 and shall be subject to the written approval of Landlord, which approval shall not be unreasonably withheld, conditioned or delayed.

(a) **Tenant's Right to Request Changes**. If Tenant shall request changes ("**Changes**"), Tenant shall request such Changes by notifying Landlord in writing in substantially the same form as the AIA standard change order form (a "**Change Request**"), which Change Request shall detail the nature and extent of any such Change. Such Change Request must be signed by Tenant's Representative. Landlord shall review and approve or disapprove such Change Request within 5 business days thereafter, provided that Landlord's approval shall not be unreasonably withheld, conditioned or delayed. If Landlord fails to respond within such 5 business day period, then Tenant may provide Landlord with a second written notice stating in bold and all caps 12 point font that Landlord's failure to respond to Tenant's Change Request within 3 business days after Landlord's receipt of the second notice shall be deemed approval by Landlord, and if Landlord does not respond within such 3 business day period, then Landlord shall be deemed to have approved such Change Request.

(b) **Implementation of Changes**. If Landlord approves such Change, Tenant may cause the approved Change to be instituted. If any TI Permit modification or change is required as a result of such Change, Tenant shall promptly provide Landlord with a copy of such TI Permit modification or change.

5. **Costs**.

(a) **Budget For Tenant Improvements**. Before the commencement of construction of the Tenant Improvements, Tenant shall obtain a detailed breakdown, by trade, of the costs incurred or that will be incurred, in connection with the design and construction of the Tenant Improvements (the "**Budget**"), and deliver a copy of the Budget to Landlord for Landlord's approval, which shall not be unreasonably withheld or delayed. The Budget shall be based upon the TI Construction Drawings approved by Landlord. The Budget shall include a payment to Landlord of administrative rent ("**Administrative Rent**") equal to 1% of the TI Costs (as hereinafter defined) for monitoring and inspecting the construction of the Tenant Improvements, which sum shall be payable from the TI Fund.

(b) **TI Allowance**. As of the Commencement Date, Landlord shall provide to Tenant a tenant improvement allowance ("**TI Allowance**") of $10.00 per rentable square foot of the Premises, The TI Allowance shall be disbursed in accordance with this Work Letter.

Tenant shall have no right to the use or benefit (including any reduction to Base Rent) of any portion of the TI Allowance not required for the construction of (i) the Tenant Improvements described in the TI Construction Drawings approved pursuant to Section 2(d) or (ii) any Changes pursuant to Section 4. Tenant shall have no right to any portion of the TI Allowance that is not disbursed before the last day of the month that is 18 months after the Commencement Date.

(c) **Costs Includable in TI Fund**. The TI Fund shall be used solely for the payment of design, permits and construction costs in connection with the construction of the Tenant Improvements, including, without limitation, the cost of electrical power and other utilities used in connection with the construction of the Tenant Improvements, the cost of preparing the TI Design Drawings and the TI Construction Drawings, all costs set forth in the Budget, including Landlord's Administrative Rent, and the cost of Changes (collectively, "**TI Costs**"). Notwithstanding anything to the contrary contained herein, the TI Fund shall not be used to purchase any furniture, personal property or other non-Building system materials or equipment, including, but not be limited to, non-ducted biological safety cabinets and other scientific equipment not incorporated into the Tenant Improvements; provided, however that Tenant may use a portion of the TI Allowance for Tenant's voice or data cabling.

(d) **Excess TI Costs**. Landlord shall have no obligation to bear any portion of the cost of any of the Tenant Improvements, subject to the terms of Section 5(d), except to the extent of the TI Allowance. If at any time and from time-to-time, the remaining TI Costs under the Budget exceed the remaining unexpended TI Allowance ("**Excess TI Costs**"), monthly disbursements of the TI Allowance shall be made in the proportion that the remaining TI Allowance bears to the outstanding TI Costs under the Budget, and Tenant shall fund the balance of each such monthly draw. For purposes of any litigation instituted with regard to such amounts, those amounts required to be paid by Tenant will be deemed Rent under the Lease. The TI Allowance and Excess TI Costs are herein referred to as the "**TI Fund**." Notwithstanding anything to the contrary set forth in this Section 5(d), Tenant shall be fully and solely liable for TI Costs and the cost of Minor Variations in excess of the TI Allowance.

(e) **Payment for TI Costs**. During the course of design and construction of the Tenant Improvements, subject to the terms of Section 5(d), Landlord shall reimburse Tenant for TI Costs once a month against a draw request in Landlord's standard form, containing evidence of payment of such TI Costs by Tenant and such certifications, lien waivers (including a conditional lien release for each progress payment and unconditional lien releases for the prior month's progress payments), inspection reports and other matters as Landlord customarily obtains, to the extent of Landlord's approval thereof for payment, no later than 30 days following receipt of such draw request. Upon completion of the Tenant Improvements (and prior to any final disbursement of the TI Fund), Tenant shall deliver to Landlord: (i) sworn statements setting forth the names of all contractors and first tier subcontractors who did the work and final, unconditional lien waivers from all such contractors and first tier subcontractors; (ii) as-built plans (one copy in print format and two copies in electronic CAD format) for such Tenant Improvements; (iii) a certification of substantial completion in Form AIA G704, (iv) a certificate of occupancy for the Premises; and (v) copies of all operation and maintenance manuals and warranties affecting the Premises.

6. **Miscellaneous**.

(a) **Consents**. Whenever consent or approval of either party is required under this Work Letter, that party shall not unreasonably withhold, condition or delay such consent or approval, except as may be expressly set forth herein to the contrary.

(b) **Modification**. No modification, waiver or amendment of this Work Letter or of any of its conditions or provisions shall be binding upon Landlord or Tenant unless in writing signed by Landlord and Tenant.

(c) **No Default Funding**. In no event shall Landlord have any obligation to fund any portion of the TI Allowance during any period that Tenant is in Default under the Lease.

EXHIBIT D TO LEASE

ACKNOWLEDGMENT OF COMMENCEMENT DATE

This **ACKNOWLEDGMENT OF COMMENCEMENT DATE** is made this _____ day of _____, ____, between **ARE-SAN FRANCISCO NO. 17, LLC**, a Delaware limited liability company ("**Landlord**"), and **ULTRAGENYX PHARMACEUTICAL INC.**, a Delaware corporation ("**Tenant**"), and is attached to and made a part of the Lease dated _____, _____ (the "**Lease**"), by and between Landlord and Tenant. Any initially capitalized terms used but not defined herein shall have the meanings given them in the Lease.

Landlord and Tenant hereby acknowledge and agree, for all purposes of the Lease, that the Commencement Date of the Base Term of the Lease is _____, _____, and the termination date of the Base Term of the Lease shall be midnight on _____, _____. In case of a conflict between the terms of the Lease and the terms of this Acknowledgment of Commencement Date, this Acknowledgment of Commencement Date shall control for all purposes.

IN WITNESS WHEREOF, Landlord and Tenant have executed this ACKNOWLEDGMENT OF COMMENCEMENT DATE to be effective on the date first above written.

TENANT:

ULTRAGENYX PHARMACEUTICAL INC.,
a Delaware corporation

By:
Its:

LANDLORD:

ARE-SAN FRANCISCO NO. 17, LLC,
a Delaware limited liability company

By: ALEXANDRIA REAL ESTATE EQUITIES, L.P.,
a Delaware limited partnership,
managing member

By: ARE-QRS CORP.,
a Maryland corporation,
general partner

By:
Its:

EXHIBIT E TO LEASE

Rules and Regulations

1. The sidewalk, entries, and driveways of the Project shall not be obstructed by Tenant, or any Tenant Party, or used by them for any purpose other than ingress and egress to and from the Premises.

2. Tenant shall not place any objects, including antennas, outdoor furniture, etc., in the parking areas, landscaped areas or other areas outside of its Premises, or on the roof of the Project.

3. Except for animals assisting the disabled, no animals shall be allowed in the offices, halls, or corridors in the Project.

4. Tenant shall not disturb the occupants of the Project or adjoining buildings by the use of any radio or musical instrument or by the making of loud or improper noises.

