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, 2021
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 Exchange Act:

Title of each class	Trading Symbol(s)	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 Exchange 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 Exchange 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 Exchange Act 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, 2021 was approximately $6.5 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 10, 2022, the Company had 69,384,774 shares of common stock issued and outstanding.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant's definitive proxy statement relating to its 2022 Annual Meeting of Stockholders, to be held on or about June 24, 2022, are incorporated by reference into Part III of this Annual Report on Form 10-K where indicated. Such proxy statement will be filed with the U.S. Securities and Exchange Commission within 120 days after the end of the fiscal year to which this report relates.

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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 fact 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 refer to 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

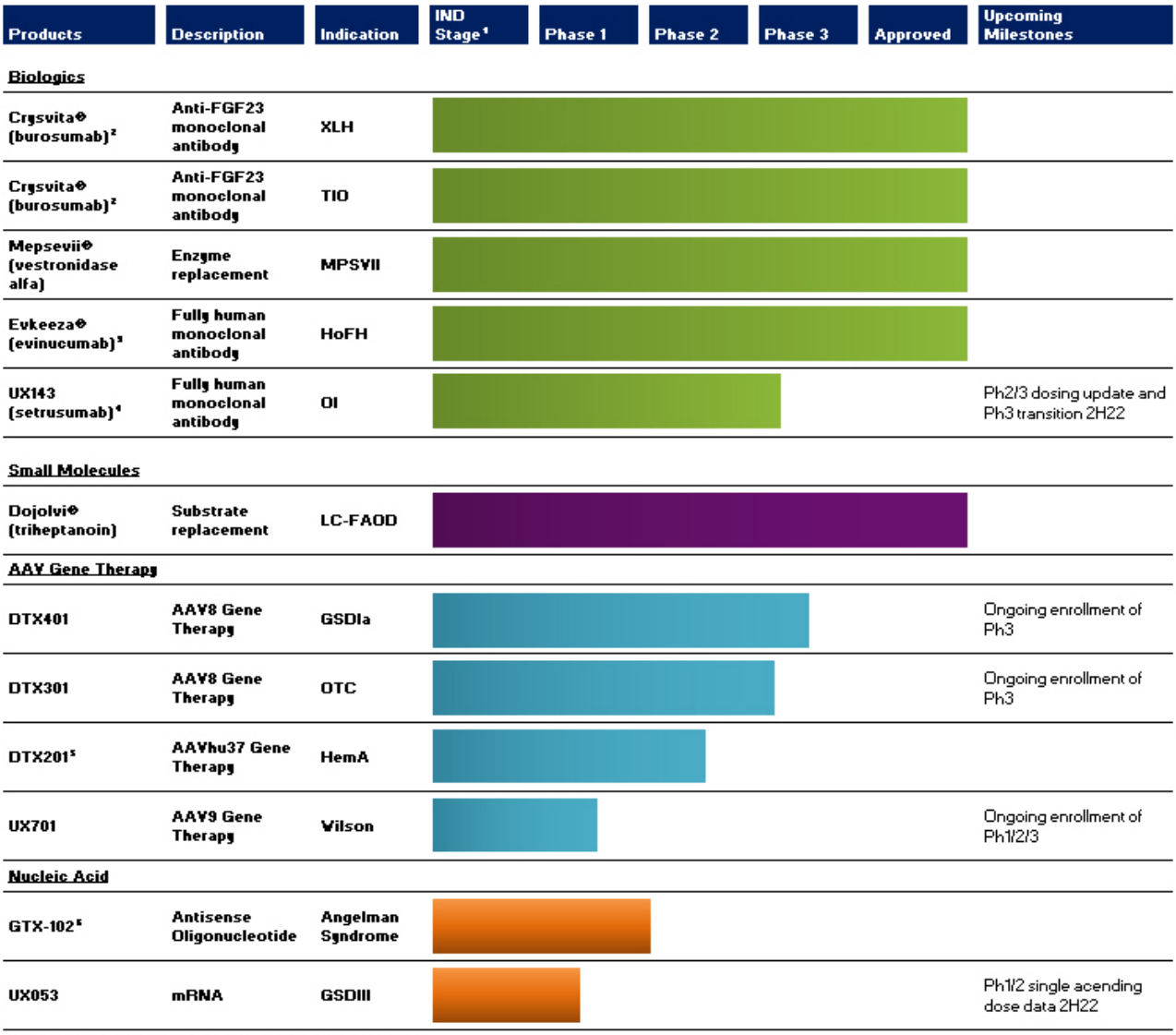
The critical components of our business strategy include the following:

- ***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 biologics, small molecules, gene therapy, and nucleic acids provide us with what we believe is an optimal set of options to treat 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 throughout the developed world, in North America, the European Union (EU), the United Kingdom, Latin America, Turkey, Asia, and select international markets. We have established our own commercial organization in these markets and a network of third-party distributors in smaller markets, and are in the process of establishing our own commercial organization in Japan. We believe our commercial organization is highly specialized and focused, due to the nature of rare disease treatment. Our commercial expansion outside of the United States (U.S.) is enabled through strategic collaborations and internal pipeline development.

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 four 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, Dojolvi® (triheptanoin) for the treatment of long-chain fatty acid oxidation disorders, or LC-FAOD, and Evkeeza® (evinacumab) for the treatment of homozygous familial hypercholesterolemia (HoFH) and we anticipate having six product candidates in the clinical pipeline in 2022. The following table summarizes our approved products and clinical product candidate pipeline:



Approved Products

Crysvita for the treatment of XLH and TIO

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 U.S. 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, Colombia, 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.

Crysvita is also developed for the treatment of tumor-induced osteomalacia, or TIO, a rare disease that 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. Crysvita is approved in the U.S. and Canada 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. 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.

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 U.S. 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 Italy, Mepsevii received reimbursement approval for the treatment of pediatric and adult patients with MPS VII. 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 U.S. The product is also approved by Health Canada and commercially available in that country. In Brazil we have received product approval from the Brazilian Health Regulatory Agency (ANVISA) and are in the process of seeking full reimbursement approval. Discussions with EU regulatory authorities related to the approval of Dojolvi are ongoing. There are approximately 8,000 to 14,000 patients in the developed world with LC-FAOD.

Data published in February 2021 under France's nominative Authorization for Temporary Use program, or Authorisations Temporaires d'Utilisation (ATU), of 18 pediatric and adult patients with LC-FAOD showed that Dojolvi (triheptanoin) led to reductions in LC-FAOD manifestations and was well-tolerated, with a median follow-up duration of 22 months (range 9-228 months). When comparing the year prior to treatment to the first year receiving Dojolvi, annual emergency hospital care visits decreased from a mean of 1.12 to 0.17, or an 85% reduction, and the mean number of emergency home care events decreased from 16.82 to 2.83, an 83% reduction. Similarly, the cumulative annual number of days of emergency home care was reduced from 286 in the year prior to receiving Dojolvi to 51 in the first year receiving Dojolvi, an 82% reduction. Further improvements in the cumulative annual number of days of emergency home care were seen in the second year receiving Dojolvi.

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

Evkeeza for the treatment of HoFH

On January 7, 2022, we announced a collaboration with Regeneron Pharmaceuticals (Regeneron) to commercialize Evkeeza outside of the U.S. Evkeeza is a fully human monoclonal antibody that binds to and blocks the function of angiopoietin-like 3 (ANGPTL3), a protein that plays a key role in lipid metabolism. Evkeeza is the first and only approved therapy for the treatment of homozygous familial hypercholesterolemia, or HoFH, a rare inherited condition. HoFH occurs when two copies of the familial hypercholesterolemia (FH)-causing genes are inherited, one from each parent, resulting in dangerously high levels (>400 mg/dL) of LDL-C, or bad cholesterol. Patients with HoFH are at risk for premature atherosclerotic disease and cardiac events as early as their teenage years. Evkeeza is approved in the U.S. and the European Economic Area (EEA) as a first-in-class therapy for use together with diet and other low-density lipoprotein-cholesterol (LDL-C) lowering therapies to treat adults and adolescents aged 12 years and older with HoFH.

Under the terms of the agreement, Regeneron received a $30.0 million upfront payment and is eligible to receive up to $63.0 million in potential regulatory and sales milestones. We received the rights to develop, commercialize and distribute the product in countries outside of the U.S. and will make payments to Regeneron based on net sales of the product. There are approximately 1,600

patients in the EEA and a total of 3,000 to 5,000 patients in the territories where we have product rights. We will also share in certain costs for global trials led by Regeneron and will have the right to opt into other potential indications.

Pursuant to the terms of the agreement with Regeneron, we were also granted an exclusive right to negotiate a separate agreement with Regeneron to collaborate on the development and commercialization outside of the U.S. of Regeneron's investigational antibody, currently in Phase 2/3 development, for the treatment of the ultra-rare disease, fibrodysplasia ossificans progressiva (FOP) under terms to be agreed upon by both companies.

Please see "—License and Collaboration Agreements—Approved Products—Regeneron" for a description of our license agreement with Regeneron Pharmaceuticals.

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 U.S. and in the EU and the United Kingdom, Regenerative Medicine Advanced Therapy (RMAT) designation and Fast Track designation in the U.S.

Throughout 2021 we shared updated longer-term safety, efficacy, and durability data from the ongoing Phase 1/2 study through press releases and presentations at various medical congresses. Most recently, we announced data at the 14th International Congress of Inborn Errors of Metabolism (ICIEM) that took place in November 2021. Across all 12 patients in the Phase 1/2 study, the mean reduction in daily cornstarch intake was 69.9% ($p < 0.0001$) ranging from 19-100% when comparing baseline to the most recent visit. The nine patients in Cohorts 1, 2, and 3 continued to demonstrate improved glucose control while tapering or discontinuing oral glucose replacement therapy with cornstarch up to three years after receiving DTX401. The three patients in Cohort 4 had completed a tapering prophylactic steroid regimen. Two of the three patients have reduced the frequency of daily oral glucose replacement therapy from six times per day at baseline to one (Patient 10) and two (Patient 11) times per day as of the announcement. These reductions in cornstarch dosing have had an impact on energy metabolism and body weight. As of the last visit, patients had an average weight decrease of 5.2% with a range of a 14.4% decrease to 3.1% increase. The notable weight loss was attributed to improved glycemic control and potentially increased physical activity reported by patients.

At the 14th ICIEM in November 2021, we also presented data demonstrating that in Cohorts 3 and 4, data collected from continuous glucose monitoring (CGM) indicated that glycemic control was maintained and even improved despite the reductions in cornstarch dependence. In Cohort 3, the average cornstarch intake was reduced by 64% during Weeks 49 to 52 compared with Weeks 1 to 4, while the time in euglycemia (60-120 mg/dL) increased by 14% over the same time period. In Cohort 4, the average cornstarch intake was reduced by 73% at Weeks 33 to 36 compared with Weeks -1 to -4, while the time in euglycemia decreased by 3% over the same time period.

All three patients in a fourth and final Phase 1/2 cohort, which utilized prophylactic steroids, have been dosed at the same dose as Cohorts 2 and 3. As of February 14, 2022, across all patients in the Phase 1/2 study, there have been no infusion-related adverse events, no treatment-related serious adverse events, and no dose-limiting toxicities reported.

The first patients have been dosed in the Phase 3 study of DTX401 following an approximate 4- to 8-week baseline screening period. The Phase 3 study has a 48-week primary efficacy analysis period and we plan to enroll approximately 50 patients eight years of age and older, randomized 1:1 to DTX401 (1.0 x 10^13 GC/kg dose) or placebo. The primary endpoint is the reduction in oral glucose replacement with cornstarch while maintaining glucose control.

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 U.S. and in the EU and the United Kingdom and Fast Track Designation in the U.S.

Throughout 2021, we shared updated longer-term safety, efficacy, and durability data from the ongoing Phase 1/2 study through press releases and presentations at various medical congresses. Most recently, we announced at the 14th ICIEM that took place in

November 2021, that the six patients who had previously responded to DTX-301 remained clinically and metabolically stable up to four years after dosing and one responder was recently identified in the prophylactic steroid cohort. The three complete responders were stable through 104, 156, and 182-weeks post-treatment with good ammonia control despite discontinuation of their alternative pathway medications and protein-restricted diets. The four other responders also remained stable through Weeks 36, 91, 104, 156, and were either continuing to taper medications and diet. As of February 14, 2022, across all responders, there have been no significant adverse events or hospitalizations related to OTC deficiency reported.

We are currently in the process of initiating a Phase 3 study that will include a 64-week primary efficacy analysis period and plan to enroll approximately 50 patients 12 years of age and older, randomized 1:1 to DTX301 (1.7 x 10^13 GC/kg dose) or placebo. The co-primary endpoints are the percentage of patients who achieve a response as measured by discontinuation or reduction in baseline disease management and the 24-hour plasma ammonia levels. The first patients in the U.S. are expected to enter an approximate 4-to 8-week baseline screening period in the first half of 2022, after which they are expected to receive a single dose of DTX301 or placebo.

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.

In October 2021, at the American Society for Bone and Mineral Research (ASBMR) annual meeting, we, along with our partner, Mereo, presented additional secondary endpoint data from the Phase 2b ASTEROID study demonstrating that treatment with UX143 resulted in dose-dependent increase in P1NP serum levels, a marker of bone formation, and a decrease in CTx serum levels, a marker of bone resorption, confirming the mechanism of action of sclerostin inhibition over the 12-month treatment period. Observed improvements in bone mineral density were continuous over the 12 months of the study, with comparable gains achieved in the first and second six months of treatment in the high dose group despite temporal changes in biomarkers.

We currently expect to start a pediatric and young adult Phase 2/3 study in the first half of 2022. The objective of the Phase 2/3 study will 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. We currently expect a separate Phase 2 study of patients under age five with OI to start in the second half of 2022. We will, also, continue to evaluate adult patients who were previously treated in the ASTEROID study.

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 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 received GTX-102 treatment 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 been fully resolved. Full safety information was submitted to the FDA. A formal clinical hold was issued by the FDA on study GTX-102-001 during the fourth quarter of 2020, which was subsequently removed by the FDA in 2021, as described below.

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.

In the second quarter of 2021, we and our partner GeneTx announced that Health Canada (HC) cleared a protocol amendment and the U.K. Medicines and Healthcare Products Regulatory Agency (MHRA) approved a Clinical Trial Application (CTA) to begin treatment of patients in Canada and the U.K. with Angelman syndrome.

In September 2021, we, and our partner GeneTx announced that the FDA removed the clinical hold and that GeneTx could begin dosing naïve patients in the Phase 1/2 study of GTX-102 in pediatric patients with Angelman syndrome.

Under the amended U.S. protocol, eight patients (4 to < 8 years of age) who were not previously treated with GTX-102 will be enrolled into two groups, an active group and an age-matched comparator group. The active group will receive four monthly 2 mg doses of GTX-102, while the comparator group will have limited assessments at baseline and at Day 128. Patients in the comparator group will then be eligible to receive GTX-102 under the same dosing strategy as the active group. All U.S. patients who have completed the dose-loading phase will then move to a maintenance phase during which they will receive 2 mg of GTX-102 every three months and continue to be monitored for response and safety.

Under the protocol approved in the U.K. and Canada, approximately 12 patients will be enrolled into two cohorts split by age: patients ages 4 to < 8 years will be enrolled into Cohort 4, and patients ages 8 to < 18 years will be enrolled into Cohort 5. Two patients in the younger cohort and two patients in the older cohort will be enrolled first and assessed after two doses by a data safety monitoring board. If recommended, then an additional four patients can be enrolled in each of the two cohorts.

