UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
WASHINGTON, DC 20549

FORM 10-Q

(Mark One)

☒ **QUARTERLY REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934.**

For the quarterly period ended June 30, 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 (State or other jurisdiction of incorporation or organization)	**27-2546083** (I.R.S. Employer Identification No.)
60 Leveroni Court **Novato, California** (Address of principal executive offices)	**94949** *(Zip Code)*

(415) 483-8800
(Registrant's telephone number, including area code)

Not Applicable
(Former Name, Former Address and Former Fiscal Year, if Changed Since Last Report)

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

Title of each class	Trading Symbol	Name of each exchange on which registered
Common Stock, $0.001 par value	**RARE**	**The Nasdaq Global Select Market**

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

Indicate by check mark whether the registrant has submitted electronically every Interactive Data File required to be submitted pursuant to Rule 405 of Regulation S-T (§ 232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit such files). YES ☑ NO ☐

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

Large accelerated filer	☑	Accelerated filer	☐
Non-accelerated filer	☐	Smaller reporting company	☐
		Emerging growth company	☐

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

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

As of July 28, 2021, the registrant had 67,836,060 shares of common stock issued and outstanding.

ULTRAGENYX PHARMACEUTICAL INC.

FORM 10-Q FOR THE QUARTER ENDED JUNE 30, 2021

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CAUTIONARY NOTE REGARDING FORWARD-LOOKING STATEMENTS

This Quarterly Report on Form 10-Q (the Quarterly Report) contains forward-looking statements that involve risks and uncertainties. We make such forward-looking statements pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995 and other federal securities laws. All statements other than statements of historical facts contained in this Quarterly 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 II, Item 1A. Risk Factors.

Any forward-looking statements in this Quarterly 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 II, Item 1A. Risk Factors and elsewhere in this Quarterly 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 Quarterly 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.

PART I. FINANCIAL INFORMATION

Item 1. ***Financial Statements***

ULTRAGENYX PHARMACEUTICAL INC.
CONDENSED CONSOLIDATED BALANCE SHEETS
(Unaudited)
(In thousands, except share amounts)

	June 30, 2021	December 31, 2020
Assets		
Current assets:		
Cash and cash equivalents	$ 290,875	$ 713,526
Marketable debt securities	554,881	488,007
Accounts receivable, net	24,720	23,093
Inventory	15,083	13,048
Prepaid expenses and other current assets	63,933	57,630
Total current assets	949,492	1,295,304
Property, plant, and equipment, net	104,568	73,515
Equity investments	103,710	155,375
Marketable debt securities	128,031	10,506
Right-of-use assets	38,619	40,524
Intangible assets, net	130,950	131,113
Goodwill	44,406	44,406
Other assets	12,668	8,812
Total assets	$ 1,512,444	$ 1,759,555
Liabilities and Stockholders' Equity		
Current liabilities:		
Accounts payable	$ 21,790	$ 12,923
Accrued liabilities	91,060	108,491
Contract liabilities	3,912	59,219
Lease liabilities	10,305	8,976
Total current liabilities	127,067	189,609
Contract liabilities	—	7,349
Lease liabilities	35,861	39,251
Deferred tax liabilities	33,306	33,306
Liability related to the sale of future royalties	344,039	335,665
Total liabilities	540,273	605,180
Stockholders' equity:		
Preferred stock — 25,000,000 shares authorized; nil outstanding as of June 30, 2021 and December 31, 2020	—	—
Common stock — 250,000,000 shares authorized; 67,764,950 and 66,818,520 shares issued and outstanding as of June 30, 2021 and December 31, 2020, respectively	68	67
Additional paid-in capital	2,850,016	2,773,195
Accumulated other comprehensive income	232	689
Accumulated deficit	(1,878,145)	(1,619,576)
Total stockholders' equity	972,171	1,154,375
Total liabilities and stockholders' equity	$ 1,512,444	$ 1,759,555

See accompanying notes.

ULTRAGENYX PHARMACEUTICAL INC.
CONDENSED CONSOLIDATED STATEMENTS OF OPERATIONS
(Unaudited)
(In thousands, except share and per share amounts)

	Three Months Ended June 30,		Six Months Ended June 30,	
	2021	2020	2021	2020
Revenues:				
Collaboration and license	$ 63,940	$ 50,161	$ 142,950	$ 77,376
Product sales	18,346	8,066	34,859	14,545
Non-cash collaboration royalty revenue	4,689	3,482	8,561	6,097
Total revenues	86,975	61,709	186,370	98,018
Operating expenses:				
Cost of sales	3,136	1,803	8,324	(1,700)
Research and development	113,205	80,709	260,723	193,670
Selling, general and administrative	53,410	42,252	106,668	89,768
Total operating expenses	169,751	124,764	375,715	281,738
Loss from operations	(82,776)	(63,055)	(189,345)	(183,720)
Interest income	441	1,797	1,080	4,716
Change in fair value of equity investments	(31,046)	95,200	(51,665)	102,868
Non-cash interest expense on liability related to the sale of future royalties	(8,517)	(8,429)	(16,935)	(16,511)
Other income (expense)	(67)	217	(862)	(239)
Income (loss) before income taxes	(121,965)	25,730	(257,727)	(92,886)
Provision for income taxes	(463)	(415)	(842)	(824)
Net income (loss)	$ (122,428)	$ 25,315	$ (258,569)	$ (93,710)
Net income (loss) per share:				
Basic	$ (1.81)	$ 0.42	$ (3.84)	$ (1.59)
Diluted	$ (1.81)	$ 0.41	$ (3.84)	$ (1.59)
Weighted-average shares used in computing net income (loss) per share:				
Basic	67,607,752	59,995,617	67,356,443	58,996,278
Diluted	67,607,752	61,146,231	67,356,443	58,996,278

See accompanying notes.

ULTRAGENYX PHARMACEUTICAL INC.
CONDENSED CONSOLIDATED STATEMENTS OF COMPREHENSIVE INCOME (LOSS)
(Unaudited)
(In thousands)

	Three Months Ended June 30,		Six Months Ended June 30,	
	2021	2020	2021	2020
Net income (loss)	$ (122,428)	$ 25,315	$ (258,569)	$ (93,710)
Other comprehensive income (loss):				
Foreign currency translation adjustments	103	89	(182)	40
Unrealized gain (loss) on available-for-sale securities	73	2,740	(275)	1,391
Other comprehensive income (loss):	176	2,829	(457)	1,431
Total comprehensive income (loss)	$ (122,252)	$ 28,144	$ (259,026)	$ (92,279)

See accompanying notes.

ULTRAGENYX PHARMACEUTICAL INC.
CONDENSED CONSOLIDATED STATEMENTS OF STOCKHOLDERS' EQUITY
(Unaudited)
(In thousands, except share amounts)

	Common Stock		Additional Paid-In	Accumulated Other Comprehensive	Accumulated	Total Stockholders'
	Shares	Amount	Capital	Income (Loss)	Deficit	Equity
Balance as of March 31, 2021	67,439,477	$ 67	$ 2,810,176	$ 56	$ (1,755,717)	$ 1,054,582
Stock-based compensation	—	—	27,099	—	—	27,099
Issuance of common stock under equity plan awards, net of tax	325,473	1	12,741	—	—	12,742
Other comprehensive income	—	—	—	176	—	176
Net loss	—	—	—	—	(122,428)	(122,428)
Balance as of June 30, 2021	67,764,950	$ 68	$ 2,850,016	$ 232	$ (1,878,145)	$ 972,171

	Common Stock		Additional Paid-In	Accumulated Other Comprehensive	Accumulated	Total Stockholders'
	Shares	Amount	Capital	Income (Loss)	Deficit	Equity
Balance as of December 31, 2020	66,818,520	$ 67	$ 2,773,195	$ 689	$ (1,619,576)	$ 1,154,375
Stock-based compensation	—	—	51,319	—	—	51,319
Issuance of common stock under equity plan awards, net of tax	946,430	1	25,502	—	—	25,503
Other comprehensive loss	—	—	—	(457)	—	(457)
Net loss	—	—	—	—	(258,569)	(258,569)
Balance as of June 30, 2021	67,764,950	$ 68	$ 2,850,016	$ 232	$ (1,878,145)	$ 972,171

	Common Stock		Additional Paid-In	Accumulated Other Comprehensive	Accumulated	Total Stockholders'
	Shares	Amount	Capital	Income (Loss)	Deficit	Equity
Balance as of March 31, 2020	59,488,873	$ 59	$ 2,162,667	$ (1,545)	$ (1,552,035)	$ 609,146
Issuance of common stock in connection with at-the-market offering, net of issuance costs	283,333	—	20,391	—	—	20,391
Stock-based compensation	—	—	22,428	—	—	22,428
Issuance of common stock under equity plan awards, net of tax	641,550	1	15,477	—	—	15,478
Other comprehensive income	—	—	—	2,829	—	2,829
Net income	—	—	—	—	25,315	25,315
Balance as of June 30, 2020	60,413,756	$ 60	$ 2,220,963	$ 1,284	$ (1,526,720)	$ 695,587

ULTRAGENYX PHARMACEUTICAL INC.
CONDENSED CONSOLIDATED STATEMENTS OF STOCKHOLDERS' EQUITY
(Unaudited)
(In thousands, except share amounts)

	Common Stock		Additional Paid-In	Accumulated Other Comprehensive	Accumulated	Total Stockholders'
	Shares	Amount	Capital	Income (Loss)	Deficit	Equity
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 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	—	—	42,585	—	—	42,585
Issuance of common stock upon exercise of warrants and under equity plan awards, net of tax	1,048,290	1	15,857	—	—	15,858
Other comprehensive income	—	—	—	1,431	—	1,431
Net loss	—	—	—	—	(93,710)	(93,710)
Balance as of June 30, 2020	60,413,756	$ 60	$ 2,220,963	$ 1,284	$ (1,526,720)	$ 695,587

See accompanying notes.

ULTRAGENYX PHARMACEUTICAL INC.
CONDENSED CONSOLIDATED STATEMENTS OF CASH FLOWS
(Unaudited)
(In thousands)

	Six Months Ended June 30,	
	2021	2020
Operating activities:		
Net loss	$ (258,569)	$ (93,710)
Adjustments to reconcile net loss to net cash used in operating activities:		
Stock-based compensation	51,345	42,558
Amortization of premium (discount) on marketable debt securities, net	2,511	(149)
Depreciation and amortization	6,488	6,036
Change in fair value of equity investments	51,665	(102,868)
Non-cash collaboration royalty revenue	(8,561)	(6,097)
Non-cash interest expense on liability related to the sale of future royalties	16,935	16,511
Other	511	(14)
Changes in operating assets and liabilities:		
Accounts receivable	(1,669)	9,482
Inventory	(2,174)	521
Prepaid expenses and other assets	(9,002)	(6,136)
Accounts payable, accrued, and other liabilities	(11,526)	(8,833)
Contract liabilities	(62,656)	134,898
Net cash used in operating activities	(224,702)	(7,801)
Investing activities:		
Purchase of property, plant, and equipment	(36,485)	(18,179)
Purchase of marketable debt securities	(664,347)	(456,331)
Purchase of equity investments	—	(9,600)
Proceeds from sale of marketable debt securities	70,548	28,850
Proceeds from maturities of marketable debt securities	406,614	273,996
Net cash used in investing activities	(223,670)	(181,264)
Financing activities:		
Proceeds from the issuance of common stock in connection with the license agreement, net	—	55,268
Proceeds from the issuance of common stock in connection with at-the-market offering, net	—	20,391
Proceeds from the issuance of common stock from exercise of warrants and equity plan awards, net	25,503	15,858
Other	(226)	(91)
Net cash provided by financing activities	25,277	91,426
Effect of exchange rate changes on cash	(323)	(198)
Net decrease in cash, cash equivalents and restricted cash	(423,418)	(97,837)
Cash, cash equivalents and restricted cash at beginning of period	726,294	436,244
Cash, cash equivalents and restricted cash at end of period	$ 302,876	$ 338,407
Supplemental disclosures of non-cash information:		
Acquired lease liabilities arising from obtaining right-of-use assets	$ 2,301	$ 10,403

See accompanying notes.

1. Organization

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

The Company is focused on the identification, acquisition, development, and commercialization of novel products for the treatment of serious rare and ultra-rare genetic diseases. The Company operates as one reportable segment. The Company has three commercially approved products. Crysvita® (burosumab) is approved in the United States by the U.S. Food and Drug Administration (FDA) and in Canada for the treatment of X-linked hypophosphatemia (XLH) in adult and pediatric patients one year of age and older, and is approved in the European Union (EU) and the United Kingdom, for the treatment of XLH with radiographic evidence of bone disease in children one year of age and older, adolescents, and adults. In Brazil, 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 United States 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 United States and Canada for the treatment of pediatric and adult patients severely affected by long-chain fatty acid oxidation disorders (LC-FAOD).