5. If Tenant desires telegraphic, telephonic or other electric connections in the Premises, Landlord or its agent will direct the electrician as to where and how the wires may be introduced; and, without such direction, no boring or cutting of wires will be permitted. Any such installation or connection shall be made at Tenant's expense.

6. Tenant shall not install or operate any steam or gas engine or boiler, or other mechanical apparatus in the Premises, except as specifically approved in the Lease. The use of oil, gas or inflammable liquids for heating, lighting or any other purpose is expressly prohibited. Explosives or other articles deemed extra hazardous shall not be brought into the Project.

7. Parking any type of recreational vehicles is specifically prohibited on or about the Project. Except for the overnight parking of operative vehicles, no vehicle of any type shall be stored in the parking areas at any time. In the event that a vehicle is disabled, it shall be removed within 48 hours. There shall be no "For Sale" or other advertising signs on or about any parked vehicle. All vehicles shall be parked in the designated parking areas in conformity with all signs and other markings. All parking will be open parking, and no reserved parking, numbering or lettering of individual spaces will be permitted except as specified by Landlord.

8. Tenant shall maintain the Premises free from rodents, insects and other pests.

9. Landlord reserves the right to exclude or expel from the Project any person who, in the judgment of Landlord, is intoxicated or under the influence of liquor or drugs or who shall in any manner do any act in violation of the Rules and Regulations of the Project.

10. Tenant shall not cause any unnecessary labor by reason of Tenant's carelessness or indifference in the preservation of good order and cleanliness. Landlord shall not be responsible to Tenant for any loss of property on the Premises, however occurring, or for any damage done to the effects of Tenant by the janitors or any other employee or person.

11. Tenant shall give Landlord prompt notice of any defects in the water, lawn sprinkler, sewage, gas pipes, electrical lights and fixtures, heating apparatus, or any other service equipment affecting the Premises.

12. Tenant shall not permit storage outside the Premises, including without limitation, outside storage of trucks and other vehicles, or dumping of waste or refuse or permit any harmful materials to be placed in any drainage system or sanitary system in or about the Premises.

13. All moveable trash receptacles provided by the trash disposal firm for the Premises must be kept in the trash enclosure areas, if any, provided for that purpose.

14. No auction, public or private, will be permitted on the Premises or the Project.

15. No awnings shall be placed over the windows in the Premises except with the prior written consent of Landlord.

16. The Premises shall not be used for lodging, sleeping or cooking or for any immoral or illegal purposes or for any purpose other than that specified in the Lease. No gaming devices shall be operated in the Premises.

17. Tenant shall ascertain from Landlord the maximum amount of electrical current which can safely be used in the Premises, taking into account the capacity of the electrical wiring in the Project and the Premises and the needs of other tenants, and shall not use more than such safe capacity. Landlord's consent to the installation of electric equipment shall not relieve Tenant from the obligation not to use more electricity than such safe capacity.

18. Tenant assumes full responsibility for protecting the Premises from theft, robbery and pilferage.

19. Tenant shall not install or operate on the Premises any machinery or mechanical devices of a nature not directly related to Tenant's ordinary use of the Premises and shall keep all such machinery free of vibration, noise and air waves which may be transmitted beyond the Premises.

20. Tenant shall cause any vendors and other service providers hired by Tenant to perform services at the Premises or the Project to maintain in effect workers' compensation insurance as required by Legal Requirements and commercial general liability insurance with coverage amounts reasonably acceptable to Landlord. Tenant shall cause such vendors and service providers to name Landlord and Alexandria Real Estate Equities, Inc. as additional insureds under such policies and shall provide Landlord with certificates of insurance evidencing the required coverages (and showing Landlord and Alexandria Real Estate Equities, Inc. as additional insureds under such policies) prior to the applicable vendor or service provider providing any services to Tenant at the Project.

21. Neither Tenant nor any of the Tenant Parties shall have the right to photograph, videotape, film, digitally record or by any other means record, transmit and/or distribute any images, pictures or videos of all or any portion of the Premises or the Project that could identify the Project or the name of the Project, or that identify Landlord or any other tenants or any affiliates of Landlord or any other tenants. The foregoing is not meant to prohibit Tenant or individual employees from taking and disseminating photos within the Premises or at the Project so long as neither the Building nor any proprietary information, equipment or improvements of Landlord are included within such photos.

EXHIBIT F TO LEASE

TENANT'S PERSONAL PROPERTY

None.

Exhibit 10.82

FIRST AMENDMENT TO LEASE AGREEMENT

THIS FIRST AMENDMENT TO LEASE AGREEMENT (this "**First Amendment**") is made as of September 30, 2020, by and between **ARE-SAN FRANCISCO NO. 17, LLC**, a Delaware limited liability company ("**Landlord**"), and **ULTRAGENYX PHARMACEUTICAL INC.**, a Delaware corporation ("**Tenant**").

RECITALS

A. Landlord and Tenant are now parties to that certain Lease Agreement dated as of December 15, 2019 (the "**Lease**"). Pursuant to the Lease, Tenant leases certain premises consisting of approximately 10,781 rentable square feet ("**Original Premises**") in a building located at 7000 Shoreline Court, South San Francisco, California ("**Building**"). The Original Premises are more particularly described in the Lease. Capitalized terms used herein without definition shall have the meanings defined for such terms in the Lease.

B. Landlord and Tenant desire, subject to the terms and conditions set forth below, to amend the Lease to, among other things, expand the Permitted Use and the size of the Original Premises by adding certain premises on the ground floor of the Building containing approximately 15,116 rentable square feet.

NOW, THEREFORE, in consideration of the foregoing Recitals, which are incorporated herein by this reference, the mutual promises and conditions contained herein, and for other good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, Landlord and Tenant hereby agree as follows:

1. Permitted Use as set forth in the basic lease provisions on page 1 of the Lease is restated as follows:

"**Permitted Use**: Research and development laboratory, GMP manufacturing, related office and other related uses consistent with the character of the Project, including, without limitation, mRNA development, toxicology lab, and QC lab, or otherwise in compliance with the provisions of Section 7 hereof."

2. **First Expansion Premises**. In addition to the Original Premises, commencing on the First Expansion Premises Commencement Date (as defined in Section 3 below), Landlord leases to Tenant, and Tenant leases from Landlord, that certain portion of the ground floor of the Building containing approximately 15,116 rentable square feet, as more particularly shown on **Exhibit A** attached hereto as the Expansion Premises (the "**First Expansion Premises**").

3. **Delivery**. Landlord shall use reasonable efforts to deliver ("**Delivery**" or "**Deliver**") the First Expansion Premises to Tenant 1 business day after the mutual execution and delivery of this First Amendment for the construction by Tenant of the Tenant Improvements. The "**First Expansion Premises Commencement Date**" shall be the date that Landlord Delivers the First Expansion Premises to Tenant. The "**First Expansion Premises Rent Commencement Date**" shall be the earlier to occur of (i) the date that the Tenant Improvements are Substantially Completed or (ii) February 28, 2021; provided, however, that in no event shall the First Expansion Premises Rent Commencement Date occur prior to January 1, 2021. As used herein, the terms "**Tenant Improvements**" and "**Substantially Completed**" shall have the meanings set forth for such terms in the work letter attached to this First Amendment as **Exhibit B** ("**First Expansion Premises Work Letter**").

Upon request of either party, the parties shall execute and deliver a written acknowledgment of the First Expansion Premises Commencement Date and First Expansion Premises Rent Commencement Date in a form attached here to as **Exhibit C**; provided, however, the failure to execute and deliver such acknowledgment shall not affect the parties' rights hereunder.

Except as set forth in the First Expansion Premises Work Letter: (i) Tenant shall accept the First Expansion Premises in their condition as of the date Landlord Delivers the First Expansion Premises to Tenant; (ii) Landlord shall have no obligation for any defects in the First Expansion Premises; and (iii) Tenant's taking possession of the First Expansion Premises shall be conclusive evidence that Tenant accepts the First

Expansion Premises and that the First Expansion Premises were in good condition at the time possession was taken.