The starting doses in Cohorts 4 and 5 will be 3.3 and 5 mg, respectively. Patients will receive three to four monthly doses, titrated individually through smaller steps than the first three cohorts in the original study with dose increases based on response and enhanced safety monitoring. Patients will then move to a maintenance phase during which they will receive GTX-102 every three months and continue to be monitored for response and safety. In this phase, individual dose titration may continue if safety is sustained, and the clinical response is not much improved in at least 2 domains up to a maximum dose of 14 mg.

In October 2021, we announced that the first patients under the amended protocol in Canada and the U.K. were dosed in the Phase 1/2 study.

In January 2022, we provided an initial update on the first four patients treated in Canada and the U.K. As of the update, all four patients had received multiple doses of GTX-102 with no treatment-related serious adverse events of any type nor adverse events related to lower extremity weakness. As of January 2022, three patients had received a preliminary assessment of clinical response and all have shown early signs of clinical activity. The data safety monitoring board (DSMB) for Cohort 4 recommended dose escalation for the first two patients and enrollment of the additional four patients in this cohort. Later in January 2022, the DSMB for Cohort 5 met and also recommended dose escalation and expansion of that cohort.

As of February 14, 2022, patients naïve to prior treatment with GTX-102 have been screened in the U.S. and dosing has begun. We currently anticipate data on full Cohorts 4 and 5 in Canada and the U.K., as well as available safety and efficacy data from the patients treated in the U.S. in mid-2022.

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 U.S. 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.

UX701 has received a 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.

In October 2021, we announced that we had begun screening and enrolling patients with Wilson disease into the 6- to 12-week baseline monitoring period prior to dosing in the seamless Phase 1/2/3 study of UX701, or the Cyprus2+ study. The study will enroll patients receiving ongoing standard of care medication for the treatment of Wilson disease (copper chelators and/or zinc) for at least 12 months, with no medication or dose changes for at least six months prior to enrollment. After initial screening, which includes testing for pre-existing antibodies to the AAV9 capsid, patients will be evaluated to ensure stable measures of disease during a 6-to 12-week baseline monitoring period (including values for 24-hour urinary copper concentration, complete blood count, and liver function tests) and patients will then be dosed with either UX701 or placebo.

During the first stage of the study, the safety and efficacy of up to three dose levels of UX701 will be evaluated over the course of 52 weeks and a dose will be selected for further evaluation in stage 2. In this first stage, 27 patients will be randomized into three cohorts in a 2:1 ratio per cohort to receive UX701 at the dose level assigned for the cohort or a placebo. The sequential doses to be evaluated are 5.0 x 10^12 GC/kg, 1.0 x 10^13 GC/kg, and 2.0 x 10^13 GC/kg. In stage 2, a new cohort of patients will be randomized 2:1 to receive the selected dose of UX701 or placebo. The primary safety and efficacy analyses will be conducted at Week 52 of stage 2. The primary efficacy endpoints are change in 24-hour urinary copper concentration and percent reduction in standard of care medication by Week 52. After the initial 52-week study period, all patients will receive long term follow up in stage 3. Patients randomized to placebo in stages 1 and 2 will become eligible to receive UX701 in stage 3.

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

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

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. UX053 is our first mRNA program to enter clinical studies. UX053 has been granted Orphan Drug Designation (ODD) by the FDA in June 2021 and European Medicines Agency (EMA) in July 2021, highlighting the significant unmet need for patients with GSDIII.

Dosing in a Phase 1/2 study of UX053 for the treatment of GSDIII began in December 2021. Part 1 of the study is open label with single-ascending doses. Part 2 is double-blind and will evaluate repeat doses at escalating levels. We currently expect preliminary data from Part 1 of the study and to initiate Part 2 of the study in the second half of 2022.

Please see "—License and Collaboration Agreements—Clinical Product Candidates—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 has been submitted for approval by Acer Therapeutics and has a target PDUFA date of June 5, 2022. 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 Pharmaceuticals is developing NNZ-2591, an IGF-1 analog, in Phase 2 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 preclinical development by Vivet Therapeutics, in collaboration with Pfizer, for Wilson disease.

With respect to UX143, there are currently no approved drugs for osteogenesis imperfecta. Most pediatric patients with osteogenesis imperfecta are managed with off-label use of bisphosphonates to increase bone density and reduce frequency of bone fracture. We are aware of another anti-sclerostin antibody, romosozumab, that is in Phase 1 clinical testing by Amgen. In addition, fresolimumab, an anti-TGFβ antibody, is in Phase 1 clinical testing led by a Baylor College of Medicine investigator in collaboration with Sanofi-Genzyme.

With respect to UX053, there are currently no pharmacologic treatments for patients with GSD III and we are not aware of any programs in clinical development.

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 U.S. and Canada, or the “profit-share territory”, and in the EU, U.K., 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 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. 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 and U.K. 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, 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, with the exception of Turkey. In Turkey, we have rights to commercialize Crysvita and KKC has the option to assume responsibility for such commercialization efforts, after a certain minimum period. 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 pays us 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.

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. 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 U.S., 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 U.S., Europe, or Japan, at which point our license becomes fully paid.

Baylor Research Institute

In September 2012, we entered into a license agreement, which was subsequently amended, 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.

Regeneron Pharmaceuticals

On January 7, 2022, we announced a license and collaboration agreement with Regeneron Pharmaceuticals, or Regeneron, to clinically develop, commercialize, and distribute Evkeeza for the treatment of homozygous familial hypercholesterolemia (HoFH) outside of the U.S. Under the terms of the agreement, Regeneron received a $30.0 million upfront payment and is eligible to receive up to $63.0 million in future milestone payments, contingent upon the achievement of certain regulatory and sales milestones. We received the rights to develop, commercialize and distribute the product in countries outside of the U.S. and will make payments to Regeneron based on net sales of the product. We will share in certain costs for global trials led by Regeneron and also have the right to opt into other potential indications.

We were also granted an exclusive right to negotiate a separate agreement with Regeneron to collaborate on the development and commercialization outside of the U.S. of Regeneron's investigational antibody, currently in Phase 2/3 development, for the treatment of the ultra-rare disease FOP under terms to be agreed upon by both companies.

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, which was subsequently amended, 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, as amended, 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. 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. The agreement expired on December 31, 2021.

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 are required to make milestone payments (up to a maximum of $5 million per Subfield) if certain development milestones are achieved over time. We will also make milestone payments of up to $25.0 million per approved product, if certain commercial milestones are achieved, and will pay low to mid-single-digit royalties on net sales of each Subfield's licensed products.

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.

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. 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. During the years ended December 31, 2021 and 2020, we sold 1,700,000 shares and 800,000 shares of Arcturus common stock, at a weighted-average price of $47.44 and $100.81, respectively. As of December 31, 2021, we held 500,000 shares of Arcturus common stock.

On a product-by-product basis, we are obligated to make development and regulatory milestone payments of up to $24.5 million, and commercial milestone payments of up to $45.0 million, if certain milestones are achieved. We are also obligated to pay Arcturus royalties on any net sales of products incorporating the licensed intellectual property that range from a mid single-digit to low double-digit percentage. Arcturus is also entitled to reimbursement of related research expenses.

Preclinical Pipeline

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 are collaborating to develop products that combine Solid's differentiated microdystrophin construct, our Producer Cell Line (PCL) manufacturing platform, and our AAV8 variants. Solid is providing development support and was granted an exclusive option to co-invest in products we develop for profit share participation in certain territories. We also entered into a Stock Purchase Agreement with Solid in October 2020 pursuant to which we purchased 7,825,797 shares of Solid's common stock for an aggregate price of $40.0 million, and we currently continue to hold all of the purchased shares.

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 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 during the fourth quarter of 2021, an additional payment of $25.0 million upon achievement of the milestones related to the technology transfer of the PCL and HEK293 platforms. Daiichi Sankyo will reimburse us for all costs associated with the transfer of the manufacturing technology and will also pay us a single-digit royalties on net sales of products manufactured with the technology platforms.

In March 2020, we also entered into a Stock Purchase Agreement 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. 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 U.S. 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 U.S., 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, 2021, we own, jointly own, or have exclusive rights to more than 160 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 50 in-force patents issued by the U.S. Patent and Trademark Office (the USPTO). Furthermore, as of December 31, 2021, we own, jointly own, or have exclusive rights to more than 325 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 for our commercial products and our clinical-stage product candidates as of December 31, 2021 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 seven 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 2023 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 and the corresponding issued foreign patents covering Mepsevii and its use in the treatment of lysosomal storage disorders such as MPS VII. These patents 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.

Dojolvi (Triheptanoin) Exclusivity

We have an exclusive license from 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 these BRI patents and patent applications, we own a pending U.S. patent application, corresponding foreign patent applications, and issued patents in Australia, Israel, Korea, 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 (Pariglasgene Brecaparvovec) 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 (not accounting for any available PTE) 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.

DTX301 (Avalotcagene Ontaparvovec) 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 (not accounting for any available PTE) and corresponding foreign patents and patent applications covering the codon-optimized version of the OTC gene used in DTX301.

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 setrusumab, processes for producing setrusumab, and setrusumab's use as a medicament. Patents emanating from this first patent family expire in 2028 (not accounting for any available PTE). We also have exclusive rights outside of Europe to two additional Mereo patent families, including an issued U.S. patent expiring in 2037 (not accounting for any available PTE), relating to methods of using anti-sclerostin antibodies including setrusumab for the treatment of OI. Beyond these Mereo patents and patent applications, we jointly own with Mereo two additional patent families relating to dosing regimens for the use of anti-sclerostin antibodies including setrusumab in the treatment of OI and other bone disorders; we expect any patents emanating from these patent families to expire in 2042 (not accounting for any available PTE).

UX701 Exclusivity

We have two in-licenses to patents and patent applications covering elements of our UX701 product candidate. First, we have in-licensed patents owned by UPENN and sublicensed to us by REGENX relating to the AAV9 capsid used in UX701 that expire between 2024 and 2026 in the U.S., and in 2024 in foreign countries. Second, we have an exclusive license from UPENN to patent applications covering AAV vectors containing certain regulatory and coding sequences packaged in UX701; we expect any patents emanating from this patent family to expire in 2037 (not accounting for any available PTE). Beyond these UPENN patents and patent applications, we own a patent family covering AAV vectors expressing a novel truncated version of the ATP7B protein produced by UX701; we expect any patents emanating from this patent family to expire in 2040 (not accounting for any available PTE).

UX053 Exclusivity

We have an in-license from Arcturus to four U.S. patents expiring between 2034 and 2038 (not accounting for any available PTE), and corresponding foreign patents and applications, that cover the cationic lipid used in our UX053 product candidate. Beyond these Arcturus patents and patent applications, we own a patent family covering the codon-optimized version of the human AGL mRNA expressed by UX053; we expect any patents emanating from this patent family to expire in 2038 (not accounting for any available PTE).

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 historically minimized 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 seek 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 to 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

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 U.S. 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

Similar to DTX 401, 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 U.S. 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 have transitioned 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 our efforts in these regions and build our organizations in other areas such as in Japan and other countries in the Asia-Pacific region. 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 U.S. 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 commercial and medical affairs organizations as well as other capabilities across North America, Europe, Turkey, Latin America and Japan 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 U.S. (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 U.S. 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 U.S., 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 U.S. 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 U.S. 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 U.S., or if it affects more than 200,000 individuals in the U.S. 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 U.S.

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 U.S., 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 U.S. 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 U.S., 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 U.S., 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 U.S. 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, 2021, more than half of our total revenues were generated under our collaboration agreement with KKC.

Human Capital

General Information

As of December 31, 2021, we had 1,119 total employees, of which 742 are in research and development and 377 are in sales, general, and administrative. Further, 1,017 are based in the U.S., including facilities at Novato, California, Brisbane, California, Cambridge, Massachusetts, and Woburn, Massachusetts, and 102 are based in our international locations. The majority of new employees hired during the year ended December 31, 2021 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 2022 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 and expanding our geographic reach through the global launches of our approved products. 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.

Response to COVID-19

We maintain a safety culture grounded on the premise of eliminating workplace incidents, risks and hazards. The COVID-19 pandemic provided an opportunity for us to demonstrate our commitment to the health and wellbeing of our employees. Effective as of January 3, 2022, we have required full vaccination against COVID-19 as a condition of employment at the company for almost all roles based in the U.S., with limited exceptions. Further, 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, and increased ventilation and implementation of new HEPA filtration devices at sites;
- Providing additional personal protective equipment and cleaning supplies, including distribution of hand sanitizers to personnel at all sites;
- Implementing protocols to address actual and suspected COVID-19 cases and potential exposure;

- Providing COVID-19 testing for employees and their households;
- Implementing daily health attestations and capacity management via online application;
- Including healthcare professionals on staff to administer testing and a health declaration process;
- Temporarily prohibiting all domestic and international non-essential travel for all employees; and
- Requiring face coverings to be worn inside all office locations.

Employee Retention and Engagement

The biotechnology industry is an extremely competitive labor market and 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.

Inclusion and Diversity

We strive toward having a diverse organization and are committed to equality, inclusion and workplace diversity. As of December 31, 2021, of the nine members of our board of directors, three directors were women, two directors self-identified as racially or ethnically diverse, and one director self-identified as LGBTQ+. As of December 31, 2021, women represented approximately 58% of our global workforce and approximately 43% of our leadership positions at the Vice President level or above. As of December 31, 2021, approximately 45% of our U.S. workforce were racially or ethnically diverse. We have included questions in our engagement survey to measure employee perception of inclusive culture, with the results from such survey on inclusion and diversity included in our corporate goals for fiscal year 2021 and as part of our corporate goals for 2022. Our business units review diversity data related to hiring, promotions, and retention on an ongoing basis. We have also established an Inclusion and Diversity Action Team (I&D Action Team) comprised of 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. In 2021, we hosted our first Inclusion & Diversity summit for our employees to expand their understanding of inclusion and diversity on issues such as disability and transgender rights. We have also organized multiple internal employee resource groups to foster dialogue and engagement related to inclusion and diversity, such as UltraProud and X2 Women in Biotech.

Benefits and Compensation

We are dedicated to fostering a workplace environment that keeps our employees inspired, including providing a comprehensive benefits program that supports the health care, family, and financial needs of our employees. All of our full-time employees are eligible for cash bonuses and equity awards in addition to other benefits including comprehensive health insurance, life and disability insurance, 401(k) matching, paid time off for volunteering, wellness programs, and tuition reimbursement.

General Information

Our Internet website address is *www.ultragenyx.com.* No portion of our website, or any other website that may be referenced, 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 the 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 annual reports on Form 10-K, our quarterly reports on Form 10-Q, and our current reports on Form 8-K, and amendments to those 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, reputation, 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 to need to raise additional capital to fund our activities.
- Clinical drug development is a lengthy, complex, 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 other adverse effects.
- 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 may cause undesirable or serious side effects that could delay or prevent their regulatory approval or result in other negative consequences.
- We face a multitude of manufacturing risks, particularly with respect to our gene therapy and mRNA product candidates.
- Our products will remain subject to regulatory scrutiny even if we obtain regulatory approval.
- Product liability lawsuits against us could cause us to incur substantial liabilities.
- 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 rely on third parties to manufacture our products and product candidates.
- 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 U.S. 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.
- If we, or our third party partners, are unable to maintain effective proprietary rights for our products or product candidates we may not be able to compete effectively.
- 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 of our biologics product and product candidates or from generic versions of our small-molecule product and 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.
- We have no experience as a company developing or operating a manufacturing facility.
- 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, developing, or commercializing additional product candidates, or we may fail to capitalize on opportunities that may be more profitable.
- 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 U.S.
- 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, or any other reasons, we may not generate significant revenue from sales of our products, even if they receive regulatory approval.