In addition to the approved products, the Company has the following ongoing clinical development programs:

- DTX401 is an adeno-associated virus 8 (AAV8) gene therapy product candidate for the treatment of patients with glycogen storage disease type Ia (GSDIa);
- 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) 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 need to raise additional capital to fully implement its business plans. Through June 30, 2021, the Company has relied primarily on its sale of equity securities, its revenues 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 Presentation

The accompanying unaudited Condensed Consolidated Financial Statements include the accounts of the Company and its wholly-owned subsidiaries and have been prepared in accordance with U.S. generally accepted accounting principles (GAAP) for interim financial information and in accordance with the instructions to Form 10-Q and Rule 10-01 of Regulation S-X. Accordingly, they do not include all of the information and footnotes required by GAAP for complete financial statements. The unaudited interim consolidated financial statements have been prepared on the same basis as the annual financial statements. In the opinion of management, the accompanying unaudited Condensed Consolidated financial Statements reflect all adjustments (consisting only of normal recurring adjustments) considered necessary for a fair presentation. These financial statements should be read in conjunction with the audited financial statements and notes thereto for the preceding fiscal year contained in the Company's Annual Report on Form 10-K filed on February 12, 2021 with the United States Securities and Exchange Commission (SEC).

The results of operations for the three and six months ended June 30, 2021 are not necessarily indicative of the results to be expected for the year ending December 31, 2021. The Condensed Consolidated Balance Sheet as of December 31, 2020 has been derived from audited financial statements at that date, but does not include all of the information required by GAAP for complete financial statements.

Use of Estimates

The accompanying consolidated financial statements have been prepared in accordance with 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

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 same such amounts shown in the consolidated statement of cash flows (in thousands):

	June 30,	
	2021	2020
Cash and cash equivalents	$ 290,875	$ 335,639
Restricted cash included in prepaid expenses and other current assets	10,000	847
Restricted cash included in other assets	2,001	1,921
Total cash, cash equivalents, and restricted cash shown in the statements of cash flows	$ 302,876	$ 338,407

Credit Losses

The Company is exposed to credit losses primarily through receivables from customers and collaborators and through its available-for-sale debt securities. 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'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. There was no material allowance recorded for losses on receivables and available-for-sale debt securities which were attributable to credit risk for the three and six months ended June 30, 2021 and 2020.

Revenue Recognition

Collaboration and license revenue

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

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 7. 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 an effect on earnings in the period of the adjustment.

3. Financial Instruments

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 determines the fair value of its equity investments in Arcturus Therapeutics Holdings Inc. (Arcturus) and Solid Biosciences Inc. (Solid) by using the quoted market prices, which are Level 1 fair value measurements.

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

	June 30, 2021			
	Level 1	**Level 2**	**Level 3**	**Total**
Money market funds	$ 206,674	$ —	$ —	$ 206,674
Certificate of deposits and time deposits	—	17,501	—	17,501
Corporate bonds	—	237,296	—	237,296
Commercial paper	—	341,522	—	341,522
Asset-backed securities	—	55,020	—	55,020
U.S. Government Treasury and agency securities	12,500	42,109	—	54,609
Debt securities in government-sponsored entities	—	28,751	—	28,751
Investments in Arcturus and Solid common stock	103,091	—	—	103,091
Total	$ 322,265	$ 722,199	$ —	$ 1,044,464

	December 31, 2020			
	Level 1	**Level 2**	**Level 3**	**Total**
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. The Company measured the fair value of the warrant by applying the Black-Scholes option pricing method and utilizing the following inputs: stock price, strike price, volatility, risk-free interest rate, and expected term. The Company recognizes the interest income on the convertible promissory note based on the effective interest rate method over the life of the note. As of June 30, 2021, the balance of the convertible promissory note was $2.2 million, including $0.4 million in interest receivable, and was recorded in other assets, and the allocated fair value of the warrant was $0.6 million and was recorded in equity investments.

In December 2020, the Company invested $1.4 million in Mazi Therapeutics, Inc. (Mazi), a private pharmaceutical company founded by a current employee of the Company, in the form of a convertible promissory note that matures in two years, if not converted earlier. As of June 30, 2021, the balance of the convertible promissory note was $1.4 million.

4. Balance Sheet Components

Cash Equivalents and Investments

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

	June 30, 2021			
		Gross Unrealized		
	Amortized Cost	Gains	Losses	Estimated Fair Value
Money market funds	$ 206,674	$ —	$ —	$ 206,674
Certificate of deposits and time deposits	17,501	—	—	17,501
Corporate bonds	237,310	45	(59)	237,296
Commercial paper	341,522	—	—	341,522
Asset-backed securities	55,015	11	(6)	55,020
U.S. Government Treasury and agency securities	54,605	7	(3)	54,609
Debt securities in government-sponsored entities	28,761	4	(14)	28,751
Total	$ 941,388	$ 67	$ (82)	$ 941,373

	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 June 30, 2021, the remaining contractual maturities of available-for-sale securities were less than five years. There have been no significant realized gains or losses on available-for-sale securities for the three and six months ended June 30, 2021 and 2020. All marketable securities with unrealized losses at June 30, 2021 have been in a loss position for less than twelve months 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):

	June 30, 2021	December 31, 2020
Work-in-process	$ 9,457	$ 7,184
Finished goods	5,626	5,864
Total inventory	$ 15,083	$ 13,048

Accrued Liabilities

Accrued liabilities consist of the following (in thousands):

	June 30, 2021	December 31, 2020
Research, clinical study, and manufacturing expenses	$ 22,551	$ 25,875
Payroll and related expenses	41,545	58,176
Other	26,964	24,440
Total accrued liabilities	$ 91,060	$ 108,491

5. Revenue

The following table disaggregates total revenues from customers (in thousands):

	Three Months Ended June 30,		Six Months Ended June 30,	
	2021	2020	2021	2020
Collaboration and license revenue:				
Crysvita collaboration revenue in profit-share territory	$ 41,756	$ 29,806	$ 78,016	$ 57,021
Crysvita royalty revenue in European territory	228	1,498	228	1,498
Daiichi Sankyo	21,956	18,857	64,706	18,857
Total collaboration and license revenue	63,940	50,161	142,950	77,376
Product sales:				
Crysvita	2,900	2,549	8,772	4,159
Mepsevii	5,399	4,185	9,006	7,610
Dojolvi	10,047	1,332	17,081	2,776
Total product sales	18,346	8,066	34,859	14,545
Crysvita non-cash collaboration royalty revenue	4,689	3,482	8,561	6,097
Total revenues	$ 86,975	$ 61,709	$ 186,370	$ 98,018

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

	Three Months Ended June 30,		Six Months Ended June 30,	
	2021	2020	2021	2020
North America	$ 75,567	$ 51,931	$ 163,309	$ 82,288
Europe	6,700	6,548	12,337	10,705
Latin America	4,708	3,230	10,724	5,025
Total revenues	$ 86,975	$ 61,709	$ 186,370	$ 98,018

The following table presents changes in the contract liabilities (in thousands):

	Six Months Ended June 30,	
	2021	2020
Balance of contract liabilities at beginning of period	$ 66,568	$ —
Additions	2,050	153,755
Deductions	(64,706)	(18,857)
Balance of contract liabilities at end of period	$ 3,912	$ 134,898

See Note 6 for additional details on contract liabilities activities.

The Company’s largest accounts receivable balance accounted for 58% and 71% of the total accounts receivable balance as of June 30, 2021 and December 31, 2020, respectively, and was due from a collaboration partner.

6. License and Research Agreements

Kyowa Kirin Collaboration and License Agreement

In August 2013, the Company entered into a collaboration and license agreement with Kyowa Kirin Co., Ltd. (KKC, formerly Kyowa Hakko Kirin Co., Ltd. or KHK). Under the terms of this collaboration and license agreement, as amended, the Company and KKC collaborate on the development and commercialization of Crysvita in the field of orphan diseases in the United States and Canada, or the profit-share territory, and in the European Union, United Kingdom, and Switzerland, or the European territory, and the Company has the right to develop and commercialize such products in the field of orphan diseases in Mexico and Central and South America, or Latin America. In May 2017, the Company entered into an agreement with a wholly-owned subsidiary of KKC pursuant to which it was granted the right to commercialize Crysvita in Turkey.

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. Crysvita was approved in the European Union and United Kingdom in February 2018 and was approved by the FDA in April 2018.

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

Collaboration revenue related to sales in profit-share territory

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

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

Royalty revenue related to sales in European territory

KKC has the commercial responsibility for Crysvita in the European territory. In December 2019, the Company sold its right to receive royalty payments based on sales in the European territory to Royalty Pharma, effective January 1, 2020, as further described in Note 7. 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 recorded the royalty revenue as non-cash royalty revenues. During the three months ended June 30, 2021 and 2020, there was a change in the 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 European territory.

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

	Three Months Ended June 30,		Six Months Ended June 30,	
	2021	2020	2021	2020
Company's share of revenue in profit-share territory	$ 41,756	$ 29,806	$ 78,016	$ 57,021
Royalty revenue in European territory	228	1,498	228	1,498
Non-cash royalty revenue in European territory	4,689	3,482	8,561	6,097
Total	$ 46,673	$ 34,786	$ 86,805	$ 64,616

Product revenue related to sales in other territories

The Company is responsible for commercializing Crysvita in Latin America and Turkey. The Company is considered the principal in these territories as the Company controls the product before it is transferred to the customer. Accordingly, the Company records revenue on a gross basis related to the sale of Crysvita once the product is delivered and the risk and title of the product is transferred to the distributor. The Company recorded product sales of $2.9 million and $8.8 million for the three and six months ended June 30, 2021, respectively, and $2.5 million and $4.2 million for the three and six months ended June 30, 2020, respectively, net of estimated product returns and other deductions. KKC has the option to assume responsibility for commercialization efforts in Turkey from the Company, after a certain minimum period.

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

Cost sharing payments

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

	Three Months Ended June 30,		Six Months Ended June 30,	
	2021	2020	2021	2020
Research and development	$ 5,171	$ 5,168	$ 11,356	$ 10,658
Selling, general and administrative	7,576	5,965	15,071	13,017
Total	$ 12,747	$ 11,133	$ 26,427	$ 23,675

Collaboration receivable and payable

The Company had accounts receivable from KKC in the amount of $14.7 million and $16.4 million from profit-share revenue and royalties and other receivables recorded in prepaid and other current assets of $3.8 million and $9.6 million and accrued liabilities of $2.7 million and $2.4 million from commercial and development activity reimbursements, as of June 30, 2021 and December 31, 2020, respectively.

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 has 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, 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.

Arcturus

In October 2015, the Company entered into a Research Collaboration and License Agreement with Arcturus whereby the Company and Arcturus would collaborate on the research and development of therapies for select rare diseases. Arcturus has the primary responsibility for conducting certain research services, funded by the Company, and the Company is responsible for development and commercialization costs.

On a product-by-product basis, the Company may be 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. The Company may also be 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. For the three and six months ended June 30, 2021 and 2020, there were no research and development expenses incurred for the funding of certain research services received from Arcturus.

In May 2020, the Company exercised an option to purchase 600,000 shares of Arcturus' common stock at $16.00 per share, or a total purchase price of $9.6 million. In December 2020, the Company sold 800,000 shares of Arcturus' common stock at a weighted-average price of $100.81 per share and received net proceeds of $79.8 million. The Company has elected to apply the fair value option to account for the equity investment in Arcturus. As of June 30, 2021, the Company held 2,200,000 shares of Arcturus' common stock.

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

	Arcturus common stock	Option to purchase additional shares of 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	(20,988)	—	(20,988)
June 30, 2021	$ 74,448	$ —	$ 74,448

The Company recorded $16.4 million and $21.0 million in unrealized losses for the three and six months ended June 30, 2021, respectively, and $95.2 million and $102.9 million in unrealized gains for the three and six months ended June 30, 2020, respectively, from the fair value adjustments on the equity investment in Arcturus securities.

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 quarter ended March 31, 2020. The Company has the 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 three months ended March 31, 2020, the Company recorded the option extension payment of $25.0 million as an in-process research and development expense.

REGENXBIO, Inc.

In March 2020, the Company executed a License Agreement with REGENXBIO, Inc. (REGENEX), 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 three months ended March 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.

Daiichi Sankyo

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

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

The Company also entered into a Stock Purchase Agreement (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 during the first quarter of 2020. The fair market value of the common stock issued to Daiichi Sankyo was $55.3 million based on the stock price of $44.43 per share on the date of issuance, resulting in a $19.7 million premium on the 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 negotiated in contemplation of one another. The Company evaluated the License Agreement and the Sublicense Agreement under ASC 606 and determined that the performance obligations under the agreements are (i) intellectual property with respect to its HeLa PCL and HEK293 transient transfection manufacturing technology platforms together with the initial technical assistance and technology transfer services, which are expected to be completed in the fourth quarter of 2021, and (ii) the transfer of any know-how and improvements after the completion of the initial technology transfer through the end of the three year technology transfer period ending March 2023.