If Tenant does not elect to lease the ROFO Premises (as defined below) pursuant to Section 13 of this First Amendment, Landlord shall construct, at Landlord's sole cost and expense, the common corridor contemplated on **Exhibit A** which (i) if Landlord reasonably determines that the corridor can be a non-rated corridor, Landlord estimates it will take approximately 20 weeks to design, permit and construct the corridor and (ii) if Landlord reasonably determines that the corridor must be a rated corridor, Landlord estimates it will take approximately 28 weeks to design, permit and construct the corridor. To be sure, either time period (20 weeks for a non-rated corridor or 28 weeks for rated corridor) begins to run from the earlier of (x) the date that Tenant notifies Landlord in writing that Tenant forever waives its right under Section 13 to lease the ROFO Premises and (y) the expiration of the 30 day period provided for in the first sentence of Section 13(a) with Tenant having not elected to exercise its right to lease the ROFO Premises.

For the period of 30 consecutive days after the First Expansion Premises Commencement Date, Landlord shall, at its sole cost and expense (which shall not constitute an Operating Expense), be responsible for any repairs that are required to be made to the Building Systems exclusively serving the First Expansion Premises, unless Tenant or any Tenant Party was responsible for the cause of such repair, in which case Tenant shall pay the cost.

Tenant agrees and acknowledges that, except as expressly provided for herein, neither Landlord nor any agent of Landlord has made any representation or warranty with respect to the condition of all or any portion of the First Expansion Premises, and/or the suitability of the First Expansion Premises for the conduct of Tenant's business, and Tenant waives any implied warranty that the First Expansion Premises are suitable for the Permitted Use.

4. **Definition of Premises and Rentable Area of Premises**. Commencing on the First Expansion Premises Commencement Date, the defined terms "**Premises**" and "**Rentable Area of Premises**" on Page 1 of the Lease is deleted in its entirety and replaced with the following:

"**Premises:** That portion of the Building containing approximately 25,897 rentable square feet, consisting of (i) approximately 10,781 rentable square feet on the second floor of the Building (the "**Original Premises**"), and (ii) approximately 15,116 rentable square feet on the ground floor of the Building (the "**First Expansion Premises**"), as determined by Landlord, all as shown on **Exhibit A**."

"**Rentable Area of Premises:** 25,897 sq. ft."

Exhibit A attached to the Lease is amended as of the First Expansion Premises Commencement Date to include **Exhibit A** attached to this First Amendment.

5. **Base Term**. Commencing on the First Expansion Premises Commencement Date, the defined term "**Base Term**" on page 1 of the Lease is deleted in its entirety and replaced with the following:

"**Base Term:** Commencing (i) with respect to the Original Premises on the Commencement Date, and (ii) with respect to the First Expansion Premises on the First Expansion Premises Commencement Date, and ending with respect to the entire Premises on March 31, 2025."

6. **Base Rent**.

a. **Original Premises**. Tenant shall continue to pay Base Rent for the Original Premises at the rate of $5.05 per rentable square foot of the Original Premises per month, subject to adjustment pursuant to Section 4 of the Lease.

b. **First Expansion Premises**. Beginning on the First Expansion Premises Rent Commencement Date, Tenant shall commence paying Base Rent for the First Expansion Premises at the rate of $5.05 per rentable

square foot of the First Expansion Premises per month, subject to adjustment pursuant to Section 4 of the Lease.

c. **Base Rent Adjustments**. Section 4 of the Lease is hereby deleted in its entirety and replaced with the following:

"4. **Base Rent Adjustments**. Base Rent for the Premises (i.e., the Original Premises and the First Expansion Premises) shall be increased on each annual anniversary of the First Expansion Premises Commencement Date (or if the First Expansion Premises Commencement Date occurs on a day other than the first day of a month, then the first day of the following month) (each an "**Adjustment Date**") by multiplying the Base Rent payable for the Premises immediately before such Adjustment Date by the Rent Adjustment Percentage and adding the resulting amount to the Base Rent payable for the Premises immediately before such Adjustment Date. The annual Base Rent adjustments on the Adjustment Date provided for in this Section 4 shall continue to apply during the Extension Term if Tenant elects to exercise its Extension Right. Base Rent, as so adjusted, shall thereafter be due as provided herein. Base Rent for any fractional calendar months shall be prorated."

7. **Definition of Tenant's Share of Operating Expenses**. Commencing on the First Expansion Premises Rent Commencement Date, the defined term "**Tenant's Share of Operating Expenses**" on page 1 of the Lease is deleted in their entirety and replaced with the following:

"**Tenant's Share of Operating Expenses:** 18.54%"

8. **Security Deposit**. Tenant shall not be required to deposit any additional Security Deposit with Landlord in connection with the leasing of the First Expansion Premises.

9. **Parking**. For the avoidance of doubt, commencing on the First Expansion Premises Commencement Date, the provisions of Section 10 of the Lease shall apply to the leasing of the First Expansion Premises.

10. **Removable Installations**. **Exhibit F** of the Lease is hereby amended to include items listed on **Exhibit D** attached hereto; provided, however, that Tenant shall have no right to remove any of such to the extent paid for in whole or in part by Landlord including, without limitation, as part of the TI Allowance. Notwithstanding anything to the contrary contained in the Lease, Tenant shall have no obligation under the Lease to remove any of the items on **Exhibit F** of the Lease (as amended by **Exhibit D** attached hereto).

11. **Shared Space Arrangement**. The following provision is added at the end of Section 22(b) of the Lease:

"Notwithstanding anything to the contrary contained in this Lease, Tenant may from time to time enter into license agreements (each, a "**Shared Space Arrangement**") with Tenant's agents, contractors, consultants or affiliates pursuant to which such agents, contractors, consultants or affiliates (including, without limitation, special purpose vehicles and collaboration with university and/or hospital researchers, regardless of whether or not the collaboration is funded by standalone investors) may occupy up to 20% of the Premises as "**Shared Space Area**", and such license agreements shall not require Landlord's consent under this Section 22; provided, however, that Tenant shall be required to provide Landlord with a copy of each such license agreement and, prior to the effective date of each such license agreement, Tenant and each licensee shall be required to execute Landlord's reasonable form of acknowledgment pursuant to which Tenant and the licensee acknowledge and agree, among other things, that: (i) the terms of the Shared Space Arrangement are subject and subordinate to the terms of this Lease, (ii) if this Lease terminates, then the Shared Space Arrangement shall terminate concurrently therewith, (iii) each licensee shall, during the term of its applicable Shared Space Arrangement, maintain the same insurance as is required of Tenant under this Lease and provide Landlord with insurance certificates evidencing the same and naming the Landlord Parties as additional insureds, and (iv) the waivers and releases set forth in the second to last paragraph of Section 17 that apply as between Landlord and Tenant shall also apply as between Landlord and licensee. Tenant shall be fully responsible for the conduct of such companies within the Shared Space Area and the Project, and

Tenant's indemnification obligations set forth in this Lease shall apply with respect to the conduct of such parties within the Shared Space Area and Project."

12. **Extension Right**. Tenant shall continue to have its Extension Right pursuant to Section 40 of the Lease; provided, however, that Tenant may only extend the Term of the Lease with respect to the then entire Premises (but excluding any space being leased to Tenant pursuant to Section 39 of the Lease.