We expect to 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, 2021, our available cash, cash equivalents, and marketable debt securities were $999.1 million. We expect we will need additional capital to continue to commercialize our products, and to develop and obtain regulatory approval for, and to commercialize, all of our product candidates. In addition, our operating plans may change as a result of many factors that may currently be unknown to us, and we may need to seek additional funds sooner than planned. Our future funding requirements will depend on many factors, including but not limited to:

- the scope, rate of progress, results, and cost of our clinical studies, nonclinical testing, and other related activities;
- the cost of manufacturing clinical and commercial supplies of our products and product candidates;
- the cost of creating additional infrastructure, including facilities and systems, such as our GMP gene therapy manufacturing plant;
- 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 can 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 by us, whether equity or debt, 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, complex, 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, complex, 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. 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 can 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, including as a result of hyperinflation;
- 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 timing, type or clarity of data from clinical trials, 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 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.

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 and time-consuming, especially since the rare diseases we are studying are commonly underdiagnosed. 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 (such as drug-related side effects), the timeline for and our success in recruiting patients, conducting studies, and obtaining regulatory approval of potential products may be delayed or impaired, 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. 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 U.S. or Europe. The regulatory framework and oversight over development of gene therapy products has evolved and may continue to evolve in the future. Within the FDA, the Center for Biologics Evaluation and Research (CBER) regulates gene therapy products. Within the CBER, the review of gene therapy and related products is consolidated in the Office of Cellular, Tissue and Gene Therapies, and the FDA has established the Cellular, Tissue and Gene Therapies Advisory Committee to advise CBER on its reviews. The CBER works closely with the National Institutes of Health (NIH). The FDA and the NIH have published guidance with respect to the development and submission of gene therapy protocols. For example, in January 2020, the FDA issued final guidance to set forth the framework for the development, review and approval of gene therapies. The final guidance pertains to the development of gene therapies for the treatment of specific disease categories, including rare diseases, and to manufacturing and long-term follow up issues relevant to gene therapy, among other topics. At the same time the FDA issued new draft guidance describing the FDA's approach for determining whether two gene therapy products were the same or different for the purpose of assessing orphan drug exclusivity; the draft guidance was finalized by the FDA in September 2021.

To obtain regulatory approval in the U.S. 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;
- the FDA may be delayed in responding to our applications or submissions due to competing priorities or limited resources, including as a result of the COVID-19 pandemic;
- 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 do 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.

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 and may occur in future studies. 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.

Additionally, notwithstanding our prior or future regulatory approvals for our product candidates, 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.

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.

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.

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 in the future remain 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 U.S. 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, material, testing method or standard is relied upon for commercial production. Switching manufacturers, materials, test methods or standards may involve substantial costs and may 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.

Product liability lawsuits against us could cause us to incur substantial liabilities and could limit commercialization of our approved products or product candidates.

We face an inherent risk of product liability exposure related to the testing of our approved products and product candidates in human clinical trials, as well as in connection with commercialization of our current and future products. If we cannot successfully defend ourselves against claims that any of our approved products or product candidates caused injuries, we could incur substantial liabilities. There can be no assurance that our product liability insurance, which provides coverage in the amount of $15.0 million per incident and $15.0 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.

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. We can offer no assurances that any current or 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. We rely on 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 U.S. as medical devices and require regulatory clearance or approval prior to commercialization. In the U.S., 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 U.S., 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. 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, 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 U.S., 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 U.S. 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 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 or mitigate a possible disruption of the manufacture of the materials necessary to produce our products and 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 U.S. 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, actual or threatened public health emergencies, and numerous other factors.

Any adverse developments affecting manufacturing operations for our products and product candidates may result in shipment delays, inventory shortages, lot failures, withdrawals or recalls, or other interruptions in the supply of our products and product candidates. Due to their stage of development, small volume requirements, and infrequency of batch production runs, we carry limited amounts of safety stock for our products and product candidates. We have, and may in the future, be required 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 or unwilling 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. For example, 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 currently manufactured by Rentschler under a commercial supply and services agreement, accompanying purchase orders, and other agreements. We experienced disruptions related to the fill and finish activities for the drug product for Mepsevii during the fourth quarter of 2019 and as a result, we identified an alternative supplier to conduct such activities. We are currently in the process of qualifying and transferring the activities to such alternative supplier, which may take a significant amount of time and expense. If we fail to qualify our alternative supplier, we could experience delays or disruptions in the supply of Mepsevii, which would negatively impact sales of the product. Pharmaceutical-grade drug substance for Dojolvi is manufactured by IOI Oleo pursuant to a supply agreement, and the drug product for Dojolvi is prepared by Haupt Pharma AG, pursuant to a master services agreement. Single source suppliers are also used for our gene therapy programs. We cannot provide assurances that identifying alternate sources, if available at all, 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. Additionally, we may not be able to enter into supply arrangements with an alternative supplier on commercially reasonable terms or at all. The terms of any new agreement 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.

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 products or 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. 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 U.S. 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 to 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, Latin America and the Asia-Pacific region. 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 increase the number and range of our commercialized products, we may experience additional complexities to our sales process and strategy and have difficulties in allocating sufficient resources to sales and marketing of certain products. Further, 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 U.S. 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 U.S. 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 U.S. After the transition date, KKC will have the right to promote the product, subject to a limited promotion right retained by us. The transition of responsibilities to KKC will require significant effort and may result in the diversion of management's attention to transition activities. We may also encounter unexpected difficulties or incur unexpected costs in connection with such transition activities. Further, 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 and we may fail to retain members of our field teams due to such uncertainties. 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 continue to 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 U.S., 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 U.S., 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 U.S., the reimbursement for our products may be reduced compared with the U.S. and may be insufficient to generate commercially reasonable revenue and profits.

Moreover, increasing efforts by governmental and third-party payors in the U.S. 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 current 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.

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 U.S. 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 U.S. 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 U.S. 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. Third parties may challenge the validity, enforceability, or scope of any issued patents 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.

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 U.S., 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 U.S. 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 U.S. 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 U.S. Publications of discoveries in the scientific literature often lag behind the actual discoveries, and patent applications in the U.S. 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, contractors and other third parties that we rely on in connection with the development, manufacture and commercialization of our products may not be sufficient to protect our proprietary technology and processes, which increase the risk that such trade secrets may become known by our competitors or may be inadvertently incorporated into the technology of others.

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 relevant 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 U.S. 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 are relevant to our products or product candidates.

We are aware of certain U.S. and foreign patents owned by third parties that a court might construe to be valid and 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 valid and relevant to setrusumab. We are additionally aware of certain U.S. and foreign patents owned by third parties that relate to nucleic acid-containing lipid particles or to certain mRNA modifications, and which a court might construe to be valid and relevant to UX053. 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.

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 the corresponding program.

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 U.S., 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. The law is complex and is still being interpreted and implemented by the FDA. As a result, its ultimate impact, implementation and meaning are subject to uncertainty. 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, and the AAV9 vector used in UX701. These patents and patent applications are licensed or sublicensed by REGENX 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 REGENX, 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, REGENX and the University of Pennsylvania may have interests which differ from ours in determining whether to enforce and the manner in which to enforce such patents.

We also have in-licensed patents and patent applications owned by Arcturus relating to the cationic lipid used in UX053. 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 Arcturus, we do not have the first right to enforce these patents, and our enforcement rights are subject to certain limitations that may adversely impact our ability to use these licensed patents to exclude others from commercializing competitive products. Moreover, Arcturus may have interests which differ from ours in determining whether to enforce and the manner in which to enforce such patents.

If KKC, the University of Pennsylvania, REGENX, Arcturus 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 U.S., 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 U.S. 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 U.S. 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 U.S. can be less extensive than those in the U.S. 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 U.S. 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 U.S., or from selling or importing products made using our inventions in and into the U.S. 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 U.S. 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, have and could again 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 March 2020, the World Health Organization declared the novel coronavirus strain 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, the pandemic has impacted enrollment of patients in certain of our clinical trials for our product candidates as patients have been more reluctant to conduct in-person visits at the sites due to concerns over COVID-19. 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 and may continue to do so in the future. 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 U.S. or internationally, due to the economic impact of the pandemic, such as changes to state coverage rules under Medicaid programs in the U.S., 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.

We have experienced delays in delivery of ancillary clinical trial materials due to government-imposed mandates and other restrictions from COVID-19 and may in the future experience delays or interruptions in supply of drug product or raw materials, or incur increased costs or expenses. For instance, the Presidential Executive Order invoking the Defense Production Act of 1950 has caused certain of our third party manufacturers or suppliers to prioritize and allocate more resources and capacity to supply materials to other companies engaged in the study or manufacture of 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 continue to seek and secure 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. We have also experienced interruptions or delays in sourcing certain equipment, materials and resources, and increased costs for certain raw materials, related to construction of our gene therapy manufacturing facility as a result of COVID-19, which could delay the anticipated timing for completion of the plant or result in significant additional expenses.

In an effort to protect the health of our employees, their families and our communities, 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. As vaccines against COVID-19 become more widely available, we have eased restrictions to our facilities and allowed our employees the option to return to work on-site. The safety protocols we implement as our employees return to work may not prevent employees from contracting COVID-19. 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, as our offices reopen, we plan to offer a significant percentage of our employees flexibility in the amount of time they work in the office. Our new office model and any adjustments to our remote working arrangements, including our vaccination policies or other workforce actions taken in response to the COVID-19 pandemic, may not meet the expectations of our workforce, which could adversely impact our ability to attract and retain certain employees.

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. 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, such as the delta or omicron variants or other factors, the timing and efficacy of treatments and vaccines against virus mutations, the public acceptance of vaccines, the duration of, or implementation of additional, restrictions to contain the outbreak and the effectiveness of other actions taken in the U.S. and other countries to contain and address the pandemic. This pandemic also amplifies many of the other risks described throughout the “Risk Factors” section of this Annual Report on Form 10-K.

We have no experience as a company developing or operating 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, which is currently expected 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. We are dependent on key partners for delivery of power, electricity and other utilities to our manufacturing facility and we cannot assure that such services will be provided

at the facility without interruptions, delays or unexpected costs. Further, as described in the risk factor above entitled, "Actual or threatened public health epidemics or outbreaks, including the ongoing COVID-19 pandemic, have and could again materially and adversely impact our business and operating results," the COVID-19 pandemic has adversely impacted delivery of raw materials, and increased costs for certain materials, for construction of our facility. 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, we cannot assure that such additional capacity will be required or that our investment will be recouped. Further, our manufacturing capabilities could be affected by cost-overruns, unexpected delays, equipment failures, lack of capacity, labor shortages, natural disasters, power failures, program failures, actual or threatened public health emergencies, and numerous other factors that could prevent us from realizing the intended benefits of our manufacturing strategy.

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 U.S., 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 U.S. and for various subtypes of LC-FAOD in Europe, as well as for Crysvita, Mepsevii, DTX301, DTX401 and UX701 in the U.S. 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 Consolidated 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 Consolidated Statement of Operations. We have not recorded any impairments related to our intangible assets through the end of December 31, 2021.

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 U.S., and in other circumstances these requirements may be more stringent in the U.S.

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, one of our programs has been the subject of review by applicable governmental authorities of compliance with various fraud and abuse laws; we cannot assure that such program, or our other operations or programs, will not be challenged from time to time by such authorities for violation of such laws. Further, 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 U.S.

Our business strategy includes international expansion. We currently conduct clinical studies and regulatory activities and we also commercialize products outside of the U.S. 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;
- supply chain disruptions, changes to regulatory processes and other adverse effects resulting from the United Kingdom's withdrawal from the EU, commonly referred to as Brexit;
- 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 the expansion of our 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 expanding our company-wide ERP system to upgrade certain existing business, operational, and financial processes related to our gene therapy manufacturing facility, which we currently expect to be completed in 2023. The ERP expansion is a complex and time-consuming project. Our results of operations could be adversely affected if we experience time delays or cost overruns during the ERP expansion 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 expanded 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.

Cybersecurity incidents, including phishing attacks and attempts to misappropriate or compromise confidential or proprietary information or sabotage enterprise IT systems are becoming increasingly frequent and more sophisticated. The information and data processed and stored in our technology systems, and those of our strategic partners, CROs, contract manufacturers, suppliers, distributors or other third parties for which we depend to operate our business, may be vulnerable to loss, damage, denial-of-service, unauthorized access or misappropriation. Data security breaches can occur as a result of malware, hacking, business email compromise, ransomware attacks, phishing or other cyberattacks directed by third parties. We, and certain of the third parties for which we depend on to operate our business, have experienced cybersecurity incidents, including third party unauthorized access to and misappropriation of financial information. Further, 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, pose a risk that sensitive data may be exposed to unauthorized persons or to the public. A system failure or security breach that interrupts our operations or the operations at one of our third-party vendors or partners could result in intellectual property and other proprietary or confidential information being lost or stolen or a material disruption of our drug development programs and commercial operations. 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 identifiable information 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. Further, we could incur significant costs to investigate and mitigate such cybersecurity incidents. A security breach that results in the unauthorized access, use or disclosure of personal identifiable information also requires us to notify individuals, governmental authorities, credit reporting agencies, or other parties, as applicable, pursuant to privacy and security laws and regulations or other obligations. Such a security breach could harm our reputation, erode confidence in our information security measures, and lead to regulatory scrutiny and result in penalties, fines, indemnification claims, litigation and potential civil or criminal liability.

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. We have also experienced power outages as a result of wildfires in the San Francisco Bay Area which are likely to continue to occur in the future. 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 2,400,000 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 have subsequently sold an aggregate of 2,500,000 shares. 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. 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 investigations, regulatory proceedings or 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, 2021, 4,040,610 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, 2021, 3,925,798 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 the Employment Inducement Plan (the Inducement Plan) with a maximum of 500,000 shares available for grant under the plan. At December 31, 2021, 457,463 shares were available for issuance under the Inducement Plan. 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 U.S. 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. In 2020, we completed our purchase of land located in Bedford, Massachusetts and we are currently in the process of constructing 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.

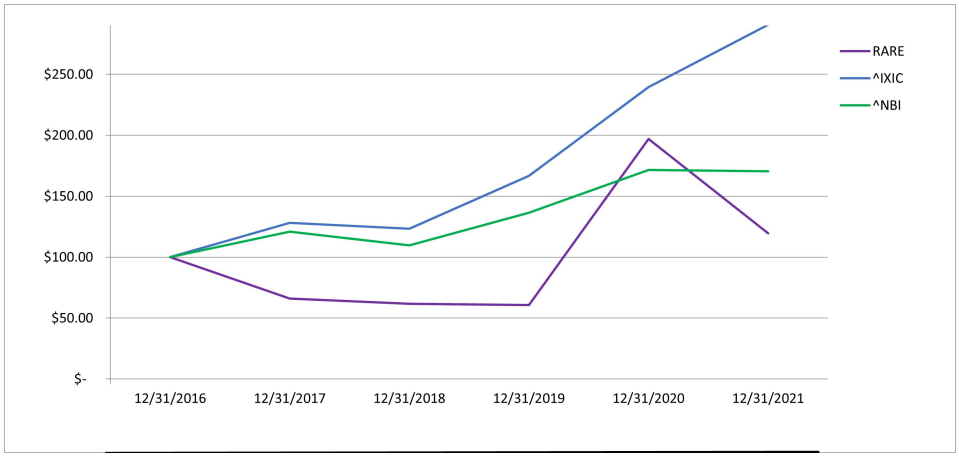
PART II

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 10, 2022, we had 4 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 (ii) the Nasdaq Biotechnology Index for the period from December 31, 2016 through December 31, 2021. The figures represented below assume an investment of $100 in our common stock at the closing price of $70.31 on December 31, 2016 and in the Nasdaq Composite Index (IXIC) and the Nasdaq Biotechnology Index (NBI) on December 31, 2016 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, 2016	December 31, 2017	December 31, 2018	December 31, 2019	December 31, 2020	December 31, 2021
Ultragenyx Pharmaceutical Inc.	RARE	$ 100.00	$ 65.97	$ 61.84	$ 60.75	$ 196.89	$ 119.60
NASDAQ Composite Index	^IXIC	$ 100.00	$ 128.24	$ 123.26	$ 166.68	$ 239.42	$ 290.63
NASDAQ Biotechnology Index	^NBI	$ 100.00	$ 121.06	$ 109.77	$ 136.56	$ 171.64	$ 170.55

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. ***Reserved***

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 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, 2021, including year-over-year comparisons versus the year ended December 31, 2020. Our Annual Report on Form 10-K for the year ended December 31, 2020 includes a discussion and analysis of our financial condition and results of operations for the year ended December 31, 2019 in Part II, Item 7. "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 the diversion of clinic and hospital staff and resources to COVID-19 patients. The continuing outbreak has caused delays in delivery of ancillary clinical trial materials as certain of our third-party manufacturers or suppliers prioritized and allocated more resources and capacity to supply drug product or raw materials to other companies engaged in the study or manufacture of 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.