As of June 30, 2021, the Company has determined that the total transaction price of the License Agreement was $183.6 million which was comprised of the $19.7 million premium from the SPA, the $125.0 million upfront payment, the $25.0 million in unconstrained milestone payments, $8.0 million from the Sublicense Agreement, and the $5.9 million estimated reimbursement amount for delivering the license and technology services. Total revenue recognized under the license agreement through June 30, 2021 is $153.9 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 will be recognized over an initial period which is estimated to end in the fourth quarter of 2021, measuring the progress toward complete satisfaction of the individual performance obligation using an input measure. Revenue for know-how and improvements after the completion of technology transfer will be recognized on a straight-line basis over the remaining technology transfer period, which ends in March 2023, as it is expected that Daiichi Sankyo will receive and consume the benefits consistently throughout the period. The estimated period to complete the technology transfer services and the related milestones payments, if any, are subject to revised estimates which could be impacted by limitations or delays from the COVID-19 pandemic, successful scale-up of the manufacturing, and other changes that may impact timing. Royalties from commercial sales will be accounted for as revenue upon achievement of such sales, assuming all other revenue recognition criteria are met.

The Company recognized $22.0 million and $64.7 million for the three and six months ended June 30, 2021, respectively, and $18.9 million for the three and six months ended June 30, 2020, in revenue related to this arrangement. Accordingly, the Company had recorded $3.9 million as contract liabilities, net, as of June 30, 2021. The Company recorded an accounts receivable related to the above agreements of $0.8 million as of June 30, 2021.

Solid Biosciences, Inc.

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

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

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

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

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

		Solid common stock
Acquisition of investment in Solid common stock in October 2020	$	26,843
Change in fair value		32,477
December 31, 2020		59,320
Change in fair value		(30,677)
June 30, 2021	$	28,643

The Company recorded $14.6 million and $30.7 million in unrealized losses for the three and six months ended June 30, 2021, respectively, from the fair value adjustments on the equity investment in Solid securities.

Mereo BioPharma 3 Limited

In December 2020, the Company entered into a License and Collaboration Agreement with Mereo BioPharma 3 Limited, or Mereo, to collaborate on the development of setrusumab. Under the terms of the agreement, the Company will lead future global development of setrusumab in both pediatric and adult patients with Osteogenesis Imperfecta, or OI. The Company was granted an exclusive license to develop and commercialize setrusumab in the U.S., Turkey, and the rest of the world, excluding the European Economic Area, United Kingdom, and Switzerland, 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 transaction in January 2021, the Company made a payment of $50.0 million to Mereo and will be required to make payments of up to $254.0 million upon the achievement of certain clinical, regulatory, and commercial milestones. The Company will pay for all global development costs as well as tiered double-digit percentage royalties to Mereo on net sales in the U.S., Turkey, and the rest of the world (excluding the Mereo Territory), and Mereo will pay the Company a fixed double-digit percentage royalty on net sales in the Mereo Territory.

Although Mereo 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 Mereo. Prior to the achievement of certain development milestones, all consideration paid to Mereo represents rights to potential future benefits associated with Mereo's in-process research and development activities, which have not reached technological feasibility and have no alternative future use. Accordingly, for the three months ended March 31, 2021, the Company recorded the upfront payment of $50.0 million as in-process research and development expense.

7. 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 9.8% for the three months ended June 30, 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		(8,561)
Non-cash interest expense		16,935
June 30, 2021	$	344,039

8. Stock-Based Awards

The 2014 Incentive Plan (the 2014 Plan) provides for automatic annual increases in shares available for grant, beginning on January 1, 2015 through January 1, 2024. As of June 30, 2021, there were 4,103,718 shares reserved under the 2014 Plan for the future issuance of equity awards, 3,956,907 shares reserved for the 2014 Employee Stock Purchase Plan, and 488,223 shares reserved for the Employment Inducement Plan.

The table below sets forth the stock-based compensation expense for the periods presented (in thousands):

	Three Months Ended June 30,				Six Months Ended June 30,			
	2021		2020		2021		2020	
Cost of sales	$	223	$	112	$	602	$	180
Research and development		15,094		12,856		28,583		23,785
Selling, general and administrative		11,825		9,441		22,255		18,616
Total stock-based compensation expense	$	27,142	$	22,409	$	51,440	$	42,581

9. Net Income (Loss) Per Share

Basic net income (loss) per share has been computed by dividing the net income (loss) by the weighted-average number of shares of common stock outstanding during the period. Diluted net income (loss) per share is calculated by dividing net income (loss) by the weighted-average number of shares of common stock and potential dilutive securities outstanding during the period. For the three and six months ended June 30, 2021 and the six months ended June 30, 2020, there were no differences between basic and diluted net loss per share since the effect of the dilutive securities would have been antidilutive and therefore were excluded from the diluted net loss per share calculation. The following table sets forth the computation of the basic and diluted net income (loss) per share (in thousands, except share and per share data):

	Three Months Ended June 30,				Six Months Ended June 30,			
	2021		2020		2021		2020	
Net income (loss), basic and diluted	$	(122,428)	$	25,315	$	(258,569)	$	(93,710)
Weighted-average shares used in computing net income (loss) per share, basic		67,607,752		59,995,617		67,356,443		58,996,278
Weighted-average effect of dilutive securities:								
Options to purchase common stock and RSUs		—		1,150,614		—		—
Weighted-average shares used in computing net income (loss) per share, diluted		67,607,752		61,146,231		67,356,443		58,996,278
Net income (loss) per share:								
Basic	$	(1.81)	$	0.42	$	(3.84)	$	(1.59)
Diluted	$	(1.81)	$	0.41	$	(3.84)	$	(1.59)

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

	Three Months Ended June 30,		Six Months Ended June 30,	
	2021	2020	2021	2020
Options to purchase common stock and restricted stock units	8,491,447	5,204,036	8,287,698	8,643,439
Employee stock purchase plan	8,621	10,952	4,334	5,476
Common stock warrants	—	—	—	59,222
	8,500,068	5,214,988	8,292,032	8,708,137

10. Equity Transactions

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. For the year ended December 31, 2020, the total proceeds that the Company received from the offering were approximately $435.6 million, net of underwriting discounts and commissions.

In May 2021, the Company entered into an Open Market Sale Agreement with Jefferies LLC, or 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 at-the-market offerings through Jefferies. As of June 30, 2021, the Company has not sold any shares under the arrangement.

11. Accumulated Other Comprehensive Income

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

	June 30, 2021	December 31, 2020
Foreign currency translation adjustments	$ 247	$ 429
Unrealized gain (loss) on available-for-sale securities	(15)	260
Total accumulated other comprehensive income	$ 232	$ 689

Item 2. *Management's Discussion and Analysis of Financial Condition and Results of Operations*

The following discussion and analysis of our financial condition and results of operations should be read in conjunction with the accompanying unaudited consolidated financial statements and related notes in Item 1 and with the audited consolidated financial statements and the related notes included in our Annual Report on Form 10-K for the year ended December 31, 2020 (the "Annual Report").

Overview

Ultragenyx Pharmaceutical Inc. (we or the Company) is a biopharmaceutical company focused on the identification, acquisition, development, and commercialization of novel products for the treatment of serious rare and ultra-rare genetic diseases. We target diseases for which the unmet medical need is high, the biology for treatment is clear, and for which there are typically no approved therapies treating the underlying disease. Our strategy, which is predicated upon time- and cost-efficient drug development, allows us to pursue multiple programs in parallel with the goal of delivering safe and effective therapies to patients with the utmost urgency.

Impact of COVID-19 Pandemic

Our business operations have been and continue to be affected by the COVID-19 pandemic. In addition to some impact on our preclinical manufacturing activities and certain regulatory interactions, we have experienced interruptions to our clinical trial activities, primarily due to delays or disruptions to patient enrollment and dosing as a result of shelter-in-place orders or quarantines, and certain data from our gene therapy product candidates was delayed as a result of the COVID-19 pandemic. The continuing outbreak has caused delays in delivery of ancillary clinical trial materials as certain of our third-party manufacturers or suppliers have prioritized and allocated more resources and capacity to supply drug product or raw materials to other companies engaged in the study 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. We have also restricted access to our facilities to personnel and third parties who perform critical activities that must be performed on-site and as a result, most of our personnel currently work remotely. Such remote working policies may negatively impact productivity and disrupt our business operations.

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

Approved Therapies and Clinical Product Candidates

Our current approved therapies and clinical-stage pipeline consist of four product categories: biologics, small molecules, gene therapy, and nucleic acid product candidates. See section entitled "Recent Program Updates" below for a description of recent updates to certain of our approved therapies and clinical-stage pipeline products.

Our biologic products include approved therapies Crysvita® (burosumab), Mepsevii® (vestronidase alfa) and UX143 in clinical development:

- Crysvita is an antibody administered via subcutaneous injection that targets fibroblast growth factor 23, or FGF23, developed for the treatment of XLH, a rare, hereditary, progressive and lifelong musculoskeletal disorder characterized by renal phosphate wasting caused by excess FGF23 production. There are approximately 48,000 patients with XLH in the developed world, including approximately 36,000 adults and 12,000 children. Crysvita is the only approved treatment that addresses the underlying cause of XLH. Crysvita is approved in the United States and Canada for the treatment of XLH in adult and pediatric patients six months of age and older. In the European Union, or the EU, and the United Kingdom, Crysvita is approved for the treatment of XLH with radiographic evidence of bone disease in children one year of age and older, adolescents, and adults. In Brazil, 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 approved in the United States for the treatment of FGF23-related hypophosphatemia in tumor-induced osteomalacia, or TIO, associated with phosphaturic mesenchymal tumors that cannot be curatively resected or localized in adults and pediatric patients 2 years of age and older. TIO can lead to severe hypophosphatemia, osteomalacia, fractures, fatigue, bone and muscle pain, and muscle weakness.

  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.

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

- UX143 (setrusumab), which is subject to our collaboration agreement with Mereo and the lead clinical asset in our bone endocrinology franchise, 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. Setrusumab is being studied for the treatment of osteogenesis imperfecta (OI) and has received orphan drug designation from the FDA and European Medicines Agency (EMA), rare pediatric disease designation from the FDA, and was accepted into the EMA's Priority Medicines program (PRIME). There are an estimated 60,000 patients in the developed world affected by OI. Initiation of a pediatric Phase 2/3 study is expected in the second half of 2021 and a separate study is currently being planned for adults with OI.

Our small molecule products include the approved therapy Dojolvi® (triheptanoin):

- 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 approved and commercially available in the United States and Canada as a source of calories and fatty acids for the treatment of pediatric and adult patients with molecularly confirmed LC-FAOD. We have submitted Dojolvi to the Brazilian Health Regulatory Agency (ANVISA) seeking marketing authorization. There are approximately 8,000 to 14,000 patients in the developed world with LC-FAOD.

Our clinical-stage gene therapy pipeline includes DTX401, DTX301, DTX201 and UX701:

- 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. GSDIa is the most common genetically inherited glycogen storage disease, with an estimated 6,000 patients in the developed world affected by GSDIa. A Pediatric Investigation Plan, or PIP, was accepted by EMA. DTX401 has been granted Orphan Drug Designation in both the United States and in the EU, Regenerative Medicine Advanced Therapy (RMAT) designation and Fast Track designation in the United States.
- 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 there are approximately 10,000 patients in the developed world with OTC deficiency, of which we estimate approximately 80% are classified as late-onset, our target population. DTX301 has received Orphan Drug Designation in both the United States and in the EU and Fast Track Designation in the United States.
- DTX201 is a Factor VIII gene therapy program for the treatment of hemophilia A that is being developed in collaboration with Bayer Healthcare LLC, or Bayer. Hemophilia A is the most common form of hemophilia with approximately 144,000 patients in the developed world. The first three cohorts with two patients each have been dosed using material from our proprietary HeLa manufacturing platform. Enrollment of additional dose cohorts in the Phase 1/2 study is currently ongoing.
- UX701 is an AAV type 9 gene therapy product candidate designed to deliver stable expression of a truncated version of the ATP7B copper transporter following a single intravenous infusion to patients with Wilson disease. Wilson disease affects more than 50,000 individuals in the developed world. UX701 was granted Orphan Drug Designation in the United States and EU.

Our clinical-stage nucleic acid pipeline includes GTX-102 for the treatment of Angelman syndrome, and UX053 for the treatment of GSDIII:

- 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 an ongoing Phase 1/2 clinical study. The study is currently on hold in the U.S. while discussions are ongoing with the FDA. The study is expected to begin enrollment later this year.
- UX053 is an mRNA product candidate designed for the treatment of patients with GSDIII, a disease caused by a glycogen debranching enzyme (AGL) deficiency that results in glycogen accumulation in the liver and muscle. GSDIII affects more than 10,000 patients in the developed world. UX053 was granted Orphan Drug Designation in the United States and EU.