13. **Additional Expansion Right**.

a. **Right of First Offer**. Subject to the provisions of this Section 13, for the period of 30 calendar days after the mutual execution and delivery of this First Amendment by the parties (the "**ROFO Period**"), Tenant shall have an exclusive right of first offer with respect to that certain space on the ground floor of the Building containing approximately 6,480 rentable square feet as more particularly shown on **Exhibit E** attached hereto as the Potential Office Expansion Premises (the "**ROFO Premises**"). If Tenant elects to lease the ROFO Premises, Tenant shall be required, prior to the expiration of the ROFO Period, to deliver written notice to Landlord ("**ROFO Notice**") of its election to lease the ROFO Premises in which case Tenant shall lease the ROFO Premises and the Lease shall be modified as follows: (a) the "**ROFO Premises Commencement Date**" shall be the date that Landlord delivers the ROFO Premises to Tenant which is targeted to be 1 day after the lease amendment contemplated in Section 12(b) below is mutually executed and delivered by Landlord and Tenant; (b) on the ROFO Premises Commencement Date, the definition of Premises shall be amended to include the ROFO Premises; (c) commencing on the date that is 6 months after the First Expansion Premises Rent Commencement Date, Tenant shall pay Base Rent per rentable square foot of the ROFO Premises at the same rate that Tenant is then paying on a per rentable square foot basis with respect to the First Expansion Premises, as adjusted on each Adjustment Date pursuant to Section 4 of the Lease; (d) commencing on the date that is 6 months after the First Expansion Premises Rent Commencement Date, Tenant shall commence paying Operating Expenses with respect to the ROFO Premises on the First Expansion Premises Rent Commencement Date; (e) Tenant's Share of Operating Expenses shall be proportionately increased, (f) Tenant shall construct improvements in the ROFO Premises ("**Identified ROFO Premises Tenant Improvements**") pursuant to the First Expansion Premises Work Letter and for the avoidance of any doubt Tenant shall receive a TI Allowance in the amount of $34 per rentable square foot of the ROFO Premises and Landlord shall, upon receipt of reasonably satisfactory invoices, reimburse Tenant for the payment made by Tenant to the TI Architect for an initial test fit and one revision, not to exceed $0.15 per rentable square foot of the ROFO Premises. For the avoidance of doubt, the Term of the Lease with respect to the ROFO Premises shall terminate concurrently with the Term of the Lease with respect to the balance of the Premises.

b. **Amended Lease**. If: (i) Tenant fails to timely deliver a ROFO Notice, or (ii) after the expiration of a period of 10 business days after Landlord's delivery to Tenant of a new lease amendment (in form and substance reasonably similar to this First Amendment) for Tenant's lease of the ROFO Premises, no lease amendment for the ROFO Premises acceptable to both parties has been executed, Tenant shall be deemed to have waived its right to lease the ROFO Premises. Landlord and Tenant agree to use reasonable good faith efforts to negotiate and finalize any such lease amendment for the ROFO Premises within the timeframe set forth in this paragraph.

c. **Exceptions**. Notwithstanding the above, the right of first offer shall, at Landlord's option, not be in effect and may not be exercised by Tenant during any period of time that Tenant is in Default under any provision of this Lease.

d. **Termination**. The right of first offer shall, at Landlord's option, terminate and be of no further force or effect even after Tenant's due and timely exercise of the right of first offer, if, after such exercise, but prior to the commencement date of the lease of such ROFO Premises, (i) Tenant fails to timely cure any default by Tenant under this Lease; or (ii) Tenant has Defaulted 3 or more times during the period from the date of the exercise of the right of first offer to the date of the commencement of the lease of the ROFO Premises, whether or not such Defaults are cured.

e. **Rights Personal**. The right of first offer is personal to Tenant and is not assignable without Landlord's consent, which may be granted or withheld in Landlord's sole discretion separate and apart from any consent by Landlord to an assignment of Tenant's interest in this Lease, except that they may be assigned in connection with any Permitted Assignment of this Lease.

f. **No Extensions**. The period of time within which the right of first offer may be exercised shall not be extended or enlarged by reason of Tenant's inability to exercise the right of first offer.

14. **California Accessibility Disclosure**. The provisions of Section 42(p) of the Lease are hereby incorporated by reference.

15. **OFAC**. Tenant and any beneficial owners of Tenant are currently (a) in compliance with and shall at all times during the Term of the Lease remain in compliance with the regulations of the Office of Foreign Assets Control ("**OFAC**") of the U.S. Department of Treasury and any statute, executive order, or regulation relating thereto (collectively, the "**OFAC Rules**"), (b) not listed on, and shall not during the term of the Lease be listed on, the Specially Designated Nationals and Blocked Persons List, Foreign Sanctions Evaders List or the Sectoral Sanctions Identifications List, which are all maintained by OFAC and/or on any other similar list maintained by OFAC or other governmental authority pursuant to any authorizing statute, executive order, or regulation, and (c) not a person or entity with whom a U.S. person is prohibited from conducting business under the OFAC Rules.

16. **Miscellaneous**.

a. This First Amendment is the entire agreement between the parties with respect to the subject matter hereof and supersedes all prior and contemporaneous oral and written agreements and discussions. This First Amendment may be amended only by an agreement in writing, signed by the parties hereto.

b. Landlord and Tenant each represents and warrants that it has not dealt with any broker, agent or other person (collectively, "**Broker**") in connection with the transaction reflected in this First Amendment and that no Broker brought about this transaction, other than Kidder Mathews and Jones Lang LaSalle. Landlord and Tenant each hereby agree to indemnify and hold the other harmless from and against any claims by any Broker, other than the brokers, if any, named in this First Amendment, claiming a commission or other form of compensation by virtue of having dealt with Tenant or Landlord, as applicable, with regard to this leasing transaction.

c. This First Amendment is binding upon and shall inure to the benefit of the parties and their respective successors and assigns.

d. This First Amendment may be executed in 2 or more counterparts, each of which shall be deemed an original, but all of which together shall constitute one and the same instrument. Counterparts may be delivered via facsimile, electronic mail (including pdf or any electronic signature process complying with the U.S. federal ESIGN Act of 2000) or other transmission method (including DocuSign) and any counterpart so delivered shall be deemed to have been duly and validly delivered and be valid and effective for all purposes. Electronic signatures shall be deemed original signatures for purposes of this First Amendment and all matters related thereto, with such electronic signatures having the same legal effect as original signatures.

e. Except as amended and/or modified by this First Amendment, the Lease is hereby ratified and confirmed and all other terms of the Lease shall remain in full force and effect, unaltered and unchanged by this First Amendment. In the event of any conflict between the provisions of this First Amendment and the provisions of the Lease, the provisions of this First Amendment shall prevail. Whether or not specifically amended by this First Amendment, all of the terms and provisions of the Lease are hereby amended to the extent necessary to give effect to the purpose and intent of this First Amendment.

[Signatures are on the next page.]

IN WITNESS WHEREOF, the parties hereto have executed this First Amendment as of the day and year first above written.

TENANT:

ULTRAGENYX PHARMACEUTICAL INC.,
a Delaware corporation

By: /s/ Shalini Sharp
Its: CFO

LANDLORD:

ARE-SAN FRANCISCO NO. 17, LLC,
a Delaware limited liability company

By: ALEXANDRIA REAL ESTATE EQUITIES, L.P.,
a Delaware limited partnership,
managing member

By: ARE-QRS CORP.,
a Maryland corporation,
general partner

By: /s/ Kristen Childs
Its: Vice President, RE Legal Affairs

Exhibit B
First Expansion Premises Work Letter

THIS FIRST EXPANSION PREMISES WORK LETTER dated September __, 2020 (this "**First Expansion Premises Work Letter**") is made and entered into by and between **ARE-SAN FRANCISCO NO. 17, LLC**, a Delaware limited liability company ("**Landlord**"), and **ULTRAGENYX PHARMACEUTICAL INC.**, a Delaware corporation ("**Tenant**"), and is attached to and made a part of that certain Lease Agreement dated as of December 15, 2019, as amended by that certain First Amendment to Lease Agreement ("**First Amendment**") dated as of even date herewith (as amended, the "**Lease**"), by and between Landlord and Tenant. Any initially capitalized terms used but not defined herein shall have the meanings given them in the Lease.

1. **General Requirements**.

(a) **Tenant's Authorized Representative**. Tenant designates Melody Spradlin ("**Tenant's Representative**") as the only person authorized to act for Tenant pursuant to this First Expansion Premises Work Letter. Landlord shall not be obligated to respond to or act upon any request, approval, inquiry or other communication ("**Communication**") from or on behalf of Tenant in connection with this First Expansion Premises Work Letter unless such Communication is in writing from Tenant's Representative. Tenant may change Tenant's Representative at any time upon not less than 5 business days advance written notice to Landlord.

(b) **Landlord's Authorized Representative**. Landlord designates Hong Leahey and Greg Gehlen (either such individual acting alone, "**Landlord's Representative**") as the only persons authorized to act for Landlord pursuant to this First Expansion Premises Work Letter. Tenant shall not be obligated to respond to or act upon any request, approval, inquiry or other Communication from or on behalf of Landlord in connection with this First Expansion Premises Work Letter unless such Communication is in writing from Landlord's Representative. Landlord may change either Landlord's Representative at any time upon not less than 5 business days advance written notice to Tenant.