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 2022 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 four commercially approved products, consisting of 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, Dojolvi® (triheptanoin) for the treatment of long-chain fatty acid oxidation disorders, or LC-FAOD, and Evkeeza® (evinacumab) for the treatment of homozygous familial hypercholesterolemia (HoFH) and we anticipate having six product candidates in the clinical pipeline in 2022. 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, revenues from our commercial products, the sale of certain future royalties, and strategic collaboration arrangements.

We have incurred net losses in each year since inception. Our net losses were $454.0 million and $186.6 for the years ended December 31, 2021 and 2020, respectively. Net loss for the years ended December 31, 2021 and 2020 included a $42.1 million loss and a $170.4 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, 2021, our total revenues increased to $351.4 million, compared to $271.0 million for the same period in 2020. The increase was driven by higher 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, 2021, we had $999.1 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

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. When development of the project 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.

We sold the right to receive certain royalty payments from net sales of Crysvita to RPI Finance Trust (RPI), an affiliate of Royalty Pharma, as further described in “Liability Related to the Sale of Future Royalties” below. 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.

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 a material effect on earnings in the period of the adjustment.

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. As of December 31, 2021, we do not hold a material amount of previously expensed inventory for our approved products.

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. 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. Our effective annual interest rate was approximately 9.6% as of December 31, 2021.

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 equity awards 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, except for certain PSUs with a market vesting condition, for which fair value is estimated using a Monte Carlo simulation model. 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, including both performance conditions and market conditions. 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, 2021, 2020, and 2019 stock-based compensation expense was $105.0 million, $85.7 million, and $82.0 million, respectively. As of December 31, 2021, we had $200.0 million of total unrecognized stock-based compensation costs, net of estimated forfeitures, which we expect to recognize over a weighted-average period of 2.33 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, 2021, our total gross deferred tax assets were $709.6 million. 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, 2021 and 2020

Revenues (dollars in thousands)

	Year Ended December 31,		Dollar	Percent
	2021	2020	Change	Change
Collaboration and license revenue:				
Crysvita collaboration revenue in profit-share territory	$ 171,198	$ 128,597	$ 42,601	33%
Crysvita royalty revenue in European territory	244	1,498	(1,254)	(84%)
Daiichi Sankyo	84,996	89,220	(4,224)	(5%)
Total collaboration and license revenue	256,438	219,315	37,123	17%
Product sales:				
Crysvita	21,422	10,350	11,072	107%
Mepsevii	16,035	15,342	693	5%
Dojolvi	39,560	13,028	26,532	204%
Total product sales	77,017	38,720	38,297	99%
Crysvita non-cash collaboration royalty revenue	17,951	12,995	4,956	38%
Total revenues	$ 351,406	$ 271,030	$ 80,376	30%

For the year ended December 31, 2021, our share of Crysvita collaboration revenue in the profit-share territory increased by $42.6 million, as compared to the same period in 2020. The increase primarily reflects the continuing increase in demand for Crysvita due to an increase in the number of patients on therapy.

Beginning in 2020, we recorded the Crysvita royalty revenue from sales in the European territory as non-cash royalty revenues. During the years ended December 31, 2021 and 2020, there were changes in the estimate of revenue reserves related to sales made prior to January 1, 2020, and as a result, we recorded $0.2 million and $1.5 million, respectively, 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 PCL and HEK293 transient transfection manufacturing technology platforms for AAV-based gene therapy products. Pursuant to the agreement, we are also continuing to 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, 2021, the collaboration and license revenue from this arrangement decreased by $4.2 million as compared to the same period in 2020, due to the relative progress toward complete satisfaction of the individual performance obligation using an input measure as we near the completion of the technology transfer. The remaining revenue allocated to the intellectual property and the technology transfer services is expected to be recognized in the first quarter of 2022.

The increase in product sales of $38.3 million for the year ended December 31, 2021 compared to the same period in 2020 was primarily due to the commercial launch of Dojolvi in the U.S. in the third quarter of 2020, the continued increase in demand for our approved products, and an increase in sales of our products under our named patient program in certain countries.

The increase in Crysvita non-cash collaboration royalty revenue of $5.0 million for the year ended December 31, 2021 compared to the same period in 2020 primarily reflects the launch progress by our collaboration partner in European countries and an increase in the number of patients on therapy.

Cost of Sales (dollars in thousands)

	Year Ended December 31,		Dollar	Percent
	2021	2020	Change	Change
Cost of sales	$ 16,008	$ 6,129	$ 9,879	161%

Cost of sales related to our approved products increased by $9.9 million for the year ended December 31, 2021, compared to the same period in 2020. The increase in cost of sales for the year ended December 31, 2021 compared to the same period in 2020 was due to an increase in demand for our approved products, including Dojolvi, which launched in the third quarter of 2020 and a credit for the manufacturing of future inventory batches of $4.6 million due to certain inventory batches that did not meet specified quality standards which was recorded during the year ended December 31, 2020. The increase in cost of sales was partially offset by lower reserves of $1.8 million for excess inventory write-downs recorded during the year ended December 31, 2021, compared to $3.0 million recorded during the year ended December 31, 2020.

Research and Development Expenses (dollars in thousands)

	Year Ended December 31,		Dollar Change	Percent Change
	2021	2020		
Commercial programs	$ 52,015	$ 44,834	$ 7,181	16%
Clinical programs:				
Gene therapy programs	108,217	78,330	29,887	38%
Nucleic acid and other biologic programs	50,681	10,192	40,489	397%
Small molecule programs	—	7,440	(7,440)	-100%
Translational research	62,207	78,212	(16,005)	-20%
Upfront license and milestone fees	50,000	33,200	16,800	51%
Infrastructure	59,294	50,507	8,787	17%
Stock-based compensation	59,097	47,949	11,148	23%
Other research and development	55,642	61,420	(5,778)	-9%
Total research and development expenses	$ 497,153	$ 412,084	$ 85,069	21%

Research and development expenses increased $85.1 million for the year ended December 31, 2021 compared to the same period in 2020. The increase in research and development expenses was primarily due to:

- for commercial programs, an increase of $7.2 million, primarily related to the continued launch of Dojolvi and the TIO indication for Crysvita following their respective FDA approvals in June 2020;
- for clinical gene therapy programs, an increase of $29.9 million, primarily related to the addition of clinical study start-up expenses for UX701 following its IND approval in January 2021 and increases in expenses related to DTX401 and DTX301 Phase 3 trial preparation;
- for clinical nucleic acid and other biologic programs, an increase of $40.5 million, primarily related to the addition of expenses related to UX053 following its IND approval in March 2021 and UX143 due to entry into a License and Collaboration Agreement with Mereo BioPharma 3 Limited, or Mereo, to collaborate on the development of UX143 effective January 2021; partially offset by the classification of expenses for the TIO indication for Crysvita to commercial programs subsequent to its approval in June 2020;
- for clinical small molecule programs, a decrease of $7.4 million, primarily related to the classification of expenses for Dojolvi to commercial programs subsequent to its approval in June 2020;
- for translational research, a decrease of $16.0 million, primarily related to the classification of expenses for UX053 to nucleic acid and other biologic programs and UX701 to gene therapy programs as a result of their IND approvals in March 2021 and January 2021, respectively, net of increased spending on new translational research projects;
- for upfront license and milestone fees, an increase of $16.8 million, primarily due to the $50.0 million upfront payment to Mereo for the year ended December 31, 2021, as compared to payments for the year ended December 31, 2020 related to the $25.0 million option extension to GeneTx and the $8.2 million in license payments to REGENXBIO, Inc. pursuant to a license agreement;
- for infrastructure, an increase of $8.8 million, primarily related to increased expenses for support of our clinical and research program pipeline, expansion of laboratory space, implementation of COVID-related policies and safety protocols, depreciation of laboratory-related leasehold improvements and equipment, and IT-related expenses;
- for stock-based compensation, an increase of $11.1 million, primarily related to an increase in employee headcount as well as the higher valuation of stock-based awards granted to employees; and
- for other research and development expenses, a decrease of $5.8 million, primarily related to increased research and development allocations to the programs represented in the commercial, clinical, and translational science programs

We expect our annual research and development expenses to continue to increase in the future as we advance our product candidates 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 Change	Percent Change
	2021	2020		
Selling, general and administrative	$ 219,982	$ 182,933	$ 37,049	20%

Selling, general and administrative expenses increased $37.0 million for the year ended December 31, 2021 compared to the same period in 2020. 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 to support our commercial activities, commercialization costs, and professional services.

We expect selling, general and administrative expenses to continue to increase in the future to support our organizational growth related to our approved products and multiple clinical-stage product candidates.

Interest Income (dollars in thousands)

	Year Ended December 31,		Dollar	Percent
	2021	2020	Change	Change
Interest income	$ 1,928	$ 7,038	$ (5,110)	(73%)

Interest income decreased $5.1 million for the year ended December 31, 2021 compared to the same period in 2020, primarily due to lower portfolio yields as a result of a decrease in interest rates, partially offset by higher average balances of marketable debt securities.

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

	Year Ended December 31,		Dollar	Percent
	2021	2020	Change	Change
Change in fair value of equity investments	$ (42,063)	$ 170,403	$ (212,466)	(125%)

For the year ended December 31, 2021, we recorded a net decrease in the fair value of our equity investments of $42.1 million. The fair value of our investment in Solid common stock decreased by $45.6 million for the period. This was offset by an increase in the fair value of our investment in Arcturus common stock of $2.9 million for the period, which included a realized gain on the sale of a portion of Arcturus common stock for net proceeds of $79.8 million, as well as an increase of $0.6 million related to the conversion of the convertible note in a private pharmaceutical company to its preferred shares, resulting in a net decrease in the fair value of equity investments of $42.1 million.

For the year ended December 31, 2020, we recorded a net increase in the fair value of our equity investments of $170.4 million. The fair value of our investment in Arcturus common stock increased by $137.9 million for the period, which included a realized gain on the sale of a portion of Arcturus common stock for net proceeds of $79.8 million. The fair value of our investment in Solid common stock increased by $32.5 million during the same period.

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	Percent
	2021	2020	Change	Change
Non-cash interest expense on liability related to the sale of future royalties	$ 29,422	$ 33,291	$ (3,869)	(12%)

The decrease in the non-cash interest expense on liability related to the sale of future royalties of $3.9 million for the year ended December 31, 2021, compared to the same period in 2020 was due to the capitalization of interest related to the construction-in-progress for the gene therapy manufacturing plant, slightly offset by the increase in the liability related to the sale of future royalties for net sales of Crysvita in the European territory. 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	Percent
	2021	2020	Change	Change
Other income (expense)	$ (1,687)	$ 607	$ (2,294)	(378%)

Other expense increased $2.3 million for the year ended December 31, 2021, compared to the same period in 2020. The fluctuations were primarily due to fluctuations in foreign exchange rates.

Provision for income taxes

	Year Ended December 31,		Dollar	Percent
	2021	2020	Change	Change
Provision for income taxes	$ (1,044)	$ (1,207)	$ 163	(14%)

The provision for incomes taxes decreased by a nominal amount for the year ended December 31, 2021, compared to the same period in 2020.

Liquidity and Capital Resources

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

As of December 31, 2021, we had $999.1 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, commercial paper, U.S government securities, asset-backed securities, debt securities in government-sponsored entities, 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 May 2021, we entered into an Open Market Sale Agreement with Jefferies LLC, (Jefferies), pursuant to which we may offer and sell shares of our common stock having an aggregate offering proceeds up to $350.0 million, from time to time, in at-the-market (ATM) offerings through Jefferies. For the year ended December 31, 2021, the Company sold 1,050,372 shares under the arrangement, resulting in net proceeds of approximately $78.9 million. As of December 31, 2021, $269.5 million remained available under our ATM facility.

For the year ended December 31, 2021, we sold 1,700,000 shares of Arcturus common stock and received net proceeds of $79.8 million.

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

	Year Ended December 31,		
	2021	2020	2019
Cash used in operating activities	$ (338,695)	$ (132,220)	$ (345,383)
Cash used in investing activities	(195,372)	(179,121)	(13,039)
Cash provided by financing activities	118,552	600,272	679,306
Effect of exchange rate changes on cash	(1,194)	1,119	(165)
Net (decrease) increase in cash, cash equivalents, and restricted cash	$ (416,709)	$ 290,050	$ 320,719

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, 2021 was $338.7 million and primarily reflected a net loss of $454.0 million and $18.0 million for non-cash collaboration royalty revenues related to the sale of future royalties to RPI, offset by non-cash charges of $105.0 million for stock-based compensation, $13.2 million for depreciation and amortization, $6.6 million for the amortization of the premium paid on marketable debt securities, $42.1 million primarily for the net change in fair value of equity investments from Arcturus and Solid, and $29.4 million for non-cash interest incurred on the liability related to the sale of future royalties to RPI, net of capitalized interest. Cash used in operating activities also reflected a $5.4 million decrease due to an increase in accounts receivable primarily related to higher revenues, a $3.1 million decrease due to an increase in inventory for Dojolvi, a $29.5 million decrease due to an increase in prepaid expenses and other assets primarily due to an increase in prepaid manufacturing expenses, prepaid clinical expenses, and prepaid fixed assets as well as an increase in receivables from our collaboration partner, and a decrease of $57.5 million in contract liabilities, net, related to the revenue recognized from the license agreements with Daiichi Sankyo. These decreases were offset by a $32.3 million increase in accounts payable, accrued liabilities, and other liabilities primarily due to an increase in accruals related to manufacturing and clinical 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 net 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 and amortization, $0.8 million for the amortization of the premium paid on marketable debt securities, 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 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 Investing Activities

Cash used in investing activities for the year ended December 31, 2021 was $195.4 million and was primarily related to purchases of property, plant, and equipment of $73.1 million and purchases of marketable debt securities of $1,012.2 million, offset by the sale of marketable debt securities of $92.9 million, proceeds from the sale of Arcturus common stock of $79.8 million, and proceeds from maturities of marketable debt securities of $718.1 million.

Cash used in investing activities for the year ended December 31, 2020 was $179.1 million and was primarily related to purchases of property, plant, and equipment of $43.9 million, purchases of marketable debt securities of $813.2 million, purchases of equity investments of $37.1 million, including $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, including $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 Flows Provided by Financing Activities

Cash provided by financing activities for the year ended December 31, 2021 was $118.6 million and was comprised of $78.9 million in net proceeds from the issuance of common stock from our ATM offering and $40.1 million in net proceeds from the issuance of common stock upon the exercise of stock options, net of taxes withheld from the vesting of restricted stock units.