The following table summarizes our approved products and clinical product candidate pipeline:

Products	Description	Indication	IND Stage[1]	Phase 1	Phase 2	Phase 3	Approved	Upcoming Milestones
Biologics								
Crysvita® (burosumab)[2]	Anti-FGF23 monoclonal antibody	XLH						
Crysvita® (burosumab)[2]	Anti-FGF23 monoclonal antibody	TIO						
Mepsevii® (vestronidase alfa)	Enzyme replacement	MPSVII						
UX143 (setrusumab)[3]	Fully human monoclonal antibody	OI						Pediatric Ph2/3 initiation in 2H21
Small Molecules								
Dojolvi® (triheptanoin)	Substrate replacement	LC-FAOD						
AAV Gene Therapy								
DTX401	AAV8 Gene Therapy	GSDIa						Ph3 initiation in 2H21
DTX301	AAV8 Gene Therapy	OTC						Ph3 initiation in 2H21
DTX201[4]	AAVhu37 Gene Therapy	HemA						
UX701	AAV9 Gene Therapy	Wilson						Ph1/2/3 initiation in 2H21
Nucleic Acid								
GTX-102[5]	Antisense Oligonucleotide	Angelman Syndrome						Resume Ph1/2 study in 2H21
UX053	mRNA	GSDIII						Ph1/2 initiation in 2H21

1: IND submitted or expected to be submitted within the near term
2: In collaboration with Kyowa Kirin Company
3: In collaboration with Mereo BioPharma
4: In collaboration with Bayer
5: Ultragenyx has option to acquire GTX-102 from GeneTx

Recent Program Updates

Crysvita for the treatment of X-Linked Hypophosphatemia (XLH)

In July 2021, our collaboration partner KKC, announced that the European Commission (EC) approved Crysvita for self-administration as a treatment option when recommended by the treating physician, for pediatric and adult patients with XLH.

In July 2021, Crysvita was approved by Colombia's Instituto Nacional de Vigilancia de Medicamentos y Alimentos, or INVIMA, for treatment of XLH in adult and pediatric patients one year of age and older.

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

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

Following a productive meeting with the FDA, we submitted an amended protocol. We have received feedback on the amended protocol and will make additional revisions in order to resume the study in the U.S.

Clinical data from newly treated patients in the U.K. and Canada are currently expected to be presented before the end of 2021.

DTX401 for the treatment of GSDIa

At the American Society of Gene & Cell Therapy (ASGCT) Annual Meeting in May 2021 we presented additional long-term clinical data demonstrating a durable response lasting more than 2.5 years following treatment with DTX401 in patients with GSDIa. We are currently in the process of initiating a Phase 3 study with a 48-week primary efficacy analysis period and plan to enroll approximately 50 patients 8 years of age and older, randomized 1:1 to DTX401 (1.0 x 10^13 GC/kg dose) or placebo. The coprimary endpoints are the reduction in oral glucose replacement with cornstarch while maintaining and improved glucose control assessed by continuous glucose monitoring. The first patient in the Phase 3 study is currently expected to be dosed in the second half of 2021.

DTX301 for the treatment of OTC deficiency

At the ASGCT Annual Meeting in May 20201 we presented additional long-term clinical data showing durable metabolic control and sustained responses lasting more than three years following treatment with DTX301 in patients with OTC deficiency. 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 patient in the Phase 3 study is currently expected to be dosed in the second half of 2021.

UX701 for the treatment of Wilson Disease

We are currently in the process of initiating a seamless, single-protocol Phase 1/2/3 study. The first part of the study is expected to enroll approximately 27 patients (nine per cohort), randomized 2:1 to DTX701, manufactured using the company’s proprietary HeLa 2.0 producer cell line (PCL) process at the 2,000 liter scale, or placebo. The dose cohorts will be enrolled sequentially using ascending doses. The patients will be followed for 52 weeks before transitioning to long-term follow-up and selecting a pivotal dose. The dose will be determined based on the safety profile, changes in biomarkers of copper metabolism, and the reduction in the use of the current standard of care. The first patient in the Phase 1/2/3 study is expected to be dosed in the second half of 2021.

UX053 for the treatment of GSDIII

In June 2021, UX053 was granted Orphan Drug Designation (ODD) in the U.S. by the FDA and in July 2021, ODD was granted by the European Commission (EC). Enrollment in a Phase 1/2 study is currently expected to begin in the second half of 2021.

Financial Operations Overview

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

We have incurred net losses in each year since inception. Our net loss was $122.4 million and $258.6 million for the three and six months ended June 30, 2021, respectively. Our net income was $25.3 million for the three months ended June 30, 2020 and our net loss was $93.7 million for the six months ended June 30, 2020. Net loss for the three and six months ended June 30, 2021 included losses of $31.0 million and $51.7 million resulting from changes in fair value of our investments in Arcturus Therapeutics Holdings Inc. (Arcturus) and Solid Biosciences Inc. (Solid) equity securities. Net income (loss) for the three and six months ended June 30, 2020 included gains of $95.2 million and $102.9 million, respectively, resulting from changes in the fair value of our investment in Arcturus. Other than changes in the fair value of our investments, 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 three months ended June 30, 2021, our total revenues increased to $87.0 million, compared to $61.7 million for the same period in 2020 and for the six months ended June 30, 2021, increased to $186.4 million, compared to $98.0 million for the same period in 2020. Revenue for the three months ended June 30, 2021 and 2020 included $22.0 million and $18.9 million, respectively, and for the six months ended June 30, 2021 and 2020 included $64.7 million and $18.9 million, respectively, in revenue from our collaboration and license agreement with Daiichi Sankyo Co., Ltd. (Daiichi Sankyo) which we executed in March 2020. The remainder of the increase was driven by higher revenue from Crysvita collaboration revenue in the profit-share territory, an increase in revenue for our approved products and an increase in collaboration royalty revenue.

As of June 30, 2021, we had $973.8 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. There have been no material changes in our critical accounting policies during the six months ended June 30, 2021, as compared to those disclosed in "Management's Discussion and Analysis of Financial Condition and Results of Operations — Critical Accounting Policies and Significant Judgments and Estimates" in our Annual Report.

Results of Operations

Comparison of the three and six months ended June 30, 2021 to the three and six months ended June 30, 2020:

Revenue (dollars in thousands)

	Three Months Ended June 30, 2021	Three Months Ended June 30, 2020	Dollar Change	% Change
Collaboration and license revenue:				
Crysvita collaboration revenue in profit-share territory	$ 41,756	$ 29,806	$ 11,950	40%
Crysvita royalty revenue in European territory	228	1,498	(1,270)	-85%
Daiichi Sankyo	21,956	18,857	3,099	16%
Total collaboration and license revenue	63,940	50,161	13,779	27%
Product sales:				
Crysvita	2,900	2,549	351	14%
Mepsevii	5,399	4,185	1,214	29%
Dojolvi	10,047	1,332	8,715	654%
Total product sales	18,346	8,066	10,280	127%
Crysvita non-cash collaboration royalty revenue	4,689	3,482	1,207	35%
Total revenues	$ 86,975	$ 61,709	$ 25,266	41%

	Six Months Ended June 30, 2021	Six Months Ended June 30, 2020	Dollar Change	% Change
Collaboration and license revenue:				
Crysvita collaboration revenue in profit-share territory	$ 78,016	$ 57,021	$ 20,995	37%
Crysvita royalty revenue in European territory	228	1,498	(1,270)	-85%
Daiichi Sankyo	64,706	18,857	45,849	243%
Total collaboration and license revenue	142,950	77,376	65,574	85%
Product sales:				
Crysvita	8,772	4,159	4,613	111%
Mepsevii	9,006	7,610	1,396	18%
Dojolvi	17,081	2,776	14,305	515%
Total product sales	34,859	14,545	20,314	140%
Crysvita non-cash collaboration royalty revenue	8,561	6,097	2,464	40%
Total revenues	$ 186,370	$ 98,018	$ 88,352	90%

For the three and six months ended June 30, 2021, the Company's share of Crysvita collaboration revenue in the profit-share territory increased by $12.0 million and $21.0 million, respectively, as compared to the same periods 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 have recorded the royalty revenue as non-cash royalty revenues. During the three months ended June 30, 2021 and 2020, there were changes in the estimates on the 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 European territory.

In March 2020, we executed a license agreement with Daiichi Sankyo, pursuant to which we granted Daiichi Sankyo a non-exclusive license to intellectual property, including know-how and patent applications, with respect to our HeLa PCL and HEK293 transient transfection manufacturing technology platforms for AAV-based gene therapy products. We will also provide certain technical assistance and technology transfer services during the technology transfer period of three years to enable Daiichi Sankyo to use the technologies for its internal gene therapy programs. For the three and six months ended June 30, 2021, the collaboration and license revenue from this arrangement, which is recognized based on the progress toward complete satisfaction of the individual performance obligation using an input measure, increased by $3.1 million and $45.8 million, respectively, as compared to the same periods in 2020. We expect to recognize the remaining revenue allocated to the intellectual property and the transfer services as revenue by the end of 2021.

The increases in product sales of $10.3 million and $20.3 million for the three and six months ended June 30, 2021, respectively, compared to the same periods in 2020 were primarily due to the commercial launch of Dojolvi in the United States in the third quarter of 2020, continuing increase in demand for Crysvita and Mepsevii, and an increase in sales of Dojolvi under our named patient program in certain countries.

The increases in Crysvita non-cash collaboration royalty revenue of $1.2 million and $2.5 million for the three and six months ended June 30, 2021, respectively, compared to the same periods 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)

	Three Months Ended June 30, 2021	Three Months Ended June 30, 2020	Dollar Change	% Change
Cost of sales	$ 3,136	$ 1,803	$ 1,333	74%

	Six Months Ended June 30, 2021	Six Months Ended June 30, 2020	Dollar Change	% Change
Cost of sales	$ 8,324	$ (1,700)	$ 10,024	-590%

Cost of sales increased by $1.3 million and $10.0 million for the three and six months ended June 30, 2021 compared to the same periods in 2020. The increase in cost of sales for the three months ended June 30, 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. The increase in cost of sales for the six months ended June 30, 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 we recorded during the six months ended June 30, 2020. The increase was offset by additional reserves of $1.7 million for excess inventory write-downs recorded during the six months ended June 30, 2021.

Prior to the approval of our products, manufacturing and related costs were expensed; accordingly, these costs were not capitalized and as a result are not fully reflected in the costs of sales during the three and six months ended June 30, 2021 and 2020. If manufacturing and related costs were capitalized prior to the approval period and the $1.7 million in write downs for the six months ended June 30, 2021 and the credit of $4.6 million for the six months ended June 30, 2020 as noted above were excluded, we estimate that cost of sales for the three and six months ended June 30, 2021 would have been approximately $3.2 million and $7.0 million, respectively, and for the three and six months ended June 30, 2020 would have been approximately $1.9 million and $3.1 million, respectively, for our commercial product sales. We expect our gross margin percentage to decrease as we produce approved products that reflect the full costs of manufacturing and as we deplete inventories that we had expensed prior to receiving approval.

Research and Development Expenses (dollars in thousands)

Research and development expenses include internal and external costs incurred for research and development of our programs and program candidates and expenses related to certain technology that we acquire or license through business development transactions. These expenses consist primarily of clinical studies performed by contract research organizations, manufacturing of drug substance and drug product performed by contract manufacturing organizations, materials and supplies, fees from collaborative and other arrangements including milestones, licenses and other fees, personnel costs including salaries, benefits and stock-based compensation, and overhead allocations consisting of various support and infrastructure costs.

Commercial programs include costs for disease monitoring programs and certain regulatory and medical affairs support activities for programs after commercial approval. Clinical programs include study conduct and manufacturing costs related to clinical program candidates. Translational research includes costs for preclinical study work and costs related to preclinical programs prior to IND filing. Upfront license and milestone fees include any significant expenses related to strategic licensing agreements. Infrastructure costs include direct costs related to laboratory, IT, and equipment depreciation costs, and overhead allocations for human resources, IT and other allocable costs.