(c) **Architects, Consultants and Contractors**. Landlord and Tenant hereby acknowledge and agree that the architect (the "**TI Architect**") for the Tenant Improvements (as defined in Section 2(a) below), the general contractor and any subcontractors for the Tenant Improvements shall be selected by Tenant, subject to Landlord's approval, which approval shall not be unreasonably withheld, conditioned or delayed. Landlord shall be named a third party beneficiary of any contract entered into by Tenant with the TI Architect, any consultant, any contractor or any subcontractor, and of any warranty made by any contractor or any subcontractor.

2. **Tenant Improvements**.

(a) **Tenant Improvements Defined**. As used herein, "**Tenant Improvements**" shall mean all improvements to the First Expansion Premises (and if Tenant leases the ROFO Premises pursuant to Section 12 of the First Amendment, the ROFO Premises) desired by Tenant of a fixed and permanent nature. Other than funding the TI Allowance (as defined below) as provided herein, Landlord shall not have any obligation whatsoever with respect to the finishing of the First Expansion Premises (and if Tenant leases the ROFO Premises pursuant to Section 13 of the First Amendment, the ROFO Premises) for Tenant's use and occupancy; provided, however, that pursuant to Section 2 of this First Amendment, Landlord shall construct, at Landlord's sole cost and expense, the common corridor contemplated on **Exhibit A** if Tenant does not elect to lease the ROFO Premises pursuant to Section 13 of the First Amendment.

(b) **Tenant's Space Plans**. Tenant shall deliver to Landlord schematic drawings and outline specifications (the "**TI Design Drawings**") detailing Tenant's requirements for the Tenant Improvements. Not more than 7 business days thereafter, Landlord shall deliver to Tenant the reasonably determined written objections, questions or comments of Landlord and the TI Architect with regard to the TI Design Drawings. Tenant shall cause the TI Design Drawings to be revised to address such reasonably determined written comments and shall resubmit

said drawings to Landlord for approval thereafter. Such process shall continue until Landlord has approved the TI Design Drawings.

(c) **Working Drawings**. Upon approval of the TI Design Drawings by Landlord, Tenant shall cause the TI Architect to prepare and deliver to Landlord for review and comment construction plans, specifications and drawings for the Tenant Improvements ("**TI Construction Drawings**"), which TI Construction Drawings shall be prepared substantially in accordance with the TI Design Drawings. Tenant shall be solely responsible for ensuring that the TI Construction Drawings reflect Tenant's requirements for the Tenant Improvements. Landlord shall deliver its written comments on the TI Construction Drawings to Tenant not later than 10 business days after Landlord's receipt of the same; provided, however, that Landlord may not disapprove any matter that is consistent with the TI Design Drawings. Tenant and the TI Architect shall consider all such comments in good faith and shall, within 10 business days after receipt, notify Landlord how Tenant proposes to respond to such comments. Any disputes in connection with such comments shall be resolved in accordance with Section 2(d) hereof. Provided that the design reflected in the TI Construction Drawings is consistent with the TI Design Drawings, Landlord shall approve the TI Construction Drawings submitted by Tenant. Once approved by Landlord, subject to the provisions of Section 4 below, Tenant shall not materially modify the TI Construction Drawings except as may be reasonably required in connection with the issuance of the TI Permit (as defined in Section 3(a) below).

(d) **Approval and Completion**. If any dispute regarding the design of the Tenant Improvements is not settled within 10 business days after notice of such dispute is delivered by one party to the other, Tenant may make the final decision regarding the design of the Tenant Improvements, provided (i) Tenant acts reasonably and such final decision is either consistent with or a compromise between Landlord's and Tenant's positions with respect to such dispute, (ii) that all costs and expenses resulting from any such decision by Tenant shall be payable out of the TI Fund (as defined in Section 5(d) below), and (iii) Tenant's decision will not affect the base Building, structural components of the Building or any Building systems (in which case Landlord shall make the final decision). Any changes to the TI Construction Drawings following Landlord's and Tenant's approval of same requested by Tenant shall be processed as provided in Section 4 hereof.

3. **Performance of the Tenant Improvements**.

(a) **Commencement and Permitting of the Tenant Improvements**. Tenant shall commence construction of the Tenant Improvements upon obtaining and delivering to Landlord a building permit (the "**TI Permit**") authorizing the construction of the Tenant Improvements consistent with the TI Construction Drawings approved by Landlord. The cost of obtaining the TI Permit shall be payable from the TI Fund. Landlord shall assist Tenant in obtaining the TI Permit. Prior to the commencement of the Tenant Improvements, Tenant shall deliver to Landlord a copy of any contract with Tenant's general contractor, the TI Architect and/or Tenant's engineer, and certificates of insurance from any contractor performing any part of the Tenant Improvement evidencing industry standard commercial general liability, automotive liability, "builder's risk", and workers' compensation insurance. Tenant shall cause the general contractor to provide a certificate of insurance naming Landlord, Alexandria Real Estate Equities, Inc., and Landlord's lender (if any) as additional insureds for the general contractor's liability coverages required above.

(b) **Selection of Materials, Etc**. Where more than one type of material or structure is indicated on the TI Construction Drawings approved by Tenant and Landlord, the option will be within Tenant's reasonable discretion if the matter concerns the Tenant Improvements, and within Landlord's sole and absolute subjective discretion if the matter concerns the structural components of the Building or any Building system.

(c) **Tenant Liability**. Tenant shall be responsible for correcting any deficiencies or defects in the Tenant Improvements.

(d) **Substantial Completion**. Tenant shall substantially complete or cause to be substantially completed the Tenant Improvements in a good and workmanlike manner, in accordance with the TI Permit subject, in each case, to Minor Variations and normal "punch list" items of a non-material nature which do not interfere with the use of the First Expansion Premises (and if Tenant leases the ROFO Premises pursuant to Section 13 of the First Amendment, the ROFO Premises) ("**Substantial Completion**" or "**Substantially Complete**"). Upon Substantial Completion of the Tenant Improvements, Tenant shall require the TI Architect and the general contractor to execute

and deliver, for the benefit of Tenant and Landlord, a Certificate of Substantial Completion in the form of the American Institute of Architects ("**AIA**") document G704. For purposes of this First Expansion Premises Work Letter, "**Minor Variations**" shall mean any modifications reasonably required: (i) to comply with all applicable Legal Requirements and/or to obtain or to comply with any required permit (including the TI Permit); (ii) to comport with good design, engineering, and construction practices which are not material; or (iii) to make reasonable adjustments for field deviations or conditions encountered during the construction of the Tenant Improvements.

4. **Changes**. Any changes requested by Tenant to the Tenant Improvements after the delivery and approval by Landlord of the TI Design Drawings, shall be requested and instituted in accordance with the provisions of this Section 4 and shall be subject to the written approval of Landlord, which approval shall not be unreasonably withheld, conditioned or delayed.

(a) **Tenant's Right to Request Changes**. If Tenant shall request changes ("**Changes**"), Tenant shall request such Changes by notifying Landlord in writing in substantially the same form as the AIA standard change order form (a "**Change Request**"), which Change Request shall detail the nature and extent of any such Change. Such Change Request must be signed by Tenant's Representative. Landlord shall review and approve or disapprove such Change Request within 5 business days thereafter, provided that Landlord's approval shall not be unreasonably withheld, conditioned or delayed. If Landlord fails to respond within such 5 business day period, then Tenant may provide Landlord with a second written notice stating in bold and all caps 12 point font that Landlord's failure to respond to Tenant's Change Request within 3 business days after Landlord's receipt of the second notice shall be deemed approval by Landlord, and if Landlord does not respond within such 3 business day period, then Landlord shall be deemed to have approved such Change Request.

(b) **Implementation of Changes**. If Landlord approves such Change, Tenant may cause the approved Change to be instituted. If any TI Permit modification or change is required as a result of such Change, Tenant shall promptly provide Landlord with a copy of such TI Permit modification or change.