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 sale of common stock in our underwritten public offering, $55.3 million in net proceeds from the sale of common stock in connection with the license agreement with Daiichi Sankyo in March 2020, $20.4 million in net proceeds from the sale 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.

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 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 construction 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, revenue from our commercial products, 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

Material contractual obligations arising in the normal course of business primarily consist of operating and finance leases, manufacturing and service contract obligations and land and building construction obligations. See Note 8 to the Consolidated Financial Statements for amounts outstanding for operating and finance leases on December 31, 2021.

Manufacturing and service contract obligations primarily relate to manufacturing of inventory for our approved products, the majority of which are due in the next 12 months. See Note 14 to the Consolidated Financial Statements for these contractual obligations.

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 amount and timing of such obligations are unknown or uncertain. These potential obligations are further described in Note 7 to the 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. During the year ended December 31, 2021, we sold 1,700,000 shares of Arcturus common stock for net proceeds of $79.8 million. The carrying value of our equity investments held in Arcturus and Solid were $18.5 million and $13.7 million, respectively, as of December 31, 2021. A hypothetical 10 percent decrease in the market price for our equity investments in Arcturus and Solid as of December 31, 2021 would decrease the fair value by $3.2 million. 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, 2021, we had cash, cash equivalents, and marketable debt securities totaling $999.1 million, which included 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. A hypothetical 100 basis point change in interest rates would not have had a material impact on the fair market value of our cash equivalents and marketable debt securities as of December 31, 2021. To date, we have not experienced a loss of principal on any of our investments and as of December 31, 2021, 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 payments related to license agreements. For the year ended December 31, 2021, a majority of our revenue, expenses, 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

Management carried out an evaluation, under the supervision and with the participation of 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(e) and 15d-15(e) under the Securities Exchange Act of 1934, or 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, 2021. 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, 2021 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, 2021, 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, 2021, 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, 2021, 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, 2021 and 2020, 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, 2021, and our report dated February 15, 2022 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

Redwood City, California
February 15, 2022

Item 9B. Other Information

None.

Item 9C. Disclosure Regarding Foreign Jurisdictions that Prevent Inspections

Not applicable

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 2022 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 "2022 Proxy Statement"), including under the headings "Proposal No. 1—Election of Class III Directors," "Information About Our Executive Officers," "Corporate Governance—Global Code of Conduct," "Proposal No. 1—Election of Class III 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 2022 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 2022 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 2022 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 2022 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	Form of Common Stock Certificate	S-1	11/8/2013	4.2	
4.2	Form of Indenture	10-Q	5/5/2021	4.2	
4.3	Description of Common Stock	10-K	2/14/2020	4.3	
10.1	Open Market Sales Agreement, dated May 7, 2021, by and between Ultragenyx Pharmaceutical Inc. and Jefferies LLC	10-Q	8/3/2021	10.6	
10.2†	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	
10.3	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	
10.4	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	
10.5†	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	
10.6†	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	
10.7†	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	
10.8*	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	

10.9*	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	
10.10*	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	
10.11*	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	
10.12*	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	
10.13*	Amendment No. 11 to Collaboration and License Agreement, effective as of December 17, 2021 between Ultragenyx Pharmaceutical Inc. and Kyowa Kirin Co., Ltd.				X
10.14*	License Agreement, dated as of September 20, 2012, between Ultragenyx Pharmaceutical Inc. and Baylor Research Institute	10-K	2/12/2021	10.12	
10.15*	Amendment to the License Agreement, dated as of March 22, 2013, between Ultragenyx Pharmaceutical Inc. and Baylor Research Institute	10-K	2/12/2021	10.13	
10.16†	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	
10.17†	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	
10.18†	Option and License Agreement, dated March 10, 2015, by and between Dimension Therapeutics, Inc. and REGENXBIO Inc.	10-K	2/21/2018	10.14	
10.19*	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	
10.20*	Second Amendment to Option and License Agreement, dated December 17, 2021, by and between REGENXBIO, Inc. and Ultragenyx Pharmaceutical Inc.				X
10.21*	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	
10.22†	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	
10.23†	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	

10.24†	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
10.25†	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
10.26	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
10.27*	Master Services Agreement, dated April 8, 2019, between Ultragenyx Pharmaceutical Inc. and Aenova Haupt Pharma Wolfratshausen GmbH	10-K	2/12/2021	10.24
10.28*	Royalty Purchase Agreement, dated as of December 17, 2019, between Ultragenyx Pharmaceutical Inc. and RPI Finance Trust	10-K	2/14/2020	10.25
10.29#	2011 Equity Incentive Plan (including forms of Stock Option Grant Notice and Stock Option Agreement thereunder)	S-1	11/8/2013	10.11
10.30#	Amendment to the 2011 Equity Incentive Plan	S-1	11/8/2013	10.12
10.31#	2014 Incentive Plan (as amended)	10-K	2/17/2017	10.20
10.32#	Form of Incentive Stock Option Agreement	S-1/A	1/17/2014	10.14
10.33#	Form of Non Statutory Stock Option Agreement (Employees)	S-1/A	1/17/2014	10.15
10.34#	Form of Non Statutory Stock Option Agreement (Employees)(ex-U.S.)	10-Q	5/10/2016	10.3
10.35#	Form of Restricted Stock Unit Agreement (Employees)	10-Q	5/10/2016	10.1
10.36#	Form of Restricted Stock Unit Agreement (Employees)(ex-U.S.)	10-Q	5/10/2016	10.2
10.37#	Form of Non-Statutory Stock Option Agreement (Directors)	S-1/A	1/17/2014	10.16
10.38#	Form of Restricted Stock Unit Agreement (Directors)	S-1/A	1/17/2014	10.18
10.39#	Form of Non-Statutory Stock Option Agreement (Annual Grant for Directors)	10-Q	8/3/2021	10.2
10.40#	Form of Restricted Stock Unit Agreement (Annual Grant for Directors)	10-Q	8/3/2021	10.3
10.41#	Form of Non-Statutory Stock Option Agreement (Grant for New Directors)	10-Q	8/3/2021	10.4
10.42#	Form of Restricted Stock Unit Agreement (Grant for New Directors)	10-Q	8/3/2021	10.5
10.43#	Form of Performance Stock Unit Agreement (2020)	10-Q	5/7/2020	10.3
10.44#	Form of Performance Stock Unit Agreement (2021)	10-Q	5/5/2021	10.1
10.45#	2014 Employee Stock Purchase Plan (as amended)	10-K	2/17/2017	10.28
10.46#	Corporate Bonus Plan	S-1/A	1/17/2014	10.27
10.47#	Employment Inducement Plan	10-K	2/12/2021	10.43
10.48#	Form of Non Statutory Stock Option Agreement (Inducement Plan)	10-K	2/12/2021	10.44
10.49#	Form of Non Statutory Stock Option Agreement (Inducement Plan) (ex-US)	10-K	2/12/2021	10.45

10.50#	Form of Restricted Stock Unit Agreement (Inducement Plan)	10-K	2/12/2021	10.46
10.51#	Form of Restricted Stock Unit Agreement (Inducement Plan)(ex-US)	10-K	2/12/2021	10.47
10.52#	Ultragenyx Pharmaceutical Inc. Deferred Compensation Plan	10-Q	8/3/2021	10.1
10.53#	Amendment No. 1 to the Ultragenyx Pharmaceutical Inc. Deferred Compensation Plan	10-Q	11/3/2021	10.1
10.54#	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
10.55#	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
10.56#	Offer Letter, dated as of October 31, 2011, between Ultragenyx Pharmaceutical Inc. and Thomas Kassberg	S-1	11/8/2013	10.19
10.57#	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
10.58#	Offer Letter, dated as of August 28, 2020 between Ultragenyx Pharmaceutical Inc. and Mardi C. Dier.	8-K	9/2/2020	10.1
10.59#	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
10.60#	Offer Letter, dated as of April 26, 2016, between Ultragenyx Pharmaceutical Inc. and Karah Parschauer	10-Q	8/9/2016	10.3
10.61#	Offer Letter, dated as of February 20, 2015, between Ultragenyx Pharmaceutical Inc. and Dennis Huang	10-K	2/17/2017	10.36
10.62#	Offer Letter, dated as of June 11, 2015, between Ultragenyx Pharmaceutical Inc. and John R. Pinion II	10-K	2/17/2017	10.37
10.63#	Offer Letter, dated as of January 15, 2018, between Ultragenyx Pharmaceutical Inc. and Camille Bedrosian, M.D.	10-K	2/21/2018	10.46
10.64#	Offer Letter, dated May 16, 2017, by and between Ultragenyx Pharmaceutical Inc. and Erik Harris	10-Q	8/2/2019	10.4
10.65#	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
10.66#	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
10.67#	Form of Indemnification Agreement	10-K	3/24/2014	10.23
10.68	Standard Lease, dated as of July 5, 2011, between Ultragenyx Pharmaceutical Inc. and Condiotti Enterprises, Inc.	S-1	11/8/2013	10.22
10.69	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
10.70	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

10.71	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
10.72	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
10.73	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
10.74	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
10.75	Lease Agreement between Marina Boulevard Property, LLC and Ultragenyx Pharmaceutical Inc., dated as of December 8, 2015	10-K	2/26/2016	10.43
10.76	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
10.77	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
10.78	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
10.79	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
10.80	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
10.81	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
10.82	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
10.83	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
10.84	Lease Agreement, dated December 15, 2019, between Ultragenyx Pharmaceutical Inc. and ARE-San Francisco No. 17, LLC.	10-K	2/12/2021	10.81
10.85	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.	10-K	2/12/2021	10.82
10.86	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.	10-K	2/12/2021	10.83
10.87	Office Lease, dated April 19, 2019, between Ultragenyx Pharmaceutical Inc. and Woburn MCB II, LLC	10-K	2/14/2020	10.70

10.88	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
(Principal Executive Officer)

Date: February 15, 2022

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 15, 2022
/s/ Mardi C. Dier Mardi C. Dier	Executive Vice President and Chief Financial Officer (Principal Financial Officer)	February 15, 2022
/s/ Theodore A. Huizenga Theodore A. Huizenga	Senior Vice President, Corporate Controller (Principal Accounting Officer)	February 15, 2022
/s/ Daniel G. Welch Daniel G. Welch	Chairman of the Board	February 15, 2022
/s/ William Aliski William Aliski	Director	February 15, 2022
/s/ Deborah Dunsire Deborah Dunsire, M.D.	Director	February 15, 2022
/s/ Lars Ekman Lars Ekman, M.D., Ph.D.	Director	February 15, 2022
/s/ Matthew K. Fust Matthew K. Fust	Director	February 15, 2022
/s/ Michael Narachi Michael Narachi	Director	February 15, 2022
/s/ Corsee D. Sanders Corsee D. Sanders, Ph.D.	Director	February 15, 2022
/s/ Shehnaaz Suliman Shehnaaz Suliman, M.D.	Director	February 15, 2022

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, 2021 and 2020, 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, 2021, 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, 2021 and 2020, and the results of its operations and its cash flows for each of the three years in the period ended December 31, 2021, 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, 2021, 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 15, 2022 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 9, 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.

Redwood City, California
February 15, 2022

ULTRAGENYX PHARMACEUTICAL INC.

CONSOLIDATED BALANCE SHEETS
(In thousands, except share and per share amounts)

	December 31,	
	2021	**2020**
ASSETS		
Current assets:		
Cash and cash equivalents	$ 307,584	$ 713,526
Marketable debt securities	432,612	488,007
Accounts receivable, net	28,432	23,093
Inventory	16,231	13,048
Prepaid expenses and other current assets	71,745	57,630
Total current assets	856,604	1,295,304
Property, plant, and equipment, net	141,247	73,515
Equity investments	34,925	155,375
Marketable debt securities	258,933	10,506
Right-of-use assets	34,936	40,524
Intangible assets, net	130,788	131,113
Goodwill	44,406	44,406
Other assets	20,558	8,812
Total assets	$ 1,522,397	$ 1,759,555
LIABILITIES AND STOCKHOLDERS' EQUITY		
Current liabilities:		
Accounts payable	$ 17,138	$ 12,923
Accrued liabilities	145,555	108,491
Contract liabilities	7,609	59,219
Lease liabilities	11,066	8,976
Total current liabilities	181,368	189,609
Contract liabilities	1,467	7,349
Lease liabilities	30,904	39,251
Deferred tax liabilities	33,306	33,306
Liability related to the sale of future royalties	351,786	335,665
Other liabilities	1,005	—
Total liabilities	599,836	605,180
Commitments and contingencies (Notes 8 and 14)		
Stockholders' equity:		
Preferred stock, par value of $0.001 per share—25,000,000 shares authorized; nil outstanding as of December 31, 2021 and December 31, 2020	—	—
Common stock, par value of $0.001 per share—250,000,000 shares authorized; 69,344,998 and 66,818,520 shares issued and outstanding as of December 31, 2021 and December 31,2020, respectively	69	67
Additional paid-in capital	2,997,497	2,773,195
Accumulated other comprehensive income (loss)	(1,404)	689
Accumulated deficit	(2,073,601)	(1,619,576)
Total stockholders' equity	922,561	1,154,375
Total liabilities and stockholders' equity	$ 1,522,397	$ 1,759,555

See accompanying notes.

ULTRAGENYX PHARMACEUTICAL INC.

CONSOLIDATED STATEMENTS OF OPERATIONS
(In thousands, except share and per share amounts)

	Year Ended December 31,		
	2021	**2020**	**2019**
Revenues:			
Collaboration and license	$ 256,438	$ 219,315	$ 83,493
Product sales	77,017	38,720	20,221
Non-cash collaboration royalty revenue	17,951	12,995	—
Total revenues	351,406	271,030	103,714
Operating expenses:			
Cost of sales	16,008	6,129	9,008
Research and development	497,153	412,084	357,355
Selling, general and administrative	219,982	182,933	161,524
Total operating expenses	733,143	601,146	527,887
Loss from operations	(381,737)	(330,116)	(424,173)
Interest income	1,928	7,038	13,238
Change in fair value of equity investments	(42,063)	170,403	13,413
Non-cash interest expense on liability related to the sale of future royalties	(29,422)	(33,291)	(1,135)
Other income (expense)	(1,687)	607	(787)
Loss before income taxes	(452,981)	(185,359)	(399,444)
Provision for income taxes	(1,044)	(1,207)	(3,283)
Net loss	$ (454,025)	$ (186,566)	$ (402,727)
Net loss per share, basic and diluted	$ (6.70)	$ (3.07)	$ (7.12)
Weighted-average shares used in computing net loss per share, basic and diluted	67,795,540	60,845,550	56,576,885

See accompanying notes.

ULTRAGENYX PHARMACEUTICAL INC.

CONSOLIDATED STATEMENTS OF COMPREHENSIVE LOSS
(In thousands)

	Year Ended December 31,		
	2021	**2020**	**2019**
Net loss	$ (454,025)	$ (186,566)	$ (402,727)
Other comprehensive income (loss):			
Foreign currency translation adjustments	(550)	735	23
Unrealized gain (loss) on available-for-sale securities	(1,543)	101	463
Other comprehensive income (loss):	(2,093)	836	486
Total comprehensive loss	$ (456,118)	$ (185,730)	$ (402,241)

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, 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	—	—	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	—	—	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
Issuance of common stock in connection with at-the-market offering, net of issuance costs	1,050,372	1	78,942	—	—	78,943
Stock-based compensation	—	—	105,260	—	—	105,260
Issuance of common stock under equity plan awards, net of tax	1,476,106	1	40,100	—	—	40,101
Other comprehensive loss	—	—	—	(2,093)	—	(2,093)
Net loss	—	—	—	—	(454,025)	(454,025)
Balance as of December 31, 2021	69,344,998	$ 69	$ 2,997,497	$ (1,404)	$ (2,073,601)	$ 922,561

See accompanying notes.