The following table provides a breakout of our research and development expenses by major program type and business activities:

	Three Months Ended June 30,		Dollar	%
	2021	2020	Change	Change
Commercial programs	$ 12,641	$ 13,839	$ (1,198)	-9%
Clinical programs:				
Gene therapy programs	29,735	9,059	20,676	228%
Nucleic acid and other biologic programs	10,571	429	10,142	*
Translational research	16,647	16,067	580	4%
Upfront license and milestone fees	—	1,200	(1,200)	-100%
Infrastructure	14,374	12,787	1,587	12%
Stock-based compensation	15,094	12,856	2,238	17%
Other research and development	14,143	14,472	(329)	-2%
Total research and development expenses	$ 113,205	$ 80,709	$ 32,496	40%

* not meaningful

	Six Months Ended June 30,		Dollar	%
	2021	2020	Change	Change
Commercial programs	$ 26,302	$ 19,696	$ 6,606	34%
Clinical programs:				
Gene therapy programs	51,097	22,259	28,838	130%
Nucleic acid and other biologic programs	19,595	1,332	18,263	*
Small molecule programs	—	7,440	(7,440)	-100%
Translational research	29,260	32,372	(3,112)	
Upfront license and milestone fees	50,000	33,200	16,800	51%
Infrastructure	29,236	25,200	4,036	16%
Stock-based compensation	28,583	23,785	4,798	20%
Other research and development	26,650	28,386	(1,736)	-6%
Total research and development expenses	$ 260,723	$ 193,670	$ 67,053	35%

Total research and development expenses increased $32.5 million and $67.1 million for the three and six months ended June 30, 2021, respectively, compared to the same periods in 2020. The change in research and development expenses was primarily due to:

- for commercial programs, a decrease of $1.2 million for the three months ended June 30, 2021, primarily related to the capitalization of Dojolvi manufacturing costs in the three months ended June 30, 2021 which were expensed during the three months ended June 30, 2020, and an increase of $6.6 million for the six months ended June 30, 2021, primarily related to the addition of expenses related to Dojolvi and the TIO indication for Crysvita following their respective FDA approvals in June 2020;
- for gene therapy programs, an increase of $20.7 million and $28.8 million for the three months and six months ended June 30, 2021, respectively, primarily related to the addition of expenses related to UX701 following its IND approval in January 2021 and expense increases related to DTX401 and DTX301 Phase 3 trial preparation;
- for nucleic acid and other biologic programs, an increase of $10.1 million and $18.3 million for the three and six months ended June 30, 2021, respectively, primarily related to the addition of expenses related to UX053 following its IND approval in March 2021 and UX143 as we entered 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 for the three and six months ended June 30, 2021;
- for small molecule programs, a decrease of $7.4 million for the six months ended June 30, 2021, primarily related to the classification of expenses for Dojolvi to commercial programs for the six months ended June 30, 2021;
- for translational research, an increase of $0.6 million and a decrease of $3.1 million for the three and six months ended June 30, 2021, respectively, 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 net of increased spending on new translational research projects;

- for upfront license and milestone fees, a decrease of $1.2 million and an increase of $16.8 million for the three and six months ended June 30, 2021, respectively, primarily due to the $50.0 million upfront payment to Mereo in January 2021, partially offset by the $25.0 million option extension payment to GeneTx and the $7.0 million upfront payment to REGENXBIO, Inc. (REGENEX) pursuant to the license agreement for REGENX's NAV AAV8 and AAV9 vectors, both of which occurred during the first quarter of 2020, and a $1.2 million one-time license fee during the three months ended June 30, 2020;
- for infrastructure, an increase of $1.6 million and $4.0 million for the three and six months ended June 30, 2021, respectively, 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 $2.2 million and $4.8 million for the three and six months ended June 30, 2021, respectively, 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 $0.3 million and $1.7 million for the three and six months ended June 30, 2021, respectively, primarily related to higher research and development efforts allocated to the programs represented in the commercial, clinical, and translational science programs above.

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)

	Three Months Ended June 30, 2021	Three Months Ended June 30, 2020	Dollar Change	% Change
Selling, general and administrative	$ 53,410	$ 42,252	$ 11,158	26%

	Six Months Ended June 30, 2021	Six Months Ended June 30, 2020	Dollar Change	% Change
Selling, general and administrative	$ 106,668	$ 89,768	$ 16,900	19%

Selling, general and administrative expenses increased $11.2 million and $16.9 million for the three and six months ended June 30, 2021, respectively, compared to the same periods 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 in support of our commercial activities, commercialization costs, and professional services costs.

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)

	Three Months Ended June 30, 2021	Three Months Ended June 30, 2020	Dollar Change	% Change
Interest income	$ 441	$ 1,797	$ (1,356)	-75%

	Six Months Ended June 30, 2021	Six Months Ended June 30, 2020	Dollar Change	% Change
Interest income	$ 1,080	$ 4,716	$ (3,636)	-77%

Interest income decreased $1.4 million and $3.6 million for the three and six months ended June 30, 2021, respectively, compared to the same periods in 2020, primarily due to lower portfolio yields as a result of a decrease in interest rates, partially offset by higher balances in our marketable debt securities.

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

	Three Months Ended June 30, 2021	Three Months Ended June 30, 2020	Dollar Change	% Change
Change in fair value of equity investments	$ (31,046)	$ 95,200	$ (126,246)	-133%

	Six Months Ended June 30, 2021	Six Months Ended June 30, 2020	Dollar Change	% Change
Change in fair value of equity investments	$ (51,665)	$ 102,868	$ (154,533)	-150%

The fair value of our equity investments decreased by $31.0 million and $51.7 million during the three and six months ended June 30, 2021, respectively, due to decreases in the fair value of Arcturus and Solid common stock, resulting in unrealized losses on our investments in Arcturus common stock of $16.4 million and $21.0 million during the three and six months ended June 30, 2021, respectively and unrealized losses on our investments in Solid common stock of $14.6 million and $30.7 million during the three and six months ended June 30, 2021, respectively. The fair value of our equity investments increased by $95.2 million and $102.9 million during the three and six months ended June 30, 2020, respectively, due to increases in the fair value of Arcturus equity investments. 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)

	Three Months Ended June 30, 2021	Three Months Ended June 30, 2020	Dollar Change	% Change
Non-cash interest expense on liability related to the sale of future royalties	$ (8,517)	$ (8,429)	$ (88)	1%

	Six Months Ended June 30, 2021	Six Months Ended June 30, 2020	Dollar Change	% Change
Non-cash interest expense on liability related to the sale of future royalties	$ (16,935)	$ (16,511)	$ (424)	3%

The non-cash interest expense on liability related to the sale of future royalties increased by $0.1 million and $0.4 million for the three and six months ended June 30, 2021, respectively, compared to the same periods in 2020 due to the increase in the liability related to the sale of future royalties for net sales of Crysvita in the European territory, partially offset by a decrease in the effective interest rate for the three and six months ended June 30, 2021 compared to same periods in 2020. 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)

	Three Months Ended June 30, 2021	Three Months Ended June 30, 2020	Dollar Change	% Change
Other income (expense)	$ (67)	$ 217	$ (284)	-131%

	Six Months Ended June 30, 2021	Six Months Ended June 30, 2020	Dollar Change	% Change
Other income (expense)	$ (862)	$ (239)	$ (623)	261%

Other expense increased by $0.3 million and $0.6 million for the three and six months ended June 30, 2021, respectively, compared to the same periods in 2020. The increase was primarily due to fluctuations in foreign exchange rates.

Provision for Income Taxes (dollars in thousands)

	Three Months Ended June 30, 2021	Three Months Ended June 30, 2020	Dollar Change	% Change
Provision for income taxes	$ (463)	$ (415)	$ (48)	12%

	Six Months Ended June 30, 2021	Six Months Ended June 30, 2020	Dollar Change	% Change
Provision for income taxes	$ (842)	$ (824)	$ (18)	2%

The provision for incomes taxes increased by a nominal amount for the three and six months ended June 30, 2021, respectively, compared to the same periods in 2020.

Liquidity and Capital Resources

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.

As of June 30, 2021, we had $973.8 million in available cash, cash equivalents, and marketable debt securities. We believe that our existing capital resources will be sufficient to fund our projected operating requirements for at least the next twelve months. Our cash, cash equivalents, and marketable debt securities are held in a variety of deposit accounts, interest-bearing accounts, corporate bond securities, U.S government securities, asset-backed securities, and money market funds. Cash in excess of immediate requirements is invested with a view toward liquidity and capital preservation, and we seek to minimize the potential effects of concentration and credit risk.

In May 2021, we entered into an Open Market Sale Agreement with 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 offerings through Jefferies. As of June 30, 2021, we had not sold any shares under the arrangement.

In March 2020, we received $75.0 million in cash from the sale of 1,243,913 shares of our common stock to Daiichi Sankyo and in April 2020, we received $125.0 million from an upfront payment related to the Daiichi Sankyo License Agreement. In November 2020, we completed an underwritten public offering in which we sold 5,111,110 shares of common stock and received net proceeds of $435.6 million. In December 2020, we sold 800,000 shares of Arcturus common stock and received net proceeds of $79.8 million.

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

	Six Months Ended June 30,	
	2021	2020
Cash used in operating activities	$ (224,702)	$ (7,801)
Cash used in investing activities	(223,670)	(181,264)
Cash provided by financing activities	25,277	91,426
Effect of exchange rate changes on cash	(323)	(198)
Net decrease in cash, cash equivalents and restricted cash	$ (423,418)	$ (97,837)

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 six months ended June 30, 2021 was $224.7 million and reflected a net loss of $258.6 million and $8.6 million for non-cash collaboration royalty revenues related to the sale of future royalties to RPI Finance Trust (RPI), an affiliate of Royalty Pharma, offset by non-cash charges of $51.3 million for stock-based compensation, $2.5 million for the amortization of the premium paid on purchased marketable debt securities, $6.5 million for depreciation and amortization, $51.7 million for a change in fair value of equity investments from Arcturus and Solid, and $16.9 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 $1.7 million decrease due to an increase in accounts receivable primarily related to higher revenues, a $2.2 million decrease due to an increase in inventory, a $9.0 million decrease due to an increase in prepaid expenses and other current assets primarily due to an increase in prepaid subscriptions, prepaid clinical studies, and prepaid fixed assets, a $11.5 million decrease in accounts payable, accrued liabilities, and other liabilities primarily due to the payout of 2020 annual bonuses, and a decrease of $62.7 million in contract liabilities, related to the revenue recognized from the license agreements with Daiichi Sankyo.

Cash used in operating activities for the six months ended June 30, 2020 was $7.8 million and reflected a net loss of $93.7 million, $0.1 million for the amortization of the discount paid on purchased investments, $102.9 million for changes in the fair value of equity investments from Arcturus, and $6.1 million for non-cash collaboration royalty revenues related to the sale of future royalties to Royalty Pharma, offset by non-cash charges of $42.6 million for stock-based compensation, $6.0 million for depreciation, and $16.5 million for non-cash interest incurred on the liability related to the sale of future royalties to Royalty Pharma. Cash used in operating activities also reflected a decrease of $6.1 million due to an increase in prepaid expenses and other current assets primarily due to an increase in prepaid manufacturing and a $8.8 million decrease in accounts payable, accrued liabilities, and other liabilities primarily due to a decrease in accrued bonus due to the payout of the 2019 annual bonus, offset by a $9.5 million increase due to a decrease in accounts receivable primarily related to change in the timing of billing to a collaboration partner offset by a $8.5 million receivable related to the license agreement with Daiichi Sankyo in June 2020, a $0.5 million increase due to a decrease in inventory, and an increase of $134.9 million in contract liabilities related to the license agreements with Daiichi Sankyo.

Cash Used in Investing Activities

Cash used in investing activities for the six months ended June, 2021 was $223.7 million and related to purchases of property, plant, and equipment of $36.5 million and purchases of marketable debt securities of $664.3 million, offset by proceeds from the sale of marketable debt securities of $70.5 million and maturities of marketable debt securities of $406.6 million.

Cash used in investing activities for the six months ended June 30, 2020 was $181.3 million and related to purchases of property, plant, and equipment of $18.2 million, purchases of investments of $456.3 million, and the exercise of the option to purchase additional Arcturus shares for $9.6 million, offset by proceeds from the sale of investments of $28.9 million and maturities of investments of $274.0 million.

Cash Provided by Financing Activities

Cash provided by financing activities for the six months ended June 30, 2021 was $25.3 million and was primarily comprised of $25.5 million in net proceeds from the issuance of common stock pursuant to equity plan awards.

Cash provided by financing activities for the six months ended June 30, 2020 was $91.4 million and was comprised of $55.3 million 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 in our ATM offering, and $15.9 million in net proceeds from the issuance of common stock pursuant to the exercise of warrants and equity plan awards.

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 and Commitments

We have contractual obligations from our operating and finance leases, manufacturing and service contracts, licenses, royalties, development and collaboration arrangements, and other research and development activities. The following table summarizes our significant binding contractual obligations at June 30, 2021 (in thousands):

	Payments due by period				
	Less than 1 year	1 to 3 years	3 to 5 years	More than 5 years	Total
Operating and finance leases	$ 13,012	$ 25,144	$ 13,816	$ 1,351	$ 53,323
Manufacturing and service contracts	8,768	472	—	—	9,240
Building construction agreement	6,411	—	—	—	6,411
Total	$ 28,191	$ 25,616	$ 13,816	$ 1,351	$ 68,974

The terms of certain of our licenses, royalties, development and collaboration agreements, as well as other research and development activities, require us to pay potential future milestone payments based on product development success. The above table excludes such obligations as the amount and timing of such obligations are unknown or uncertain.

Off-Balance Sheet Arrangements

We have not engaged in any off-balance sheet arrangements, as defined in the rules and regulations of the SEC.