5. **Costs**.

(a) **Budget For Tenant Improvements**. Before the commencement of construction of the Tenant Improvements, Tenant shall obtain a detailed breakdown, by trade, of the costs incurred or that will be incurred, in connection with the design and construction of the Tenant Improvements (the "**Budget**"), and deliver a copy of the Budget to Landlord for Landlord's approval, which shall not be unreasonably withheld or delayed. The Budget shall be based upon the TI Construction Drawings approved by Landlord. The Budget shall include a payment to Landlord of administrative rent ("**Administrative Rent**") equal to 1% of the TI Costs (as hereinafter defined) for monitoring and inspecting the construction of the Tenant Improvements, which sum shall be payable from the TI Fund.

(b) **TI Allowance**. Landlord shall provide to Tenant a tenant improvement allowance (the "**TI Allowance**") of $34.00 per rentable square foot of the First Expansion Premises (and if Tenant leases the ROFO Premises pursuant to Section 13 of the First Amendment, the ROFO Premises) which is included in the Base Rent set forth in Section 5(b) of the First Amendment. The TI Allowance shall be disbursed in accordance with this First Expansion Premises Work Letter.

Landlord shall, upon receipt of reasonably satisfactory invoices, reimburse Tenant for the payment made by Tenant for an initial test fit and one revision, not to exceed $0.15 per rentable square foot of the First Expansion Premises (and if Tenant leases the ROFO Premises pursuant to Section 13 of the First Amendment, the ROFO Premises).

Tenant shall have no right to the use or benefit (including any reduction to or payment of Base Rent) of any portion of the TI Allowance not required for the construction of (i) the Tenant Improvements described in the TI Construction Drawings approved pursuant to Section 2(d) or (ii) any Changes pursuant to Section 4. Notwithstanding the foregoing, Tenant shall have the right to use any unused portion of the TI Allowance for Alterations of a fixed and permanent nature reasonably acceptable to Landlord in any portion of the Premises (or any other premises leased by Tenant from Landlord at the Building). Tenant shall have no right to any portion of the TI Allowance that is not disbursed before the December 31, 2021.

(c) **Costs Includable in TI Fund**. The TI Fund shall be used solely for the payment of design, permits and construction costs in connection with the construction of the Tenant Improvements, including, without limitation, the cost of electrical power and other utilities used in connection with the construction of the Tenant Improvements, the cost of preparing the TI Design Drawings and the TI Construction Drawings, all costs set forth in the Budget, including Landlord's Administrative Rent, and the cost of Changes (collectively, "**TI Costs**"). Notwithstanding anything to the contrary contained herein, the TI Fund shall not be used to purchase any furniture, personal property or other non-Building system materials or equipment, including, but not be limited to, non-ducted biological safety cabinets and other scientific equipment not incorporated into the Tenant Improvements; provided, however that Tenant may use a portion of the TI Allowance for Tenant's voice or data cabling.

(d) **Excess TI Costs**. Landlord shall have no obligation to bear any portion of the cost of any of the Tenant Improvements, subject to the terms of Section 5(d), except to the extent of the TI Allowance. If at any time and from time-to-time, the remaining TI Costs under the Budget exceed the remaining unexpended TI Allowance ("**Excess TI Costs**"), monthly disbursements of the TI Allowance shall be made in the proportion that the remaining TI Allowance bears to the outstanding TI Costs under the Budget, and Tenant shall fund the balance of each such monthly draw. For purposes of any litigation instituted with regard to such amounts, those amounts required to be paid by Tenant will be deemed Rent under the Lease. The TI Allowance and Excess TI Costs are herein referred to as the "**TI Fund**." Notwithstanding anything to the contrary set forth in this Section 5(d), Tenant shall be fully and solely liable for TI Costs and the cost of Minor Variations in excess of the TI Allowance.

(e) **Payment for TI Costs**. During the course of design and construction of the Tenant Improvements, subject to the terms of Section 5(d), Landlord shall reimburse Tenant for TI Costs once a month against a draw request in Landlord's standard form, containing evidence of payment of such TI Costs by Tenant and such certifications, lien waivers (including a conditional lien release for each progress payment and unconditional lien releases for the prior month's progress payments), inspection reports and other matters as Landlord customarily obtains, to the extent of Landlord's approval thereof for payment, no later than 30 days following receipt of such draw request. Upon completion of the Tenant Improvements (and prior to any final disbursement of the TI Fund), Tenant shall deliver to Landlord: (i) sworn statements setting forth the names of all contractors and first tier subcontractors who did the work and final, unconditional lien waivers from all such contractors and first tier subcontractors; (ii) as-built plans (one copy in print format and two copies in electronic CAD format) for such Tenant Improvements; (iii) a certification of substantial completion in Form AIA G704, (iv) a certificate of occupancy for the First Expansion Premises (and if Tenant leases the ROFO Premises pursuant to Section 13 of the First Amendment, the ROFO Premises); and (v) copies of all operation and maintenance manuals and warranties affecting the First Expansion Premises (and if Tenant leases the ROFO Premises pursuant to Section 13 of the First Amendment, the ROFO Premises).

6. **Miscellaneous**.

(a) **Consents**. Whenever consent or approval of either party is required under this First Expansion Premises Work Letter, that party shall not unreasonably withhold, condition or delay such consent or approval, unless expressly set forth herein to the contrary.

(b) **Modification**. No modification, waiver or amendment of this First Expansion Premises Work Letter or of any of its conditions or provisions shall be binding upon Landlord or Tenant unless in writing signed by Landlord and Tenant.

(c) **No Default Funding**. In no event shall Landlord have any obligation to fund any portion of the TI Allowance during any period that Tenant is in Default under the Lease.

EXHIBIT C

Acknowledgment of First Expansion Premises Commencement Date

This **ACKNOWLEDGMENT OF FIRST EXPANSION PREMISES COMMENCEMENT DATE** is made this _____ day of _____, 2021, between **ARE-SAN FRANCISCO NO. 17, LLC**, a Delaware limited liability company ("**Landlord**"), and **ULTRAGENYX PHARMACEUTICAL INC.**, a Delaware corporation ("**Tenant**"), and is attached to and made a part of the Lease Agreement dated as of December 15, 2019, as amended by that certain First Amendment to Lease Agreement dated as of _____ ___, 2020 (as amended, the "**Lease**"), by and between Landlord and Tenant. Any initially capitalized terms used but not defined herein shall have the meanings given them in the Lease.

Landlord and Tenant hereby acknowledge and agree, for all purposes of the Lease, that the First Expansion Premises Commencement Date is _____, _____, the First Expansion Premises Rent Commencement Date is _____, _____, and the expiration date of the Base Term is March 31, 2025. In case of a conflict between the terms of the Lease and the terms of this Acknowledgment of First Expansion Premises Commencement Date, this Acknowledgment of First Expansion Premises Commencement Date shall control for all purposes.

IN WITNESS WHEREOF, Landlord and Tenant have executed this ACKNOWLEDGMENT OF FIRST EXPANSION PREMISES COMMENCEMENT DATE to be effective on the date first above written.

TENANT:

ULTRAGENYX PHARMACEUTICAL INC.,
a Delaware corporation

By:
Its:

LANDLORD:

ARE-SAN FRANCISCO NO. 17, LLC,
a Delaware limited liability company

By: ALEXANDRIA REAL ESTATE EQUITIES, L.P.,
a Delaware limited partnership,
managing member

By: ARE-QRS CORP.,
a Maryland corporation,
general partner

By:
Its:

Exhibit 10.83

SECOND AMENDMENT TO LEASE AGREEMENT

THIS SECOND AMENDMENT TO LEASE AGREEMENT (this "**Second Amendment**") is made as of October 21, 2020, by and between **ARE-SAN FRANCISCO NO. 17, LLC**, a Delaware limited liability company ("**Landlord**"), and **ULTRAGENYX PHARMACEUTICAL INC.,** a Delaware corporation ("**Tenant**").