ULTRAGENYX PHARMACEUTICAL INC.

CONSOLIDATED STATEMENTS OF CASH FLOWS
(In thousands)

	Year Ended December 31,		
	2021	**2020**	**2019**
Operating activities:			
Net loss	$ (454,025)	$ (186,566)	$ (402,727)
Adjustments to reconcile net loss to net cash used in operating activities:			
Stock-based compensation	104,952	85,735	81,995
Amortization of premium (discount) on marketable debt securities, net	6,606	848	(6,214)
Depreciation and amortization	13,239	12,261	8,539
Change in fair value of equity investments	42,063	(170,403)	(13,413)
Non-cash collaboration royalty revenue	(17,951)	(12,995)	—
Non-cash interest expense on liability related to the sale of future royalties	29,422	33,291	1,135
Other	235	946	2,621
Changes in operating assets and liabilities:			
Accounts receivable	(5,432)	9,840	(20,104)
Inventory	(3,117)	(1,346)	(4,451)
Prepaid expenses and other assets	(29,508)	2,748	(8,216)
Accounts payable, accrued, and other liabilities	32,313	26,853	13,312
Contract liabilities, net	(57,492)	66,568	—
Deferred tax liabilities	—	—	2,140
Net cash used in operating activities	(338,695)	(132,220)	(345,383)
Investing activities:			
Purchase of property, plant, and equipment	(73,093)	(43,905)	(24,832)
Purchase of marketable debt securities	(1,012,187)	(813,237)	(692,824)
Purchase of equity investments	—	(37,062)	(14,339)
Proceeds from sale of marketable debt securities	92,896	50,990	42,718
Proceeds from sale of equity investments	79,843	79,842	—
Proceeds from maturities of marketable debt securities	718,111	589,806	676,238
Other	(942)	(5,555)	—
Net cash used in investing activities	(195,372)	(179,121)	(13,039)
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
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	78,943	20,391	24,828
Proceeds from the issuance of common stock from exercise of warrants and equity plan awards, net	40,101	89,293	9,829
Other	(492)	(236)	—
Net cash provided by financing activities	118,552	600,272	679,306
Effect of exchange rate changes on cash	(1,194)	1,119	(165)
Net (decrease) increase in cash, cash equivalents, and restricted cash	(416,709)	290,050	320,719
Cash, cash equivalents, and restricted cash at beginning of year	726,294	436,244	115,525
Cash, cash equivalents, and restricted cash at end of year	$ 309,585	$ 726,294	$ 436,244

See accompanying notes.

ULTRAGENYX PHARMACEUTICAL INC.

CONSOLIDATED STATEMENTS OF CASH FLOWS
(In thousands)

	Year Ended December 31,		
	2021	**2020**	**2019**
Supplemental disclosures of non-cash investing and financing information:			
Acquired lease liabilities arising from obtaining right-of-use assets	$ 3,142	$ 18,775	$ 21,861
Stock-based compensation capitalized into ending inventory	$ 1,453	$ 1,304	$ 1,206
Costs of property, plant and equipment included in accounts payable, accrued, and other liabilities	$ 18,993	$ 8,515	$ 10,367
Non-cash interest expense on liability related to the sale of future royalties capitalized into ending property, plant and equipment	$ 4,650	$ —	$ —

See accompanying notes.

1. Organization and Basis of Presentation

Ultragenyx Pharmaceutical Inc. (the Company) is a biopharmaceutical company incorporated in Delaware.

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 operates as one reportable segment. The Company has four commercially approved products. Crysvita® (burosumab) is approved in the United States (U.S.) 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, Colombia, and Mexico, Crysvita is approved for treatment of XLH in adult and pediatric patients one year of age and older. Crysvita is also approved in the U.S. by the FDA 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, is approved in the U.S., Canada, and Brazil for the treatment of pediatric and adult patients severely affected by long-chain fatty acid oxidation disorders (LC-FAOD).

On January 7, 2022, the Company announced a collaboration with Regeneron Pharmaceuticals (Regeneron) to commercialize Evkeeza® (evinacumab) outside of the U.S. Evkeeza is approved in the U.S. and the European Economic Area (EEA) for the treatment of homozygous familial hypercholesterolemia (HoFH).

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);
- 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 is subject to the Company's collaboration agreement with Mereo BioPharma 3 (Mereo), 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 (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; and
- UX053 is a messenger RNA (mRNA) product candidate designed for the treatment of patients with Glycogen Storage Disease Type III (GSDIII), a disease caused by a glycogen debranching enzyme (AGL) deficiency that results in glycogen accumulation in the liver and muscle.

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, 2021, the Company has relied primarily on its sale of equity securities, its revenue from commercial products, 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 Statements of Cash Flows (in thousands):

	December 31,		
	2021	2020	2019
Cash and cash equivalents	$ 307,584	$ 713,526	$ 433,584
Restricted cash included in prepaid expenses and other current assets	—	10,847	161
Restricted cash included in other assets	2,001	1,921	2,499
Total cash, cash equivalents, and restricted cash shown in the statements of cash flows	$ 309,585	$ 726,294	$ 436,244

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 Arcturus common stock and received an option to purchase an additional 600,000 shares of Arcturus common stock, which was exercised in May 2020. During the years ended December 31, 2021 and 2020, the Company sold 1,700,000 shares and 800,000 shares, respectively, of Arcturus common stock. 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 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 Consolidated 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 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 years ended December 31, 2021 and 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. Interest costs incurred during the construction of major capital projects are capitalized until the underlying asset is ready to be placed in service, at which point the interest costs are amortized as depreciation expense over the life of the underlying asset. 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. When development of the project 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 Statements 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 Company sold the right to receive certain royalty payments from net sales of Crysvita to RPI Finance Trust (RPI), an affiliate of Royalty Pharma, as further described in "Note 9. 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.

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 a material effect on earnings in the period of the adjustment.

Leases

Lease agreements are evaluated to determine whether an arrangement is or contains a lease in accordance with ASC 842, *Leases*. 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. The Company has elected to not separate lease and non-lease components. 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, U.S. Government Treasury and agency securities, and debt securities in government-sponsored entities 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 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, 2021			
	Level 1	Level 2	Level 3	Total
Financial Assets:				
Money market funds	$ 266,765	$ —	$ —	$ 266,765
Certificates of deposits and time deposits	—	16,000	—	16,000
Corporate bonds	—	349,691	—	349,691
Commercial paper	—	187,624	—	187,624
Asset-backed securities	—	41,245	—	41,245
U.S. Government Treasury and agency securities	—	87,435	—	87,435
Debt securities in government-sponsored entities	—	19,549	—	19,549
Investments in Arcturus and Solid common stock	32,200	—	—	32,200
Other	—	942	—	942
Total	$ 298,965	$ 702,486	$ —	$ 1,001,451

	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

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 using a Black-Scholes option pricing model. As of December 31, 2021 and 2020, the balance of the convertible promissory note was $2.4 million and $2.1 million, respectively, including $0.5 million and $0.2 million, respectively, in interest receivable, and was recorded in other assets, and the allocated fair value of the warrant was $0.6 million and $0.6 million, respectively, and was recorded in equity investments.

In December 2020, the Company invested $1.4 million in a private pharmaceutical company in the form of a convertible promissory note (Note). In October 2021, pursuant to a qualified financing event, the outstanding balance of the Note was fully converted into 606,506 shares of preferred stock. The equity investment is recorded at cost less impairment, if any, adjusted for observable price changes in orderly transactions for identical or similar investments. As of December 31, 2021, the carrying value of the investment was $2.1 million.

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, 2021			
		Gross Unrealized		
	Amortized Cost	Gains	Losses	Estimated Fair Value
Money market funds	$ 266,765	$ —	$ —	$ 266,765
Certificates of deposit and time deposits	16,000	—	—	16,000
Corporate bonds	350,667	3	(979)	349,691
Commercial paper	187,624	—	—	187,624
Asset-backed securities	41,282	1	(38)	41,245
U.S. Government Treasury and agency securities	87,642	1	(208)	87,435
Debt securities in government-sponsored entities	19,612	—	(63)	19,549
Total	$ 969,592	$ 5	$ (1,288)	$ 968,309

	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

At December 31, 2021, the remaining contractual maturities of available-for-sale securities were less than three 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, 2021 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,	
	2021	2020
Work-in-process	$ 10,504	$ 7,184
Finished goods	5,727	5,864
Total	$ 16,231	$ 13,048

Property, Plant, and Equipment, net

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

	December 31,	
	2021	2020
Leasehold improvements	$ 44,081	$ 39,356
Research and development equipment	38,661	28,394
Furniture and office equipment	5,413	5,051
Computer equipment and software	10,238	8,181
Land	15,487	11,722
Construction-in-progress	76,849	17,649
Other	556	554
Property, plant, and equipment, gross	191,285	110,907
Less accumulated depreciation	(50,038)	(37,392)
Property, plant, and equipment, net	$ 141,247	$ 73,515

Depreciation expense for the years ended December 31, 2021, 2020, and 2019 was $12.9 million, $12.1 million and $8.3 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,	
	2021	2020
Research, clinical study, and manufacturing expenses	$ 40,880	$ 25,875
Payroll and related expenses	62,591	58,176
Other	42,084	24,440
Total	$ 145,555	$ 108,491

5. Intangible Assets, net

The Company has IPR&D assets of $129.0 million and $129.0 million as of December 31, 2021 and 2020, respectively. 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.

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 $0.3 million, $0.2 million, and $0.2 million for the years ended December 31, 2021, 2020, and 2019, 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,		
	2021	2020	2019
Collaboration and license revenue:			
Crysvita collaboration revenue in profit-share territory	$ 171,198	$ 128,597	$ 74,869
Crysvita royalty revenue in European territory	244	1,498	8,120
Daiichi Sankyo	84,996	89,220	—
Bayer	—	—	504
Total collaboration and license revenue	256,438	219,315	83,493
Product sales:			
Crysvita	21,422	10,350	4,286
Mepsevii	16,035	15,342	12,634
Dojolvi	39,560	13,028	3,301
Total product sales	77,017	38,720	20,221
Crysvita non-cash collaboration royalty revenue	17,951	12,995	—
Total revenues	$ 351,406	$ 271,030	$ 103,714

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

	Year Ended December 31,		
	2021	2020	2019
North America	$ 301,110	$ 237,666	$ 86,442
Europe	26,660	21,318	12,085
All other	23,636	12,046	5,187
Total revenues	$ 351,406	$ 271,030	$ 103,714

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

	Year Ended December 31,		
	2021	2020	2019
Balance of product sales reserve at beginning of year	$ 3,913	$ 1,818	$ 1,240
Provisions	9,586	5,763	3,846
Payments	(6,120)	(2,785)	(2,739)
Adjustments	(198)	(883)	(529)
Balance of product sales reserve at end of year	$ 7,181	$ 3,913	$ 1,818

The following table presents changes in the contract assets (liabilities) for the years ended December 31, 2021 and 2020 (in thousands):

	December 31,	
	2021	2020
Balance of contract liabilities at beginning of period	$ (66,568)	$ —
Additions	(27,504)	(155,788)
Deductions	84,996	89,220
Balance of contract liabilities at end of period, net	$ (9,076)	$ (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 71% of the total accounts receivable balance as of December 31, 2021 and 2020, 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 U.S. 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 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. In April 2023, which is the transition date for the profit-share 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.

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 9. 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 years ended December 31, 2021 and 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 $0.2 million and $1.5 million, respectively, as royalty revenue in the European territory.

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

	Year Ended December 31,		
	2021	2020	2019
Company's share of revenue in profit-share territory	$ 171,198	$ 128,597	$ 74,869
Royalty revenue in European territory	244	1,498	8,120
Non-cash royalty revenue in European territory	17,951	12,995	—
Total	$ 189,393	$ 143,090	$ 82,989

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. The Company recorded product sales of $21.4 million, $10.4 million, and $4.3 million for the years ended December 31,

2021, 2020, and 2019, 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 Latin America 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,		
	2021	2020	2019
Research and development	$ 21,657	$ 21,476	$ 27,309
Selling, general and administrative	32,629	25,186	21,828
Total	$ 54,286	$ 46,662	$ 49,137

Collaboration receivable and payable

The Company had accounts receivable from KKC in the amount of $20.2 million and $16.4 million from profit-share revenue and royalties and other receivables recorded in prepaid and other current assets of $16.0 million and $9.6 million and accrued liabilities of $2.3 million and $2.4 million from commercial and development activity reimbursements, as of December 31, 2021 and 2020, 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, as amended, BRI exclusively licensed to the Company its territories for certain intellectual property related to Dojolvi (triheptanoin) for the treatment of LC-FAOD.

For the year ended December 31, 2020, the Company paid $2.0 million 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 was 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.

The Company has no further obligations under the contract. The Company may record future milestone payments as revenue if it becomes probable that a significant reversal in the amount of revenue recognized will not occur and when the uncertainty associated with the variable consideration is subsequently resolved.

University of Pennsylvania

The Company has a research, collaboration, and license agreement with University of Pennsylvania School of Medicine (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. 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, as well as low to mid-single-digit royalties on net sales of each licensed product.

Arcturus Research Collaboration and License Agreement

In October 2015, the Company entered into a Research Collaboration and License Agreement with Arcturus Therapeutics Holdings Inc. (Arcturus) to collaborate on the research and development of therapies for select rare diseases. Arcturus was responsible for conducting certain research services, funded by the Company, and the Company was responsible for development and commercialization costs.

On a product-by-product basis, the Company is obligated to make development and regulatory milestone payments of up to $24.5 million, and commercial milestone payments of up to $45.0 million, if certain milestones are achieved. For the year ended December 31, 2021, the Company achieved a $1.0 million development milestone related to UX053, which was paid with a corresponding credit received from Arcturus for prior research and collaboration activities. The Company is also obligated to pay Arcturus royalties on any net sales of products incorporating the licensed intellectual property that may range from a mid single-digit to low double-digit percentage. Pursuant to the agreement, the Company incurred nil, $0.4 million, and $0.8 million for the years ended December 31, 2021, 2020, and 2019, 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 (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 under the License Agreement, Arcturus common stock, and an option to purchase an additional 600,000 shares of Arcturus' common stock at $16.00 per share. In May 2020, the Company exercised its option to purchase 600,000 shares of Arcturus common stock for a total purchase price of $9.6 million.

During the years ended December 31, 2021 and 2020, the Company sold 1,700,000 shares and 800,000 shares of Arcturus common stock, at a weighted-average price of $47.44 and $100.81, respectively. As of December 31, 2021 and 2020, the Company held 500,000 shares and 2,200,000 shares, respectively, of Arcturus common stock.

Due to the decrease in ownership and in accordance with the terms of the Equity Purchase Agreement, the Company no longer had the right to have its director nominee included in the annual slate of Arcturus director nominees and as a result, the Company's director designee resigned from the Arcturus board of directors effective August 25, 2021. The Company will continue to apply the fair value option to account for the equity investment.

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 Arcturus common stock	Total
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
Change in fair value	2,912	—	2,912
Sale of shares	(79,843)	—	(79,843)
December 31, 2021	$ 18,505	$ —	$ 18,505

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 a $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 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. The Company 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 an additional $25.0 million payment upon achievement of the milestones related to technology transfer of the PCL and HEK293 platforms in the fourth quarter of 2021. Daiichi Sankyo is also obligated to pay a single-digit royalties on net sales of products manufactured in the technology platforms. Daiichi Sankyo will reimburse the Company for all costs associated with the transfer of the manufacturing technology.

In March 2020, the Company also entered into a Stock Purchase Agreement (SPA) 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. 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 SPA. 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 SPA are being accounted for as one arrangement because they were entered into at or near the same time and were 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 PCL and HEK293 transient transfection manufacturing technology platforms together with the initial technical assistance and technology transfer services, which were substantially 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.