Item 3. *Quantitative and Qualitative Disclosures about Market Risk*

Equity Risk

We have exposure to equity risk with respect to the equity investments that we hold in Arcturus and Solid. The carrying value of our equity investment held in Arcturus was $74.4 million and $95.4 million as of June 30, 2021 and December 31, 2020, respectively, and the carrying value of our equity investment held in Solid was $28.6 million and $59.3 million as of June 30, 2021 and December 31, 2020, respectively. The fair value of our equity investments decreased by $31.0 million and $51.7 million during the three and six months ended June 30, 2021, respectively, due to a decrease in the fair value of Arcturus and Solid common stock, resulting in unrealized losses on our investments in Arcturus common stock of $16.4 million and $21.0 million for the three and six months ended June 30, 2021, respectively and in unrealized losses in our investments in Solid common stock of $14.6 million and $30.7 million for the three and six months ended June 30, 2021, respectively. A hypothetical 10 percent decrease in the market price for our equity investments in Arcturus and Solid as of June 30, 2021 and December 31, 2020 would decrease the fair value by $10.3 million and $15.5 million, respectively. Given the historic volatility of the publicly traded stock price of Arcturus and Solid, the fair value of our investments in Arcturus and Solid is subject to wide fluctuations which may have a significant impact on our net income (loss) in future periods.

Interest Rate Risk

Our exposure to market risk for changes in interest rates relates primarily to interest earned on our cash equivalents and marketable debt securities. The primary objective of our investment activities is to preserve our capital to fund operations. A secondary objective is to maximize income from our investments without assuming significant risk. Our investment policy provides for investments in low-risk, investment-grade debt instruments. As of June 30, 2021, we had cash, cash equivalents, and marketable debt securities totaling $973.8 million, compared to $1,212.0 million as of December 31, 2020, which include bank deposits, money market funds, U.S. government treasury and agency securities, and investment-grade corporate bond securities which are subject to default, changes in credit rating, and changes in market value. The securities in our investment portfolio are classified as available for sale and are subject to interest rate risk and will decrease in value if market interest rates increase. A hypothetical 100 basis point change in interest rates during any of the periods presented would not have had a material impact on the fair market value of our cash equivalents and marketable debt securities as of June 30, 2021 or December 31, 2020. To date, we have not experienced a loss of principal on any of these investments and as of June 30, 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 for license agreements. For the three months ended June 30, 2021, a majority of our revenue and expense activities and capital expenditures were denominated in U.S. dollars. A hypothetical 10% change in foreign exchange rates during any of the periods presented would not have had a material impact on our consolidated financial statements.

Item 4. 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 Quarterly Report, pursuant to Rules 13a-15(b) and 15d-15(b) 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 June 30, 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.

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 quarter ended June 30, 2021, that has materially affected, or is reasonably likely to materially affect our internal control over financial reporting.

PART II. OTHER INFORMATION

Item 1. *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 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 Quarterly Report, including our financial statements and notes thereto, before deciding to invest in our common stock. The risks and uncertainties described below are not the only ones we face. Additional risk and uncertainties not presently known to us or that we presently deem less significant may also impair our business operations. If any of the following risks actually materialize, our operating results, financial condition, and liquidity could be materially adversely affected. As a result, the trading price of our common stock could decline and you could lose part or all of your investment. Our company's business, financial condition and operating results can be affected by a number of factors, whether currently known or unknown, including but not limited to those described below, any one or more of which could, directly or indirectly, cause our actual financial condition and operating results to vary materially from past, or from anticipated future, financial condition and operating results. Any of these factors, in whole or in part, could materially and adversely affect our business, prospects, financial condition, operating results and stock price.

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

The following description of the risk factors associated with our business includes any material changes to and supersedes the description of the risk factors associated with our business previously disclosed in Part I, Item 1A of the Annual Report.

Risk Factor Summary

- We have a history of operating losses and anticipate that we will continue to incur losses for the foreseeable future.
- We have limited experience in generating revenue from product sales.
- We expect we will need to raise additional capital to fund our activities.
- Clinical drug development is a lengthy and expensive process with uncertain outcomes.
- If we do not achieve our projected development goals in the time frames we announce and expect, we may experience delays in commercialization of our products and the reputation of our management may be adversely affected.
- We may experience difficulty in enrolling patients, which could delay or prevent clinical studies of our product candidates.
- The regulatory approval processes of the FDA and comparable foreign authorities are lengthy and inherently unpredictable.
- Our product candidates, including our gene therapy product candidates, may cause undesirable or serious side effects that could delay or prevent their regulatory approval, limit the commercial profile of an approved label, or result in other negative consequences following marketing approval, if any.
- Our products will remain subject to regulatory scrutiny even if we obtain regulatory approval.
- We may not realize the full commercial potential of our product candidates if we are unable to source and develop effective biomarkers.
- We rely on third parties to conduct our nonclinical and clinical studies and perform other tasks for us.
- We are dependent on KKC for the clinical and commercial supply of Crysvita for all major markets and for the development and commercialization of Crysvita in certain major markets.
- We have no experience as a company developing a manufacturing facility, such as our gene therapy manufacturing facility in Massachusetts.

- We rely on third parties to manufacture our products and product candidates and face a multitude of manufacturing risks.
- The loss of, or failure to supply by, any of any of our single-source suppliers for our drug substance and drug product could adversely affect our business.
- The actions of distributors and specialty pharmacies could affect our ability to sell or market products profitably.
- A competitor could misappropriate or disclose our trade secrets.
- Our revenue may be adversely affected if the market opportunities for our products and product candidates are smaller than expected.
- Our competitors may develop therapies that are similar, more advanced, or more effective than ours.
- We may not successfully manage expansion of our company, including building an integrated commercial organization.
- Our exclusive right to promote Crysvita in the United States and Canada expires in 2023.
- Commercial success of our products depends on the degree of market acceptance by physicians, patients, third-party payors, and others in the medical community
- We face uncertainty related to insurance coverage and reimbursement status of our newly approved products.
- We may be adversely affected by the United Kingdom's withdrawal from the EU.
- If we, or our third-party partners, are unable to maintain effective proprietary rights for our products, product candidates, or any future product candidates, we may not be able to compete effectively in our markets.
- Claims of intellectual property infringement may prevent or delay our development and commercialization efforts.
- We may not be successful in obtaining or maintaining necessary rights to our product candidates through acquisitions and in-licenses.
- We may face competition from biosimilars or from generic versions of Dojolvi or our small-molecule product candidates, which may result in a material decline in sales of affected products.
- We could lose license rights that are important to our business if we fail to comply with our obligations in the agreements under which we license intellectual property and other rights from third parties.
- We may become involved in lawsuits to protect or enforce our patents or the patents of our licensors, or be subject to claims that challenge the inventorship or ownership of our patents.
- Changes in U.S. patent law could diminish the value of patents in general, thereby impairing our ability to protect our products.
- We may not be able to protect our intellectual property rights throughout the world.
- The ongoing COVID-19 pandemic has impacted our operations and could materially and adversely affect our business and operating results.
- Our success depends in part on our ability to retain our President and Chief Executive Officer and other qualified personnel.
- Our revenue may be impacted if we fail to obtain or maintain orphan drug exclusivity for our products.
- Our operating results may be adversely impacted if our intangible assets become impaired.
- We may not be successful in identifying, licensing, discovering, developing, or commercializing additional product candidates or we may fail to capitalize on opportunities that may be more profitable or for which there is a greater likelihood of success.
- We may fail to comply with laws and regulations or changes in laws and regulations could adversely affect our business.
- We are exposed to risks related to international expansion of our business outside of the United States.
- Our business may be adversely affected in the event of computer system failures or security breaches.
- We or our third-party partners may be adversely affected by earthquakes or other serious natural disasters that are not adequately protected by business continuity and disaster recovery plans.
- We may incur various costs and expenses and risks related to acquisition of companies or products or strategic transactions.
- The market price of our common stock is highly volatile.

- Future sales and issuances of our common stock could dilute the percentage ownership of our current stockholders and result in a decline in stock price.

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

- Provisions in our amended and restated certificate of incorporation and by-laws, as well as provisions of Delaware law, could make it more difficult for a third-party to acquire us or increase the cost of acquiring us or could limit our stockholders' ability to obtain a favorable judicial forum for disputes with us or our directors, officers or employees.

- We face general risks related to our ability to maintain effective internal controls over financial reporting, additional tax liabilities related to our operations, our ability to use our net operating loss carryforwards and costs of litigation

Risks Related to Our Financial Condition and Capital Requirements

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

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

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

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

We have limited experience in generating revenue from product sales.

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

- obtaining regulatory and marketing approvals with broad indications for product candidates for which we complete clinical studies;
- developing a sustainable and scalable manufacturing process for our products and any approved product candidates and establishing and maintaining supply and manufacturing relationships with third parties that can conduct the processes and provide adequate (in amount and quality) product supply to support market demand for our products and product candidates, if approved;
- launching and commercializing our products and product candidates for which we obtain regulatory and marketing approval, either directly or with a collaborator or distributor;
- obtaining market acceptance of our products and product candidates as viable treatment options;

- obtaining adequate market share, reimbursement and pricing for our products and product candidates;
- our ability to sell our products and product candidates on a named patient basis or through an equivalent mechanism and the amount of revenue generated from such sales;
- our ability to find patients so they can be diagnosed and begin receiving treatment;
- addressing any competing technological and market developments;
- negotiating favorable terms, including commercial rights, in any collaboration, licensing, or other arrangements into which we may enter, any amendments thereto or extensions thereof;
- maintaining, protecting, and expanding our portfolio of intellectual property rights, including patents, trade secrets, and know-how; and
- attracting, hiring, and retaining qualified personnel.

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

We expect we will 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 June 30, 2021, our available cash, cash equivalents, and marketable debt securities were $973.8 million. We expect we will need additional capital to continue to commercialize our products, and to develop and obtain regulatory approval for, and to commercialize, all of our product candidates. In addition, our operating plans may change as a result of many factors that may currently be unknown to us, and we may need to seek additional funds sooner than planned. Our future funding requirements will depend on many factors, including but not limited to:

- the scope, rate of progress, results, and cost of our clinical studies, nonclinical testing, and other related activities;
- the cost of manufacturing clinical and commercial supplies of our products and product candidates;
- the cost of creating additional infrastructure, including facilities and systems;
- the number and characteristics of the product candidates that we pursue;
- the cost, timing, and outcomes of regulatory approvals;
- the cost and timing of establishing and operating our international subsidiaries;
- the cost and timing of establishing and operating field forces, marketing, and distribution capabilities;
- the cost and timing of other activities needed to commercialize our products; and
- the terms and timing of any collaborative, licensing, acquisition (including whether we exercise our option to acquire GeneTx pursuant to the terms of our Unitholder Option Agreement with them), and other arrangements that we may establish, including any required milestone, royalty, and reimbursements or other payments thereunder.

Any additional fundraising efforts may divert our management's attention from their day-to-day activities, which may adversely affect our ability to develop our product candidates and commercialize our products. In addition, we cannot guarantee that future financing will be available in sufficient amounts or on terms acceptable to us, if at all. The terms of any financing may adversely affect the holdings or the rights of our stockholders and the issuance of additional securities, whether equity or debt, by us, or the possibility of such issuance, may cause the market price of our shares to decline. The sale of additional equity or convertible securities would dilute all of our stockholders. If we incur debt, it could result in increased fixed payment obligations and we may be required to agree to certain restrictive covenants, such as limitations on our ability to incur additional debt, limitations on our ability to acquire, sell, or license intellectual property rights, and other operating restrictions that could adversely impact our ability to conduct our business. We have in the past sought and may in the future seek funds through a sale of future royalty payments similar to our transaction with Royalty Pharma or through collaborative partnerships, strategic alliances, and licensing or other arrangements, such as our transaction with Daiichi Sankyo, and we may be required to relinquish rights to some of our technologies or product candidates, future revenue streams, research programs, and other product candidates or otherwise agree to terms unfavorable to us, any of which may have a material adverse effect on our business, operating results, and prospects. Even if we believe we have sufficient funds for our current or future operating plans, we may seek additional capital if market conditions are favorable or if we have specific strategic considerations.

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

Risks Related to the Discovery and Development of Our Product Candidates

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

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

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

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

- delays or failures in generating sufficient preclinical, toxicology, or other *in vivo* or *in vitro* data to support the initiation or continuation of human clinical studies or filings for regulatory approval;
- failure to demonstrate a starting dose for our product candidates in the clinic that might be reasonably expected to result in a clinical benefit;
- delays or failures in developing gene therapy, messenger RNA (mRNA), DNA, small interfering RNA (siRNA) or other novel and complex product candidates, which are expensive and difficult to develop and manufacture;
- delays resulting from a shutdown, or uncertainty surrounding the potential for future shutdowns of the U.S. government, including the FDA;
- delays or failures in reaching a consensus with regulatory agencies on study design;
- delays in reaching agreement on acceptable terms with contract research organizations, or CROs, clinical study sites, and other clinical trial-related vendors;
- failure or delays in obtaining required regulatory agency approval and/or IRB or EC approval at each clinical study site or in certain countries;
- failure to correctly design clinical studies which may result in those studies failing to meet their endpoints or the expectations of regulatory agencies;
- changes in clinical study design or development strategy resulting in delays related to obtaining approvals from IRBs or ECs and/or regulatory agencies to proceed with clinical studies;
- imposition of a clinical hold by regulatory agencies after review of an IND application or amendment, another equivalent application or amendment, or an inspection of our clinical study operations or study sites;
- delays in recruiting suitable patients to participate in our clinical studies;
- difficulty collaborating with patient groups and investigators;
- failure by our CROs, other third parties, or us to adhere to clinical study requirements;
- failure to perform in accordance with the FDA's and/or ICH's good clinical practices requirements or applicable regulatory guidelines in other countries;
- delays in patients' completion of studies or their returns for post-treatment follow-up;
- patients dropping out of a study;
- adverse events associated with the product candidate occurring that are viewed to outweigh its potential benefits;

- changes in regulatory requirements and guidance that require amending or submitting new clinical protocols;
- greater than anticipated costs associated with clinical studies of our drug candidates;
- clinical studies of our drug candidates producing negative or inconclusive results, which may result in us deciding, or regulators requiring us, to conduct additional clinical or nonclinical studies or to abandon drug development programs;
- competing clinical studies of potential alternative product candidates or investigator-sponsored studies of our product candidates; and
- delays in manufacturing, testing, releasing, validating, or importing/exporting sufficient stable quantities of our product candidates for use in clinical studies or the inability to do any of the foregoing.