RECITALS

A. Landlord and Tenant are now parties to that certain Lease Agreement dated as of December 15, 2019, as amended by that certain First Amendment to Lease Agreement dated as of September 30, 2020 (the "**First Amendment**") (as amended, the "**Lease**"). Pursuant to the Lease, Tenant leases certain premises consisting of approximately 25,897 rentable square feet of space (the "**Existing Premises**") in a building located at 7000 Shoreline Court, South San Francisco, California (the "**Building**"). The Existing Premises are more particularly described in the Lease. Capitalized terms used herein without definition shall have the meanings defined for such terms in the Lease.

B. Tenant has elected to exercise its right of first offer pursuant to Section 13 of the First Amendment with respect to the ROFO Premises.

C. Landlord and Tenant desire, subject to the terms and conditions set forth below, to amend the Lease to, among other things, expand the size of the Existing Premises by adding the ROFO Premises on the ground floor of the Building containing approximately 6,480 rentable square feet, as more particularly shown on **Exhibit A** attached hereto (the "**Second Expansion Premises**").

NOW, THEREFORE, in consideration of the foregoing Recitals, which are incorporated herein by this reference, the mutual promises and conditions contained herein, and for other good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, Landlord and Tenant hereby agree as follows:

1. **Second Expansion Premises**. In addition to the Existing Premises, commencing on the Second Expansion Premises Commencement Date (as defined in Section 2 below), Landlord leases to Tenant, and Tenant leases from Landlord, the Second Expansion Premises.

2. **Delivery**. Landlord shall use reasonable efforts to deliver ("**Delivery**" or "**Deliver**") the Second Expansion Premises to Tenant 1 business day after the mutual execution and delivery of this Second Amendment for the construction by Tenant of the Tenant Improvements pursuant to the terms of the First Expansion Premises Work Letter attached to the First Amendment as **Exhibit B**. The "**Second Expansion Premises Commencement Date**" shall be the date that Landlord Delivers the Second Expansion Premises to Tenant. The "**Second Expansion Premises Rent Commencement Date**" shall be the date that is 7 months after the First Expansion Premises Rent Commencement Date (as defined in the First Amendment). As used herein, the terms "**Tenant Improvements**" and "**Substantially Completed**" shall have the meanings set forth for such terms in the First Expansion Premises Work Letter.

Upon request of either party, the parties shall execute and deliver a written acknowledgment of the Second Expansion Premises Commencement Date and Second Expansion Premises Rent Commencement Date in a form attached here to as **Exhibit B**; provided, however, the failure to execute and deliver such acknowledgment shall not affect the parties' rights hereunder.

Except as set forth in the First Expansion Premises Work Letter: (i) Tenant shall accept the Second Expansion Premises in their condition as of the date Landlord Delivers the Second Expansion Premises to Tenant; (ii) Landlord shall have no obligation for any defects in the Second Expansion Premises; and (iii) Tenant's taking possession of the Second Expansion Premises shall be conclusive evidence that Tenant accepts the Second Expansion Premises and that the Second Expansion Premises were in good condition at the time possession was taken.

For the period of 30 consecutive days after the Second Expansion Premises Commencement Date, Landlord shall, at its sole cost and expense (which shall not constitute an Operating Expense), be responsible for any repairs that are required to be made to the Building Systems exclusively serving the Second Expansion Premises, unless Tenant or any Tenant Party was responsible for the cause of such repair, in which case Tenant shall pay the cost.

Tenant agrees and acknowledges that, except as expressly provided for herein, neither Landlord nor any agent of Landlord has made any representation or warranty with respect to the condition of all or any portion of the Second Expansion Premises, and/or the suitability of the Second Expansion Premises for the conduct of Tenant's business, and Tenant waives any implied warranty that the Second Expansion Premises are suitable for the Permitted Use.

3. **Definition of Premises and Rentable Area of Premises**. Commencing on the Second Expansion Premises Commencement Date, the defined terms "**Premises**" and "**Rentable Area of Premises**" on Page 1 of the Lease is deleted in its entirety and replaced with the following:

"**Premises:** That portion of the Building containing approximately 32,377 rentable square feet, consisting of (i) approximately 10,781 rentable square feet on the second floor of the Building (the "**Original Premises**"), (ii) approximately 15,116 rentable square feet on the ground floor of the Building (the "**First Expansion Premises**"), and (iii) approximately 6,480 rentable square feet on the ground floor of the Building (the "**Second Expansion Premises**"), as determined by Landlord, all as shown on **Exhibit A**."

"**Rentable Area of Premises:** 32,377 sq. ft."

Exhibit A attached to the Lease is amended as of the Second Expansion Premises Commencement Date to include **Exhibit A** attached to this Second Amendment.

4. **Base Term**. Commencing on the Second Expansion Premises Commencement Date, the defined term "**Base Term**" on page 1 of the Lease is deleted in its entirety and replaced with the following:

"**Base Term:** Commencing (i) with respect to the Original Premises on the Commencement Date, (ii) with respect to the First Expansion Premises on the First Expansion Premises Commencement Date, and (iii) with respect to the Second Expansion Premises on the Second Expansion Premises Commencement Date, and ending with respect to the entire Premises on March 31, 2025."

5. **Base Rent**.

a. **Original Premises and First Expansion Premises**. Tenant shall continue to pay Base Rent for the Original Premises and the First Expansion Premises as provided for in the Lease.

b. **Second Expansion Premises**. Commencing on the Second Expansion Premises Rent Commencement Date, Tenant shall commence paying Base Rent with respect to the Second Expansion Premises at the same rate per rentable square foot that Tenant is then paying with respect to the First Expansion Premises, as adjusted pursuant to Section 4 of the Lease.

6. **Definition of Tenant's Share of Operating Expenses**. Commencing on the date that is 7 months after the First Expansion Premises Rent Commencement Date, the defined term "**Tenant's Share of Operating Expenses**" on page 1 of the Lease is deleted in their entirety and replaced with the following:

"**Tenant's Share of Operating Expenses:** 23.17%"

7. **Security Deposit**. Tenant shall not be required to deposit any additional Security Deposit with Landlord in connection with the leasing of the Second Expansion Premises.

8. **Parking**. For the avoidance of doubt, commencing on the Second Expansion Premises Commencement Date, the provisions of Section 10 of the Lease shall apply to the leasing of the Second Expansion Premises.

9. **Common Corridor**. For the avoidance of doubt, because Tenant has elected to expand the Premises to include the Second Expansion Premises, Tenant acknowledges and agrees that Landlord has no obligation to construct the common corridor referenced in Section 2 and on **Exhibit A** of the First Amendment.

10. **Address for Rent Payment.** Commencing on the date of this Second Amendment, the "Address for Rent Payment" on Page 1 of the Lease is hereby deleted in its entirety and replaced with the following:

"Landlord's Lockbox Instructions:

REMITTANCES SENT VIA **CHECK** SHOULD BE SENT TO:

[***]

REMITTANCES SENT VIA **OVERNIGHT COURIER** SHOULD BE SENT TO:

[***]

11. **Brokers**. Landlord and Tenant each represents and warrants that it has not dealt with any broker, agent or other person (collectively, "**Broker**") in connection with the transaction reflected in this Second Amendment and that no Broker brought about this transaction, other than Kidder Mathews (as Tenant's representative) and Jones Lang LaSalle (as Landlord's representative). Landlord and Tenant each hereby agrees to indemnify and hold the other harmless from and against any claims by any Broker, other than Kidder Mathews and Jones Lang LaSalle, claiming a commission or other form of compensation by virtue of having dealt with Tenant or Landlord, as applicable, with regard to this leasing transaction.

12. **California Accessibility Disclosure.** The provisions of Section 42(p) of the Lease are hereby incorporated by reference.

13. **OFAC**. Tenant and any beneficial owners of Tenant are currently (a) in compliance with and shall at all times during the Term of the Lease remain in compliance with the regulations of the Office of Foreign Assets Control ("**OFAC**") of the U.S. Department of Treasury and any statute, executive order, or regulation relating thereto (collectively, the "**OFAC Rules**"), (b) not listed on, and shall not during the Term of the Lease be listed on, the Specially Designated Nationals and Blocked Persons List maintained by OFAC and/or on any other similar list maintained by OFAC or other governmental authority pursuant to any authorizing statute, executive order, or regulation, and (c) not a person or entity with whom a U.S. person is prohibited from conducting business under the OFAC Rules.