As of December 31, 2021, the Company has determined that the total transaction price of the License Agreement was $183.3 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 $5.6 million estimated reimbursement amount for delivering the license and technology services. Total revenue recognized under the license agreement through December 31, 2021 is $174.2 million.

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 is being recognized over an initial period which is substantially complete and was based on 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. 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 years ended December 31, 2021 and 2020, the Company recognized $85.0 million and $89.2 million, respectively, in revenue related to this arrangement. The Company had recorded contract liabilities of $9.1 million and $66.6 million and an accounts receivable related to the above agreements of $0.1 million and $1.2 million, respectively, as of December 31, 2021 and 2020.

Solid Biosciences, Inc.

In October 2020, the Company entered into a strategic Collaboration and License Agreement with Solid Biosciences Inc. (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 is collaborating to develop products that combine Solid's differentiated microdystrophin construct, the Company's PCL manufacturing platform, and the Company's AAV8 variants. Solid is providing 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
Change in fair value	(45,625)
December 31, 2021	$ 13,695

8. Leases

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

	Year Ended December 31, 2021	Year Ended December 31, 2020
Operating lease expense	$ 11,209	$ 10,164
Variable lease expense	4,142	3,298
Financing:		
Amortization	310	158
Interest expense	58	40
Total	$ 15,719	$ 13,660

Cash paid for amounts included in the measurement of operating lease liabilities for the year ended December 31, 2021 was $11.8 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, 2021 were as follows (in thousands):

Year Ending December 31,	Operating	Financing	Total
2022	$ 12,873	$ 606	$ 13,479
2023	13,072	349	13,421
2024	11,092	75	11,167
2025	6,247	—	6,247
2026	2,681	—	2,681
Thereafter	776	—	776
Total future lease payments	46,741	1,030	47,771
Less: Amount representing interest	(5,749)	(52)	(5,801)
Present value of future lease payments	40,992	978	41,970
Less: Lease liabilities, current	(10,498)	(568)	(11,066)
Lease liabilities, non-current	$ 30,494	$ 410	$ 30,904

Lease liabilities are based on the net present value of the remaining lease payments over the remaining lease term. As of December 31, 2021, the weighted-average remaining operating and financing lease terms were 3.84 years and 3.88 years, respectively, and the weighted-average discount rates used to determine the lease liability for operating and financing leases were 6.64% and 5.44%, respectively.

9. Liability Related to the Sale of Future Royalties

In December 2019, the Company entered into a Royalty Purchase Agreement with RPI. Pursuant to the agreement, 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. The Company's effective annual interest rate was approximately 9.6% as of December 31, 2021.

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
December 31, 2019	$ 315,369
Non-cash collaboration royalty revenue	(12,995)
Non-cash interest expense	33,291
December 31, 2020	335,665
Non-cash collaboration royalty revenue	(17,951)
Non-cash interest expense	34,072
December 31, 2021	$ 351,786

10. Equity

At-the-Market Offerings

In July 2017, the Company entered into an at-the-market (ATM) sales agreement with Cowen and Company, LLC (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 and 2019, the Company sold 283,333 and 468,685 shares of common stock, respectively, resulting in net proceeds of approximately $20.4 million and $24.8 million, respectively, after commissions and other offering costs. The Company has completed the sale of all available amounts under this ATM facility.

In May 2021, the Company entered into an Open Market Sale Agreement with Jefferies LLC (Jefferies) pursuant to which the Company may offer and sell shares of the Company's common stock having an aggregate offering proceeds up to $350.0 million, from time to time, in ATM offerings through Jefferies. For the year ended December 31, 2021, the Company sold 1,050,372 shares under the arrangement resulting in net proceeds of approximately $78.9 million.

Underwritten Public Offering

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, 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.

11. 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. In February 2021, the Company adopted the Employment Inducement Plan (the Inducement Plan), with a maximum of 500,000 shares available for grant under the Inducement Plan. Under the terms of the 2014 Plan and Inducement 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 and Inducement 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 of December 31, 2021, an aggregate of 12,462,795 shares of common stock have been authorized for issuance under the 2011 Plan, the 2014 Plan, and the Inducement Plan.

Stock Option Activity

The following table summarizes activity under the Company's stock option 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, 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
Options granted	1,217,820	128.63		
Options exercised	(687,835)	53.14		
Options cancelled	(336,383)	81.78		
Outstanding — December 31, 2021	6,198,205	$ 75.96	6.81	$ 112,242
Vested and exercisable — December 31, 2021	3,669,577	$ 64.93	5.66	$ 80,283
Vested and expected to vest — December 31, 2021	5,951,372	$ 75.09	6.73	$ 109,665

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, 2021, 2020, and 2019 was $38.3 million, $56.9 million, and $6.5 million, respectively. Cash received from the exercise of options was $36.6 million, $88.1 million, and $7.7 million as of December 31, 2021, 2020, and 2019, respectively.

The weighted-average estimated fair value of stock options granted was $70.84, $35.22, and $37.15 per share of the Company's common stock during the years ended December 31, 2021, 2020, and 2019, respectively. The total estimated grant date fair value of options vested during the years ended December 31, 2021, 2020, and 2019 was $48.1 million, $45.4 million, and $45.3 million, respectively.

Restricted Stock Units

The following table summarizes activity under the Company's Restricted Stock Units (RSU) plans and related information:

	RSUs Outstanding	
	Number of Shares	Weighted- Average Grant Date Fair Value
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
RSUs granted	738,905	122.71
RSUs vested	(559,595)	63.41
RSUs cancelled	(187,852)	80.55
Unvested — December 31, 2021	1,672,625	$ 87.48

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, 2021, 2020, and 2019 was $35.5 million, $27.2 million, and $20.8 million, respectively. The aggregate intrinsic value of the shares of the RSUs vested during the years ended December 31, 2021, 2020, and 2019 was $69.9 million, $29.5 million, and $18.4 million, respectively.

Performance Stock Units

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

	PSUs Outstanding	
	Number of Shares	Weighted- Average Grant Date Fair Value
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
PSUs granted	62,000	158.11
PSUs vested	(168,274)	54.40
PSUs cancelled	(12,400)	54.28
Unvested — December 31, 2021	93,892	$ 123.46

The fair value of the PSUs is determined on the grant date based on the fair value of the Company's common stock, except for certain PSUs with a market vesting condition, for which fair value is estimated using a Monte Carlo simulation model. 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, including both performance conditions and market conditions. As of December 31, 2021, the specified criteria were deemed probable of achievement or already achieved. Stock-based compensation for 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, 2021, 2020, and 2019 was $9.2 million, $10.3 million, and $3.2 million, respectively, with an aggregate intrinsic value of the shares of $18.9 million, $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, 2021, the Company issued 69,738 shares of common stock under the ESPP. As of December 31, 2021, an aggregate of 3,925,798 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,		
	2021	2020	2019
Cost of sales	$ 871	$ 827	$ 1,084
Research and development	59,097	47,949	44,205
Selling, general and administrative	45,011	36,959	36,706
Total stock-based compensation expense	$ 104,979	$ 85,735	$ 81,995

Stock-based compensation of $1.7 million, $1.2 million, and $1.4 million was capitalized into inventory for the years ended December 31, 2021, 2020, and 2019, respectively. Capitalized stock-based compensation is recognized as cost of sales when the related product is sold. As of December 31, 2021, the total unrecognized compensation expense related to unvested equity awards, net of estimated forfeitures, was $200.0 million, which the Company expects to recognize over an estimated weighted-average period of 2.33 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,		
	2021	2020	2019
Expected term (years)	6.06	6.20	6.22
Expected volatility	60%	61%	61%
Risk-free interest rate	1.0%	0.8%	2.4%
Expected dividend rate	0.0%	0.0%	0.0%

12. Defined Contribution Plan

The Company sponsors a retirement plan in which substantially all of its full-time employees in the U.S. 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 $5.5 million, $4.3 million, and $3.6 million as contribution expenses for the years ended December 31, 2021, 2020, and 2019, respectively.

13. Income Taxes

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

	Year Ended December 31,		
	2021	2020	2019
Domestic	$ 455,314	$ 189,449	$ 399,709
Foreign	(2,333)	(4,090)	(265)
Total loss before income taxes	$ 452,981	$ 185,359	$ 399,444

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

	Year Ended December 31,		
	2021	2020	2019
Current provision for income taxes:			
Federal	$ —	$ —	$ —
State	(14)	15	51
International	1,058	1,192	1,092
Total current tax provision	1,044	1,207	1,143
Deferred tax provision:			
Federal	—	—	—
State	—	—	2,140
International	—	—	—
Total deferred tax provision	—	—	2,140
Total provision for income taxes	$ 1,044	$ 1,207	$ 3,283

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,		
	2021	2020	2019
Federal statutory income tax rate	21.0 %	21.0 %	21.0 %
State income taxes, net of federal benefit	—	—	(0.5)
Federal tax credits	7.2	13.7	5.2
Other	0.5	(0.5)	(0.2)
Premium on equity issuance	—	2.2	—
Nondeductible permanent items	(0.8)	(0.9)	(0.4)
Stock-based compensation	1.3	0.9	(1.0)
Uncertain tax positions	(1.4)	(2.7)	(1.0)
Change in valuation allowance	(27.9)	(33.9)	(23.6)
Foreign rate differential	(0.1)	(0.5)	(0.3)
Provision for income taxes	(0.2) %	(0.7) %	(0.8) %

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,	
	2021	2020
Deferred tax assets:		
Loss carryforwards	$ 306,119	$ 222,902
Tax credits	218,131	184,961
Stock options	33,564	39,154
Accruals and reserves	25,735	24,922
Fixed assets and intangibles	18,263	7,242
Liability related to sale of future royalties	90,826	86,664
Basis difference in equity investments	3,912	—
Other	13,060	28,642
Gross deferred tax assets	709,610	594,487
Valuation allowance	(700,669)	(561,139)
Total deferred tax assets	8,941	33,348
Deferred tax liabilities:		
In-process research and development	(33,306)	(33,306)
Basis difference in equity investments	—	(23,019)
Right-of-use lease assets	(8,941)	(10,329)
Gross deferred tax liabilities	(42,247)	(66,654)
Net deferred tax liabilities	$ (33,306)	$ (33,306)

As of December 31, 2021 and 2020, the Company had approximately $1,085.4 million and $750.2 million, respectively, of federal net operating loss carryforwards available to reduce future taxable income that will begin to expire in 2031. As of December 31, 2021 and 2020, the Company had approximately $777.0 million and $616.8 million, respectively, of state net operating loss carryforwards available to reduce future taxable income that will begin to expire in 2031.

As of December 31, 2021 and 2020, the Company had federal research tax credit carryforwards of $22.9 million and $17.7 million, respectively, available to reduce future tax liabilities that will begin to expire in 2030. As of December 31, 2021 and 2020, the Company had state research credit carryforwards of $44.6 million and $34.5 million, respectively, available to reduce future tax liabilities that will be carried forward indefinitely.

As of December 31, 2021 and 2020, the Company had federal Orphan Drug Credits of $208.1 million and $179.8 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, 2021.

The valuation allowance increased by $139.5 million and $74.3 million during the years ended December 31, 2021 and 2020, 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,		
	2021	2020	2019
Balance at beginning of year	$ 46,662	$ 39,954	$ 33,727
Additions based on tax positions related to current year	8,542	6,950	5,575
Additions for tax positions of prior years	356	382	652
Reductions for tax positions of prior years	(200)	(624)	—
Balance at end of year	$ 55,360	$ 46,662	$ 39,954

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, 2021 and 2020, 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, 2021, the Company had not made a provision for any incremental foreign withholding taxes on approximately $4.1 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, forty state tax jurisdictions, and ten foreign countries. The federal and state income tax returns from inception to December 31, 2021 remain subject to examination.

14. 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, 2021, the aggregate payments under contractually binding manufacturing and service agreements are as follows (in thousands):

	Year Ended December 31,	
	2022	2023
Manufacturing and Services	19,225	774

The terms of certain of the Company's licenses, royalties, development and collaboration agreements, as well as other research and development activities, require the Company to pay potential future milestone payments based on product development success. The amount and timing of such obligations are unknown or uncertain. These potential obligations are further described in "Note 7. License and Research Agreements".

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.

15. 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, 2021, 2020, and 2019 (in thousands, except share and per share data):

	Year Ended December 31,		
	2021	2020	2019
Numerator:			
Net loss	$ (454,025)	$ (186,566)	$ (402,727)
Denominator:			
Weighted-average shares used to compute net loss per share, basic and diluted	67,795,540	60,845,550	56,576,885
Net loss per share, basic and diluted	$ (6.70)	$ (3.07)	$ (7.12)

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,		
	2021	2020	2019
Options to purchase common stock, RSUs, and PSUs	8,214,063	8,532,236	7,978,666
Employee stock purchase plan	3,511	2,626	3,953
Common stock warrants	—	29,449	149,700
	8,217,574	8,564,311	8,132,319

16. Accumulated Other Comprehensive Income (Loss)

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

	Year Ended December 31,	
	2021	2020
Cumulative foreign currency translation adjustment	$ (121)	$ 429
Unrealized gain (loss) on securities available-for-sale	(1,283)	260
Total accumulated other comprehensive income (loss)	$ (1,404)	$ 689

17. Subsequent Events

On January 7, 2022, the Company announced a collaboration with Regeneron to commercialize Evkeeza for HoFH outside of the U.S. Under the terms of the agreement, Regeneron received a $30.0 million upfront payment and is eligible to receive up to $63.0 million in future milestone payments, contingent upon the achievement of certain regulatory and sales milestones. Pursuant to the terms of the agreement, the Company received the rights to develop, commercialize and distribute the product in countries outside of the U.S. and will make payments to Regeneron based on net sales of the product. The Company will share in certain costs for global trials led by Regeneron and also have the right to opt into other potential indications.

[***] = 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 NO. 11 TO COLLABORATION AND LICENSE AGREEMENT

This Amendment No. 11 to the Collaboration and License Agreement, ("**Amendment**") is made and entered into by and between Kyowa Kirin Co., Ltd. (formerly, Kyowa Hakko Kirin Co., Ltd.), a company organized and existing under the laws of Japan, with an address at 1-9-2 Otemachi, Chiyoda-ku, Tokyo, 100-0004, Japan **("KKC") ** and Ultragenyx Pharmaceutical Inc., a company organized and existing under the laws of the State of Delaware, with an address at 60 Leveroni Court, Novato, California 94949, USA **("UGNX").**

RECITALS

WHEREAS, KKC and UGNX entered into a Collaboration and License Agreement effective as of August 29, 2013, an Amendment No. 1 to Collaboration and License Agreement effective as of August 24, 2015, an Amendment No. 2 to Collaboration and License Agreement effective as of November 28, 2016, an Amendment No. 3 to Collaboration and License Agreement effective as of September 29, 2017, an Amendment No. 4 to Collaboration and License Agreement effective as of January 29, 2018, an Amendment No. 5 to Collaboration and License Agreement effective as of April 30, 2018**,** an Amendment No. 6 to Collaboration and License Agreement effective as of February 1, 2019, an Amendment No. 7 to Collaboration and License Agreement effective as of December 5, 2018, an Amendment No. 8 to Collaboration and License Agreement effective as of July 4, 2019, an Amendment No. 9 to Collaboration and License Agreement effective as of December 23, 2019; and an Amendment No. 10 to Collaboration and License Agreement effective as of April 1, 2020 (collectively, the "**Collaboration Agreement**").