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

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

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

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

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

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

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

In addition to the rarity of these diseases, the eligibility criteria of our clinical studies will further limit the pool of available study participants as we will require patients to have specific characteristics that we can measure or to assure their disease is either severe enough or not too advanced to include them in a study. The process of finding and diagnosing patients is costly, especially since the rare diseases we are studying are commonly 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, the timeline for recruiting patients, conducting studies, and obtaining regulatory approval of potential products may be delayed, the commercial prospects of our product candidates will be harmed, and our ability to generate product revenue from any of these product candidates could be delayed or prevented. Furthermore, many of the factors that cause, or lead to, a delay in the commencement or completion of clinical studies may also ultimately lead to the denial of regulatory approval of our product candidates. Delays in completing our clinical studies will increase our costs, slow down our product candidate development and approval process, and jeopardize our ability to commence product sales and generate revenue.

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

Our future success is dependent on our ability to successfully commercialize our products and develop, obtain regulatory approval for, and then successfully commercialize one or more product candidates. We are not permitted to market or promote any of our product candidates before we receive regulatory approval from the FDA or comparable foreign regulatory authorities. We have only obtained regulatory approval for three products, and it is possible that none of our existing product candidates or any product candidates we may seek to develop in the future will ever obtain regulatory approval. Further, as the clinical trial requirements of regulatory authorities and the criteria these regulators use to determine the safety and efficacy of a product candidate vary substantially according to the type, complexity, novelty and intended use and market of the product candidates, the regulatory approval process for novel product candidates, such as our gene therapy product candidates, can be more expensive and take longer than for other product candidates, leading to fewer product approvals. To date, very few gene therapy products have received regulatory approval in the United States or Europe.

To obtain regulatory approval in the United States and other jurisdictions, we must comply with numerous and varying requirements regarding safety, efficacy, chemistry, manufacturing and controls, clinical studies (including good clinical practices), commercial sales, pricing, and distribution of our product candidates, as described in "Item 1. Business – Government Regulation" of our Annual Report. Even if we are successful in obtaining approval in one jurisdiction, we cannot ensure that we will obtain approval in any other jurisdictions. In addition, approval policies, regulations, positions of the regulatory agencies on study design and/or endpoints, or the type and amount of clinical data necessary to gain approval may change during the course of a product candidate's clinical development, which may cause delays in the approval or the decision not to approve an application. Communications with the regulatory agencies during the approval process are also unpredictable; favorable communications early in the process do not ensure that approval will be obtained and unfavorable communications early on do not guarantee that approval will be denied. Applications for our product candidates could fail to receive regulatory approval, or could be delayed in receiving regulatory approval, for many reasons, including but not limited to the following:

- regulatory authorities may disagree with the design, implementation, or conduct of our clinical studies;
- regulatory authorities may change their guidance or requirements for a development program for a product candidate;
- the population studied in the clinical program may not be sufficiently broad or representative to assure efficacy and safety in the full population for which we seek approval;
- regulatory authorities may disagree with our interpretation of data from nonclinical studies or clinical studies;
- the data collected from clinical studies of our product candidates may not be sufficient to support the submission of an NDA, or biologics license application, or BLA, or other submission or to obtain regulatory approval;
- we may be unable to demonstrate to regulatory authorities that a product candidate's risk-benefit ratio for its proposed indication is acceptable;
- regulatory authorities may fail to approve the manufacturing processes, test procedures and specifications, or facilities used to manufacture our clinical and commercial supplies;
- the U.S. government may be shut down, which could delay the FDA;
- failure of our nonclinical or clinical development to comply with an agreed upon Pediatric Investigational Plan (PIP), which details the designs and completion timelines for nonclinical and clinical studies and is a condition of marketing authorization in the EU; and
- the approval policies or regulations of regulatory authorities may significantly change in a manner rendering our clinical data insufficient for approval.

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

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

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

Undesirable side effects caused by our product candidates could cause us or regulatory authorities to interrupt, delay, or halt clinical studies or further development, and could result in a more restrictive label, the delay or denial of regulatory approval by the FDA or other comparable foreign authorities, or a Risk Evaluation and Mitigation Strategy, or REMS, plan, which could include a medication guide outlining the risks of such side effects for distribution to patients, restricted distribution, a communication plan for healthcare providers, and/or other elements to assure safe use. Our product candidates are in development and the safety profile has not been established. Further, as one of the goals of Phase 1 and/or 2 clinical trials is to identify the highest dose of treatment that can be safely provided to study participants, adverse side effects, including serious adverse effects, have occurred in certain studies as a result of changes to the dosing regimen during such studies. For instance, patients in our Phase 1/2 study of GTX-102 experienced a serious adverse event of lower extremity weakness believed to be related to local inflammation due to GTX-102 at the highest doses of the product. Gene therapy product candidates using AAV vectors, like DTX301, have been associated with immunologic reaction to the capsid protein or gene at early time points after administration. For example, in our discontinued Phase 1/2 clinical trial of DTX101 in hemophilia B, we observed elevated laboratory alanine transaminase levels, or ALTs. In previous clinical trials involving AAV viral vectors for gene therapy, some subjects experienced adverse events, including the development of a T-cell mediated immune response against the vector capsid proteins. In addition, theoretical side effects of AAV vectors include replication and spread of the virus to other parts of the body and insertional oncogenesis, which is the process whereby the insertion of a gene near a gene that is important in cell growth or division results in uncontrolled cell division, which could potentially enhance the risk of malignant transformation or cancer. Potential procedure-related events are similar to those associated with standard coronary diagnostic procedures, and may include vascular injury (e.g., damage to the femoral, radial or brachial arteries at the site of vascular access, or damage to the coronary arteries) or myocardial injury. Future product candidates may also cause these or similar side effects as development proceeds. Results of our studies or investigator-sponsored trials could reveal a high and unacceptable severity and prevalence of these or other side effects. In such an event, our studies could be suspended or terminated, and the FDA or comparable foreign regulatory authorities could order us to cease further development of or deny or withdraw approval of our product candidates for any or all targeted indications.

Drug-related side effects could affect patient recruitment and the ability of enrolled patients to complete a study. Such side effects could also result in potential product liability claims. There can be no assurance that our product liability insurance, which provides coverage in the amount of $10.0 million per incident and $10.0 million in the aggregate, will be sufficient in light of our current or planned clinical programs. We may not be able to maintain insurance coverage at a reasonable cost or in sufficient amounts to protect us against losses due to liability, or losses may exceed the amount of insurance that we carry. A product liability claim or series of claims brought against us could cause our stock price to decline and, if judgments exceed our insurance coverage, could adversely affect our results of operations and business. In addition, regardless of merit or eventual outcome, product liability claims may result in impairment of our business reputation, withdrawal of clinical study participants, costs due to related litigation, distraction of management's attention from our primary business, initiation of investigations by regulators, substantial monetary awards to patients or other claimants, the inability to commercialize our product candidates, and decreased demand for our product candidates, if approved for commercial sale.

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

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

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

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

Gene therapy remains a novel technology. Public perception may be influenced by claims that gene therapy is unsafe, and gene therapy may not gain the acceptance of the public or the medical community. For example, certain gene therapy trials using AAV8 vectors (although at significantly higher doses than those used in our gene therapy product candidates) and other vectors led to several well-publicized adverse events, including cases of leukemia and death. The risk of cancer or death remains a concern for gene therapy and we cannot assure you that it will not occur in any of our planned or future clinical studies. In addition, there is the potential risk of delayed adverse events following exposure to gene therapy products due to persistent biological activity of the genetic material or other components of products used to carry the genetic material. Serious adverse events in our clinical trials, or other clinical trials involving gene therapy products, particularly AAV gene therapy products such as candidates based on the same capsid serotypes as our product candidates, or occurring during use of our competitors' products, even if not ultimately attributable to the relevant product candidates, and the resulting publicity, could result in increased government regulation, unfavorable public perception, potential regulatory delays in the testing or approval of our gene therapy product candidates, stricter labeling requirements for those gene therapy product candidates that are approved and a decrease in demand for any such gene therapy product candidates, all of which would have an adverse effect on our business, financial condition, results of operations and prospects. Refer to the risk factor above entitled, "*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*" for a description of the serious adverse events experienced by patients in our Phase 1/2 study of GTX-102.

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

Our products and any product candidates that are approved are subject to ongoing regulatory requirements for manufacturing, labeling, packaging, storage, distribution, advertising, promotion, sampling, record-keeping, conduct of post-marketing studies, and submission of safety, efficacy, and other post-market information, including both federal and state requirements in the United States and requirements of comparable foreign regulatory authorities, as described in "Item 1. Business – Government Regulation" in our Annual Report.

Manufacturers and manufacturers' facilities are required to comply with extensive FDA, and comparable foreign regulatory authority, requirements, including ensuring that quality control and manufacturing procedures conform to Good Manufacturing Practices (GMP) regulations. As such, we and our contract manufacturers are subject to continual review and inspection to assess compliance with GMP and adherence to commitments made in any NDA, BLA, MAA, or other comparable application for approval in another jurisdiction. Regulatory authorities may, at any time, audit or inspect a manufacturing facility involved with the preparation of our products, product candidates or the associated quality systems for compliance with the regulations applicable to the activities being conducted. If we, our collaborators, such as KKC, or any of our third-party manufacturers fail to maintain regulatory compliance, the FDA or other applicable regulatory authority can impose regulatory sanctions including, among other things, the temporary or permanent suspension of a clinical study or commercial sales, recalls or seizures of product or the temporary or permanent closure of a facility or withdrawal of product approval. If supply from one approved manufacturer is interrupted due to failure to maintain regulatory compliance, an alternative manufacturer would need to be qualified through an NDA or BLA supplement or MAA variation, or equivalent foreign regulatory filing, which could result in delays in product supply. The regulatory agencies may also require additional studies if a new manufacturer is relied upon for commercial production. Switching manufacturers may involve substantial costs and is likely to result in a delay in our desired clinical and commercial timelines. Accordingly, we and others with whom we work are required continue to expend time, money, and effort in all areas of regulatory compliance, including manufacturing, production, and quality control.

Any regulatory approvals that we receive for our product candidates may be subject to limitations on the approved indicated uses for which the product may be marketed or other conditions of approval, or contain requirements for potentially costly post-marketing testing, including Phase 4 clinical studies, and surveillance to monitor the safety and efficacy of the product candidate. We could also be asked to conduct post-marketing clinical studies to verify the safety and efficacy of our products in general or in specific patient subsets. If original marketing approval was obtained via the accelerated approval or conditional marketing authorization pathways, we would be required to conduct a successful post-marketing clinical study to confirm clinical benefit for our products. An unsuccessful post-marketing study or failure to complete such a study could result in the withdrawal of marketing approval. We will be required to report certain adverse events and manufacturing problems, if any, to the FDA and comparable foreign regulatory authorities. The holder of an approved NDA, BLA, MAA, or other comparable application must submit new or supplemental applications and obtain approval for certain changes to the approved product, product labeling, or manufacturing process.

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

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

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

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

We are developing companion diagnostic tests to identify the right patients for certain of our product candidates and to monitor response to treatment. In certain cases, diagnostic tests may need to be developed as companion diagnostics and regulatory approval obtained in order to commercialize some product candidates. We currently use and expect to continue to use biomarkers to identify the right patients for certain of our product candidates. We may also need to develop predictive biomarkers in the future. For example, to evaluate therapeutic response of DTX301, we are measuring ammonia levels and other biomarkers, including ^{13}C-acetate, which are established measures of OTC deficiency disease status and ureagenesis. We offer no assurances that ^{13}C-acetate or any other future potential biomarker will in fact prove predictive, be reliably measured, or be accepted as a measure of efficacy by the FDA or other regulatory authorities. In addition, our success may depend, in part, on the development and commercialization of companion diagnostics. We also expect the FDA will require the development and regulatory approval of a companion diagnostic assay as a condition to approval of our gene therapy product candidates. There has been limited success to date industrywide in developing and commercializing these types of companion diagnostics. Development and manufacturing of companion diagnostics is complex and there are limited manufacturers with the necessary expertise and capability. Even if we are able to successfully develop companion diagnostics, we may not be able to manufacture the companion diagnostics at a cost or in quantities or on timelines necessary for use with our product candidates. To be successful, we need to address a number of scientific, technical and logistical challenges. We are currently working with a third party to develop companion diagnostics, however, we have little experience in the development and commercialization of diagnostics and may not ultimately be successful in developing and commercializing appropriate diagnostics to pair with any of our product candidates that receive marketing approval. The University of Pennsylvania School of Medicine currently conducts some of our clinical assays pursuant to a sponsored research agreement, one of which is required for our ongoing Phase 1/2 clinical trial. We also use third parties for the automation, characterization and validation, of our bioanalytical assays, companion diagnostics and the manufacture of its critical reagents.