14. **Miscellaneous**.

a. This Second Amendment is the entire agreement between the parties with respect to the subject matter hereof and supersedes all prior and contemporaneous oral and written agreements and discussions. This Second Amendment may be amended only by an agreement in writing, signed by the parties hereto.

b. This Second Amendment is binding upon and shall inure to the benefit of the parties hereto, their respective successors and assigns.

c. This Second Amendment may be executed in 2 or more counterparts, each of which shall be deemed an original, but all of which together shall constitute one and the same instrument. Counterparts may be delivered via facsimile, electronic mail (including pdf or any electronic signature process complying with the U.S. federal ESIGN Act of 2000) or other transmission method and any counterpart so delivered shall be deemed to have been duly and validly delivered and be valid and effective for all purposes. Electronic

signatures shall be deemed original signatures for purposes of this Second Amendment and all matters related thereto, with such electronic signatures having the same legal effect as original signatures.

d. Except as amended and/or modified by this Second Amendment, the Lease is hereby ratified and confirmed and all other terms of the Lease shall remain in full force and effect, unaltered and unchanged by this Second Amendment. In the event of any conflict between the provisions of this Second Amendment and the provisions of the Lease, the provisions of this Second Amendment shall prevail. Whether or not specifically amended by this Second Amendment, all of the terms and provisions of the Lease are hereby amended to the extent necessary to give effect to the purpose and intent of this Second Amendment.

[Signatures on the next page]

IN WITNESS WHEREOF, the parties hereto have executed this Second Amendment as of the day and year first above written.

LANDLORD:

ARE-SAN FRANCISCO NO. 17, LLC,
a Delaware limited liability company

By: ALEXANDRIA REAL ESTATE EQUITIES, L.P.,
a Delaware limited partnership,
managing member

By: ARE-QRS CORP.,
a Maryland corporation,
its General Partner

By: /s/ Kristen Childs
Its: Vice President, RE Legal Affairs
Date:

TENANT:

ULTRAGENYX PHARMACEUTICAL INC.,
a Delaware corporation

By: /s/ Shalini Sharp
Its: CFO
Date: 21-OCT-2020

EXHIBIT B

Acknowledgment of Second Expansion Premises Commencement Date

This **ACKNOWLEDGMENT OF SECOND EXPANSION PREMISES COMMENCEMENT DATE** is made this _____ day of _____, 202__, between **ARE-SAN FRANCISCO NO. 17, LLC**, a Delaware limited liability company ("**Landlord**"), and **ULTRAGENYX PHARMACEUTICAL INC.**, a Delaware corporation ("**Tenant**"), and is attached to and made a part of the Lease Agreement dated as of December 15, 2019, as amended by that certain First Amendment to Lease Agreement dated as of September 30, 2020, and as further amended by that certain Second Amendment to Lease Agreement dated as of October __, 2020 (as amended, the "**Lease**"), by and between Landlord and Tenant. Any initially capitalized terms used but not defined herein shall have the meanings given them in the Lease.

Landlord and Tenant hereby acknowledge and agree, for all purposes of the Lease, that the Second Expansion Premises Commencement Date is _____, _____, the Second Expansion Premises Rent Commencement Date is _____, _____, and the expiration date of the Base Term is March 31, 2025. In case of a conflict between the terms of the Lease and the terms of this Acknowledgment of Second Expansion Premises Commencement Date, this Acknowledgment of Second Expansion Premises Commencement Date shall control for all purposes.

IN WITNESS WHEREOF, Landlord and Tenant have executed this ACKNOWLEDGMENT OF SECOND EXPANSION PREMISES COMMENCEMENT DATE to be effective on the date first above written.

TENANT:

ULTRAGENYX PHARMACEUTICAL INC.,
a Delaware corporation

By:
Its:

LANDLORD:

ARE-SAN FRANCISCO NO. 17, LLC,
a Delaware limited liability company

By: ALEXANDRIA REAL ESTATE EQUITIES, L.P.,
a Delaware limited partnership,
managing member

By: ARE-QRS CORP.,
a Maryland corporation,
general partner

By:
Its:

Exhibit 21.1

Significant Subsidiaries of Ultragenyx Pharmaceutical Inc.

Name of Subsidiary	Jurisdiction of Incorporation
Ultragenyx Holdco LLC	Delaware
Ultragenyx UK Ltd	United Kingdom
Ultragenyx Europe GmbH	Switzerland
Ultragenyx Germany GmbH	Germany
Ultragenyx Brasil Farmacêutica Ltda	Brazil
Ultragenyx Argentina SRL	Argentina
Ultragenyx Netherlands B.V.	Netherlands
Ultragenyx France SAS	France
Ultragenyx Colombia SAS	Colombia
Ultragenyx Canada Inc.	Canada
Ultragenyx México, S. de R.L. de C.V.	Mexico

Exhibit 23.1

CONSENT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

We consent to the incorporation by reference in the following Registration Statements:

(1) Registration Statement (Form S-3 No. 333-223123) of Ultragenyx Pharmaceutical Inc.,

(2) Registration Statements (Form S-8 Nos. 333-194773, 333-201843, 333-209729, 333-216110, 333-223124, 333-229746 and 333-236428) pertaining to the 2011 Equity Incentive Plan, as amended, 2014 Incentive Plan and 2014 Employee Stock Purchase Plan of Ultragenyx Pharmaceutical Inc., and

(3) Registration Statement (Form S-8 No. 333-221381) pertaining to the Dimension Therapeutics, Inc. 2015 Stock Option and Incentive Plan and the Dimension Therapeutics, Inc. 2013 Stock Plan, both as assumed by Ultragenyx Pharmaceutical Inc.;

of our reports dated February 11, 2021, with respect to the consolidated financial statements of Ultragenyx Pharmaceutical Inc. and the effectiveness of internal control over financial reporting of Ultragenyx Pharmaceutical Inc. included in this Annual Report (Form 10-K) of Ultragenyx Pharmaceutical Inc. for the year ended December 31, 2020.

/s/ Ernst & Young LLP

San Jose, California
February 11, 2021

Exhibit 31.1

CERTIFICATION PURSUANT TO SECTION 302 OF THE SARBANES-OXLEY ACT OF 2002

I, Emil D. Kakkis, certify that:

1. I have reviewed this Annual Report on Form 10-K of Ultragenyx Pharmaceutical Inc.;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

   a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

   b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

   c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

   d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

   a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

   b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Dated: February 11, 2021

/s/ Emil D. Kakkis

Emil D. Kakkis, M.D., Ph.D.
President and Chief Executive Officer
(Principal Executive Officer)

Exhibit 31.2

CERTIFICATION PURSUANT TO SECTION 302 OF THE SARBANES-OXLEY ACT OF 2002

I, Mardi C. Dier, certify that:

1. I have reviewed this Annual Report on Form 10-K of Ultragenyx Pharmaceutical Inc.;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

   a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

   b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

   c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

   d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

   a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

   b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Dated: February 11, 2021

/s/ Mardi C. Dier
Mardi C. Dier
Chief Financial Officer and Executive Vice President
(Principal Financial Officer)

Exhibit 32.1

CERTIFICATION PURSUANT TO SECTION 906 OF
THE SARBANES-OXLEY ACT OF 2002 (18 U.S.C. SECTION 1350)

In connection with the accompanying Annual Report of Ultragenyx Pharmaceutical Inc. (the "Company") on Form 10-K for the year ended December 31, 2020 (the "Report"), I, Emil D. Kakkis, M.D., Ph.D., as President and Chief Executive Officer of the Company, and Mardi C. Dier, as Chief Financial Officer and Executive Vice President of the Company, certify, pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, that:

(1) The Report fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934; and

(2) The information contained in the Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

Dated: February 11, 2021

/s/ Emil D. Kakkis
Emil D. Kakkis, M.D., Ph.D.
President and Chief Executive Officer
(Principal Executive Officer)

Dated: February 11, 2021

/s/ Mardi C. Dier
Mardi C. Dier
Chief Financial Officer and Executive Vice President
(Principal Financial Officer)