WHEREAS, as part of [***], KKC desires to change the market authorization holder with respect to the Licensed Product, which includes the holder of the Drug Identification Number ("**DIN**") and Notice of Compliance ("**NOC**") of the Licensed Product in Canada, from its Affiliate, Kyowa Kirin Limited ("**KKL**") to Kyowa Kirin, Inc. ("**KKUS**");

WHEREAS, such name change of the DIN/NOC holder necessitates certain regulatory and contractual actions;

WHEREAS, the Parties desire to set forth the agreed to actions herein to effectuate the name change of the DIN/NOC holder and to further amend the Collaboration Agreement as set forth below.

AGREEMENT

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 **December 17, 2021** (the ***"Amendment Effective Date").***

2. Any capitalized terms that are not defined in this Amendment will have their respective meanings set forth in the Collaboration Agreement.

3. Since KKC has changed its company name as of July 1, 2019, the abbreviation “KHK” of “Kyowa Hakko Kirin Co., Ltd.” in the Collaboration Agreement will be read as “KKC” after the Amendment Effective Date.

4. Section 5.13 **(a) Regulatory Matters in Canada**, shall be amended by adding the following language:

“KKL, as the holder of Drug Identification Number (“**DIN**”) and Notice of Compliance (“**NOC**”) of the Licensed Product in Canada as of August 26, 2021, will transfer the DIN/NOC holder to KKUS. The Parties agree that KKUS shall prepare all filings and materials in connection with the change to any market authorization holder, including the DIN/NOC holder, that are required to be made to Health Canada Including the Office of Submissions and Intellectual Property (“**OSIP**”) and the Office of Patented Medicines Liaison (“**OPML**”) and any other regulatory authority as may be required to affect said change in DIN/NOC holder or any other market authorization holder, including, but not limited to, as applicable the following: (i) Letter of name change and address change and any other documentation required to affect said administrative change; (ii) Letter to OPML to update the patent information for the DIN/NOC holder, the name and address for service in Canada, the name of the manufacturer of the Licensed Product,; and (iii) Any requisite label (including, cartons, vial labels, package inserts and product monograph) updates, changes and notifications and submissions/communications of same to Health Canada. KKUS shall provide all such documents to be filed in connection with the DIN/NOC holder change to Health Canada (including OSIP and OPML) to the individual set forth on Schedule A attached hereto or such other UGNX representatives identified by UGNX in advance to KKUS (“**UGNX Contact**”) for review in advance of such filings and KKUS shall ensure that all such documents are prepared in compliance with Applicable Laws. UGNX agrees to promptly review such materials for completeness and accuracy and the UGNX Contact will provide written approval/sign-off indicating said completeness and accuracy (email acceptable) to KKUS’ regulatory contact. Following such approval and sign off, pursuant to Sections 5.13(b) and (c) below, UGNX shall make such filings, and communicate directly with, Health Canada and any other regulatory

authority as may be required to affect said change in DIN/NOC holder or any other market authorization holder. The Parties further agree that UGNX shall prepare the updated “Form IV Patent Lists” for the Licensed Product (“Form IVs”) by carrying forward any patents on the current Form IVs pursuant to the Patented Medicines (Notice of Compliance) Regulations and timely submit such updated Form IVs in connection with the change in DIN/NOC holder. In addition, until the Profit Share Territory Transition Date, UGNX shall prepare and timely file any Form IVs for new patents that are to be added to the patent list for the Licensed Product, as required by law or as may be directed by KKC or KKUS from time to time. UGNX shall provide the prepared Form IVs set forth above to KKC and KKUS at least [***] Business Days prior to the filing due date for review and signature or as otherwise directed by KKC or KKUS (provided that, KKC or KKUS provides at least [***] Business Days prior notice to UGNX), as the case maybe. Submission of such Form IVs by UGNX shall occur only after review and signature by either KKC or KKUS, as appropriate. The Parties further agree that UGNX will continue to timely prepare and file all necessary Form IVs following the procedure described in this Section until the Profit Share Territory Transition Date.

5. Section 5.14 **Canadian Labeling and Packaging**, shall be amended by adding the following language:

   “KKUS shall also update the labels, packaging, leaflet and the product monograph of the Licensed Product to reflect the name change of DIN/NOC holder In Canada. The label, packaging, leaflet and monograph of the Licensed Product shall be updated as follows:

Manufactured by /
Fabriqué par :
Kyowa Kirin, Inc.
Bedminster, NJ 07921

Imported and Distributed by /
Importé et Distribué par:
Innomar Strategies Inc
3470 Superior Court
Oakville, ON
Canada, L6L 0C4

Vial labels and product monograph will state: “Kyowa Kirin, Inc.”

The leaflet will state: “This leaflet was prepared by Kyowa Kirin, Inc.” and will be translated to French for the French leaflet. UGNX will timely notify Health Canada (or other regulatory Canadian authority, as applicable), as of when Licensed Product with new label is being distributed/sold in Canada. It is understood that Health Canada does provide a grace period for product with old vial labels to be used, distributed and remain on the market and UGNX will utilize, distribute and exhaust the stock of currently labeled Licensed Product to the extent permitted by Applicable Law (including regulations and Health Canada) prior to commencing

distribution or utilization of newly labeled Licensed Product. KKUS and UGNX shall promptly notify each other once either becomes aware (upon notification/communication with Health Canada or otherwise) of the time period it is required to cease utilizing distributing and exhausting currently labeled Licensed Product and of inventory of all Licensed Product on hand (including a break down into currently and newly labelled Licensed Product) and UGNX shall cooperate with KKUS on the timing of importing and sale of Licensed Product (currently and newly labelled) to ensure continuity of supply of the Licensed Product in Canada. If there is currently labeled Licensed Product in stock at the time transfer to newly labeled Licensed Product is required, then the Parties will consider options to minimize Licensed Product wastage, such as over-labelling and will discuss same before a decision is reached. KKUS shall have final decision as to what happens with the currently labeled Licensed Product. The Parties agree that the obligations set forth in this paragraph shall terminate as of the Profit Share Territory Transition Date, except to the extent otherwise extended by mutual agreement.

6. Section 5.15 **Other Reports to Health Canada and other Regulatory Authorities with respect to the Commercialization of the Licensed Products in Canada**, Section 5.15(c) shall be deleted and replaced in its entirety as follows:

"(c) Prior to the Profit Share Territory Transition Date, except to the extent otherwise extended by mutual agreement, UGNX shall be responsible for drafting all other NDS supplements, including, as applicable but not limited to, module 1 administrative documents and patent information, and Health Canada submissions. UGNX shall ensure prior to filing any NDS (supplements or otherwise), that it has an updated list of all patents that may be eligible for listing on the Patent List pursuant to the Patented Medicines (Notice of Compliance) Regulations and confirm same with KKUS, and shall ensure that all Form IVs documents are prepared, updated and carried forward with each filing (including any administrative or other change and/or drug submission) and the information on said Form IVs and the patent register in Canada are kept up to date to ensure protection of the Licensed Product's intellectual property, regulatory and other rights. Prior to the Profit Share Territory Transition Date, except to the extent otherwise extended by mutual agreement, UGNX shall submit all routine or planned NDS supplements and other Regulatory Filings in Canada, including, but not limited to, Form IVs documents to KKUS for review and approval at least [***] Business Days prior to submission to Health Canada or other Regulatory Authorities. For non-routine submissions to Health Canada or other Canadian Regulatory Authorities that require expedited processing, UGNX shall discuss and agree with KKUS on timing for the KKUS review. Prior to the Profit Share Territory Transition Date, except to the extent otherwise extended by mutual agreement, UGNX shall ensure that the name and address for service in Canada on all Form IVs is KKUS's appointed counsel in Canada, as may be updated from time to time on notification by KKUS to UGNX and that the "contact" listed in the Form IVs is kept up to date.

7. Paragraph 6.9 **Third Party Logistics in Canada** shall be deleted and replaced in its entirety as follows:

"6.9 **Third Party Logistics in Canada.** To the extent of the Commercialization of the Licensed Products in Canada, KKC's Affiliate, Kyowa Kirin Services Limited ("**KKS**") has novated its rights and obligations effective [***] to KKC's Affiliate, [***] under the Third Party Logistics Provider agreement ("**3PL Agreement**"). The Third Party Logistics Provider will hold on consignment [***]-titled Licensed Product per the terms of the 3PL Agreement. UCI shall be responsible for the creation of Customer accounts at the Third Party Logistics Provider and shall provide all related and necessary information to the Third Party Logistics Provider to ensure that the Third Party Logistics Provider can fulfill its obligations under the 3PL Agreement with [***]. [***] will provide weekly reports to UCI reflecting the Third Party Logistics Provider's data related to Customer account management."

8. A new Section 9.4.3 shall be added to Section 9.4 **Licensed Product-Related Contracts with Respect to Commercialization of the Licensed Product in Canada** as follows:

"9.4.3 UGNX shall timely amend as necessary any supply, pricing, rebate or discount agreements or other commercial contracts related to the Licensed Products, including, but not limited to, the following product listing agreements between:

(a) [***];

(b) [***];

(c) [***];

(d) [***]; and

(e) [***],

to accurately reflect the name change of the DIN/NOC holder within [***] days, or earlier if required by the respective agreements or by Applicable Law, of UGNX notice to Health Canada of the DIN/NOC name change and shall provide copies of such executed amendments to KKUS. UGNX shall use Commercially Reasonable Efforts to ensure that: no such agreements or contracts shall terminate as a result of said change of the DIN/NOC holder; and there is no gap in continuity of: listing of the Licensed Product on any public or private formulary; or reimbursement or coverage of the Licensed Product with any public or private payor. UGNX shall promptly notify KKUS if it becomes aware of any such termination or gap in continuity.

9. Except as expressly provided in this Amendment, all other terms, conditions and provisions of the Collaboration Agreement shall continue in full force and effect as provided therein.

10. This Amendment may be executed in one or more counterparts, including via electronic means, all of which shall be considered one and the same agreement and shall become effective when one or more counterparts have been signed by each of the parties.

IN WITNESS WHEREOF, the Parties have executed this Amendment to be effective as of the Amendment Effective Date.

KYOWA KIRIN CO., LTD.		**ULTRAGENYX PHARMACEUTICAL INC.**	
By:	/s/ Yasuo Fujii	By:	/s/ Thomas Kassberg
Name:	Yasuo Fujii	Name:	Thomas Kassberg
Title:	Executive Officer Global Business Develop Head Director, Business Development Dept.	Title:	Chief Business Officer

Exhibit 10.20

[***] = 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

SECOND AMENDMENT TO OPTION AND LICENSE AGREEMENT

This SECOND AMENDMENT TO OPTION AND LICENSE AGREEMENT ("Second Amendment") is entered into as of December 17, 2021 ("Second Amendment Effective Date") by and between REGENXBIO Inc., a corporation organized under the laws of the State of Delaware, with offices at 9804 Medical Center Drive, Rockville, MD 20850 ("Licensor"), and Ultragenyx Pharmaceutical Inc., a corporation organized under the laws of the State of Delaware, with offices at 840 Memorial Drive, Cambridge, MA 02139 ("Licensee"). Licensor and Licensee are hereinafter referred to individually as a "Party" and collectively as the "Parties."

WHEREAS, Licensor and Licensee entered into that certain Option and License Agreement dated March 10, 2015, as amended by that First Amendment to Option and License Agreement dated March 18, 2019 (collectively, the "Original Agreement");

WHEREAS, Licensee has succeeded Dimension Therapeutics, Inc. ("Dimension") pursuant to Dimension's merger with and into Licensee; and

WHEREAS, the Parties desire to make certain amendments to the Original Agreement;

NOW, THEREFORE, in consideration of the promises and covenants contained in this Amendment, and intending to be legally bound, the Parties hereby agree as follows:

1. Definitions. Capitalized terms not defined in this Second Amendment have the meanings given such terms in the Original Agreement.

2. Amendments.

    a. Section 4.2 of the Agreement is hereby amended and restated in its entirety to read as follows:

        1.2 Specific Milestones. Without limiting Section 4.1, Licensee will meet the following milestones for each Licensed Indication with respect to which a Commercial Option is exercised:

Event	**Date**
Filing of an investigational new drug application with the FDA for the proposed initial clinical trial of a Licensed Product targeting the Licensed Indication	[***] from the Grant Date for the Licensed Indication

Licensee will provide Licensor written notice within [***] of the accomplishment of the foregoing milestone. If Licensee fails to meet the milestone for a particular Licensed Indication within the Field, the date of the milestone may, at Licensee's option, be extended for a period of [***] from the original deadline date upon a payment to Licensor of $[***] within [***] of the original deadline date; provided that Licensee will be entitled only to [***] for each Licensed Indication within the Field, and [***] extension will require a separate payment of $[***].

Notwithstanding the foregoing, for the Licensed Indication of Wilson Disease, for which Licensee exercised a Commercial Option under the Original Agreement with a Grant Date of August 3, 2015, and for which Licensee has previously extended the date of the milestone by [***], to [***], Licensee is entitled to a second extension of the date of the milestone for an additional period of [***] upon a payment to Licensor of $[***] within [***] days of [***] ("Wilson Extension"). If Licensee extends the date of the milestone for the Licensed Indication of Wilson Disease using the Wilson Extension, Licensee shall pay Licensor the following:

(a) an additional payment of $[***] upon the achievement of the foregoing milestone for the Licensed Indication of Wilson Disease; and

(b) an additional payment of $[***] for the first Licensed Product for the Licensed Indication of Wilson Disease to achieve NDA approval in the United States.

For clarity, the milestone payment set forth in Section 4.2(b) is in addition to any milestone payments set forth in Section 3.3.

[***].

3. Incorporation. Article 10 of the Original Agreement is hereby incorporated *mutatis mutandis* into this Second Amendment.

4. Effect on Original Agreement. Except as specifically amended by this Second Amendment, the Original Agreement will remain in full force and effect and is hereby ratified and confirmed. Each future reference to the Original Agreement will refer to the Original Agreement as amended by this Second Amendment. To the extent a conflict arises between the terms of the Original Agreement and this Second Amendment, the terms of this Second Amendment shall prevail but only to the extent necessary to accomplish their intended purpose.

IN WITNESS WHEREOF, the Parties, intending to be legally bound, have caused this First Amendment to License Agreement to be executed by their duly authorized representatives.

REGENXBIO INC.	ULTRAGENYX PHARMACEUTICAL INC.
By: /s/ Kenneth T. Mills	By: /s/ Vimal Srivastava
Name: Kenneth T. Mills	Name: Vimal Srivastava
Title: President & CEO	Title: SVP, Business Development & Alliance Management

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
Ultragenyx Japan K.K.	Japan

Exhibit 23.1

CONSENT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

We consent to the incorporation by reference in the following Registration Statements:

(1) 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, as amended and 2014 Employee Stock Purchase Plan, as amended of Ultragenyx Pharmaceutical Inc., and

(2) 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.;

(3) Registration Statement (Form S-8 No. 333-253007) pertaining to the 2014 Incentive Plan, as amended, the 2014 Employee Stock Purchase Plan, as amended and the Employment Inducement Plan of Ultragenyx Pharmaceutical Inc.;

(4) Registration Statement (Form S-3 No. 333-253008) and related Prospectus of Ultragenyx Pharmaceutical Inc. for the registration of common stock, preferred stock, debt securities, warrants and units;

of our reports dated February 15, 2022, 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, 2021.

/s/ Ernst & Young LLP

Redwood City, California
February 15, 2022

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 15, 2022

/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 15, 2022

/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, 2021 (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 15, 2022

/s/ Emil D. Kakkis
Emil D. Kakkis, M.D., Ph.D.
President and Chief Executive Officer
(Principal Executive Officer)

Dated: February 15, 2022

/s/ Mardi C. Dier
Mardi C. Dier
Chief Financial Officer and Executive Vice President
(Principal Financial Officer)