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

Risks Related to our Reliance on Third Parties

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

We have relied upon and plan to continue to rely upon third parties, including CROs, collaborative partners, and independent investigators to analyze, collect, monitor, and manage data for our ongoing nonclinical and clinical programs. We rely on third parties for execution of our nonclinical and clinical studies, and for estimates regarding costs and efforts completed, and we control only certain aspects of their activities. For example, pursuant to the terms of our collaboration with GeneTx on the development of GeneTx's GTX-102, an antisense oligonucleotide (ASO) for the treatment of Angelman syndrome, subject to certain limited rights we have, GeneTx retains the decision-making authority on all matters in connection with the research, development, manufacturing and regulatory activities with respect to the program. Nevertheless, we are responsible for ensuring that each of our studies is conducted in accordance with the applicable protocol, legal, regulatory, and scientific standards, and our reliance on the CROs and other third parties does not relieve us of our regulatory responsibilities. We and our CROs and other vendors and partners are required to comply with GMP, GCP, and GLP, which are regulations and guidelines enforced by the FDA, the Competent Authorities of the Member States of the European Economic Area, and comparable foreign regulatory authorities for all of our product candidates in development. Regulatory authorities enforce these regulations through periodic inspections of study sponsors, principal investigators, study sites, and other contractors. If we or any of our CROs or other vendors and partners, including the sites at which clinical studies are conducted, fail to comply with applicable regulations, the data generated in our nonclinical and clinical studies may be deemed unreliable and the FDA, EMA, or comparable foreign regulatory authorities may deny approval and/or require us to perform additional nonclinical and clinical studies before approving our marketing applications, which would delay the approval process. We cannot make assurances that upon inspection by a given regulatory authority, such regulatory authority will determine that any of our clinical studies comply with GCP regulations or that nonclinical studies comply with GLP regulations. In addition, our clinical studies must be conducted with products produced under GMP regulations. If the regulatory authorities determine that we have failed to comply with GLP, GMP, or GCP regulations, they may deny approval of our product candidates and/or we may be required to repeat clinical or nonclinical studies, which would delay the regulatory approval process.

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

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

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

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

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

- KKC has no obligation under our agreement to use diligent efforts to commercialize Crysvita in Europe. The timing and amount of any royalty payments that are made by KKC based on sales of Crysvita in Europe will depend on, among other things, the efforts, allocation of resources, and successful commercialization of Crysvita by KKC in Europe.

- the timing and amount of any payments we may receive under our agreement with KKC will depend on, among other things, the efforts, allocation of resources, and successful commercialization of Crysvita by KKC in the United States and Canada under our agreement;
- KKC may change the focus of its commercialization efforts or pursue higher-priority programs;
- KKC may make decisions regarding the indications for our product candidates in countries where it has the sole right to commercialize the product candidates that limit commercialization efforts in those countries or in countries where we have the right to commercialize our product candidates;
- KKC may make decisions regarding market access and pricing in countries where it has the sole right to commercialize our product candidates which can negatively impact our commercialization efforts in countries where we have the right to commercialize our product candidates;
- KKC may fail to manufacture or supply sufficient drug product of Crysvita in compliance with applicable laws and regulations or otherwise for our development and clinical use or commercial use (including as a result of the COVID-19 pandemic), which could result in program delays or lost revenue;
- KKC may elect to develop and commercialize Crysvita indications with a larger market than XLH and at a lower price, thereby reducing the profit margin on sales of Crysvita for any orphan indications, including XLH;
- if KKC were to breach or terminate the agreement with us, we would no longer have any rights to develop or commercialize Crysvita or such rights would be limited to non-terminated countries;
- KKC may terminate its agreement with us, adversely affecting our potential revenue from licensed products; and
- the timing and amounts of expense reimbursement that we may receive are uncertain, and the total expenses for which we are obligated to reimburse KKC may be greater than anticipated.

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

During the fourth quarter 2020, we completed our purchase of land located in the Town of Bedford, Massachusetts for construction of our gene therapy manufacturing facility and began construction of the base building for the facility. We expect that the new facility will provide us with enhanced control of material supply for both clinical trials and the commercial market, enable the more rapid implementation of process changes, and allow for better long-term margins for our gene therapy products. We currently anticipate construction of the facility to be completed in 2023. We do not have experience as a company, however, in developing a manufacturing facility and we may experience unexpected costs or delays or ultimately be unsuccessful in developing the facility or capability. 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 below 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, our manufacturing capabilities could be affected by cost-overruns, unexpected delays, equipment failures, lack of capacity, labor shortages, natural disasters, power failures, program failures, and numerous other factors that could prevent us from realizing the intended benefits of our manufacturing strategy and have a material adverse effect on our business.

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

The manufacturing process used to produce our gene therapy, mRNA, DNA and siRNA product candidates is novel, complex, and has not been validated for commercial use. Several factors could cause production interruptions, including equipment malfunctions, regulatory inspections, facility contamination, raw material shortages or contamination, natural disasters, disruption in utility services, human error or disruptions in the operations of our suppliers. Further, given that cGMP gene therapy, mRNA, DNA and siRNA manufacturing is a nascent industry, there are a small number of CMOs with the experience necessary to manufacture our gene therapy product candidates and we may have difficulty finding or maintaining relationships with such CMOs or hiring experts for internal manufacturing and accordingly, our production capacity may be limited.

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

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

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

As we currently lack the resources and the capability to manufacture our products and most of our product candidates on a clinical or commercial scale, we rely on third parties to manufacture our products and product candidates. Although we oversee the contract manufacturers, we cannot control the manufacturing process of, and are substantially dependent on, our contract manufacturing partners for compliance with the regulatory requirements. See "- *Even if we obtain regulatory approval for our product candidates, our products will remain subject to regulatory scrutiny"* risk factor above. Further, we depend on our manufacturers to purchase from third-party suppliers the materials necessary to produce our products and product candidates. There are a limited number of suppliers for raw materials that we use to manufacture our drugs, placebos, or active controls, and there may be a need to identify alternate suppliers to prevent a possible disruption of the manufacture of the materials necessary to produce our products and our product candidates for our clinical studies, and, if approved, ultimately for commercial sale. We also do not have any control over the process or timing of the acquisition of these raw materials by our manufacturers. We may also experience interruptions in supply of product if the product or raw material components fail to meet our quality control standards or the quality control standards of our suppliers.

Further, manufacturers that produce our products and product candidates may not have experience producing our products and product candidates at commercial levels and may not produce our products and product candidates at the cost, quality, quantities, locations, and timing needed to support profitable commercialization. We have not yet secured manufacturing capabilities for commercial quantities of all of our product candidates and may be unable to negotiate binding agreements with manufacturers to support our commercialization activities on commercially reasonable terms. Even if our third-party product manufacturers develop acceptable manufacturing processes that provide the necessary quantities of our products and product candidates in a compliant and timely manner, the cost to us for the supply of our products and product candidates manufactured by such third parties may be high and could limit our profitability. For instance, KKC is our sole supplier of commercial quantities of Crysvita. The supply price to us for commercial sales of Crysvita in Latin America and the transfer price for commercial sales of the product in the United States and Canada is 35% of net sales through December 31, 2022 and 30% thereafter, which is higher than the typical cost of goods sold by companies focused on rare diseases.

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

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

Any adverse developments affecting manufacturing operations for our products and product candidates may result in shipment delays, inventory shortages, lot failures, withdrawals or recalls, or other interruptions in the supply of our products and product candidates. For instance, during the fourth quarter of 2019, we experienced disruptions from our third-party supplier related to the fill and finish activities for the manufacture of Mepsevii, which negatively impacted our inventory of the product. Due to their stage of development, small volume requirements, and infrequency of batch production runs, we carry limited amounts of safety stock for our products and product candidates. We 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 to fulfill its supply obligations, we would not be able to manufacture and distribute the product or product candidate until a qualified alternative supplier is identified, which could significantly impair our ability to commercialize such product or delay the development of such product candidate. The drug substance and drug product for Crysvita are made by KKC pursuant to our license and collaboration agreement with KKC. The drug substance and drug product for Mepsevii are 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 our supply agreement with IOI Oleo, 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. Other than as described above, we have not currently secured any other suppliers for the drug substance or drug product of our products and product candidates and, although we believe that there are alternate sources of supply that could satisfy our clinical and commercial requirements, we cannot provide assurance that identifying alternate sources and establishing relationships with such sources would not result in significant expense or delay in the commercialization of our products or the development of our product candidates. 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.

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

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

Risks Related to Commercialization of Our Products and Product Candidates

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

We focus our research and product development on treatments for rare and ultra-rare genetic diseases. Given the small number of patients who have the diseases that we are targeting, it is critical to our ability to grow and become profitable that we continue to successfully identify patients with these rare and ultra-rare genetic diseases. Some of our current clinical programs may be most appropriate for patients with more severe forms of their disease. For instance, while adults make up the majority of the XLH patients, they often have less severe disease that may reduce the penetration of Crysvita in the adult population relative to the pediatric population. Given the overall rarity of the diseases we target, it is difficult to project the prevalence of the more severe forms, or the other subsets of patients that may be most suitable to address with our products and product candidates, which may further limit the addressable patient population to a small subset. Our projections of both the number of people who have these diseases, as well as the subset of people with these diseases who have the potential to benefit from treatment with our products and product candidates, are based on our beliefs and estimates. These estimates have been derived from a variety of sources, including the scientific literature, surveys of clinics, patient foundations, or market research, and may prove to be incorrect. Further, new studies may change the estimated incidence or prevalence of these diseases. The number of patients may turn out to be lower than expected. The effort to identify patients with diseases we seek to treat is in early stages, and we cannot accurately predict the number of patients for whom treatment might be possible. Additionally, the potentially addressable patient population for each of our products and product candidates may be limited or may not be amenable to treatment with our products and product candidates, and new patients may become increasingly difficult to identify or access, which would adversely affect our results of operations and our business. Further, even if we obtain significant market share for our products and product candidates, because the potential target populations are very small, we may never become or remain profitable nor generate sufficient revenue growth to sustain our business.

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

The biotechnology and pharmaceutical industries are intensely competitive and subject to rapid and significant technological change. We are currently aware of various existing treatments that may compete with our products and product candidates. See "Item 1. Business – Competition" in our Annual Report.

We have competitors both in the United States and internationally, including major multinational pharmaceutical companies, specialty pharmaceutical companies, biotechnology companies, startups, academic research institutions, government agencies, and public and private research institutions. Many of our competitors have substantially greater financial, technical, and other resources, such as larger research and development staff and experienced marketing and manufacturing organizations. Additional mergers and acquisitions in the biotechnology and pharmaceutical industries may result in even more resources being concentrated in our competitors. As a result, these companies may obtain regulatory approval more rapidly than we are able to and may be more effective in selling and marketing their products as well. Smaller or early-stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large, established companies. Competition may increase further as a result of advances in the commercial applicability of technologies and greater availability of capital for investment in these industries. Our competitors may succeed in developing, acquiring, or licensing on an exclusive basis, products that are more effective or less costly than any product candidate that we may develop, or achieve earlier patent protection, regulatory approval, product commercialization, and market penetration than we do. Additionally, technologies developed by our competitors may render our potential products and product candidates uneconomical or obsolete, and we may not be successful in marketing our products and product candidates against competitors.

We may not be able to effectively manage the expansion of our organization, including building an integrated commercial organization. If we are unable to expand our existing commercial infrastructure or enter into agreements with third parties to market and sell our products and product candidates, as needed, we may be unable to increase our revenue.

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

We, as a company, have limited, recent experience selling and marketing our product and only some of our employees have prior experience promoting other similar products in the past while employed at other companies. As we 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 United States and Canada expires in 2023.

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

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

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

- the efficacy of the product as demonstrated in clinical studies and potential advantages over competing treatments;
- the prevalence and severity of any side effects, including any limitations or warnings contained in a product’s approved labeling;
- the clinical indications for which approval is granted;
- relative convenience and ease of administration;
- the cost of treatment, particularly in relation to competing treatments;

- the willingness of the target patient population to try new therapies and of physicians to prescribe these therapies;
- the effectiveness of our field forces and marketing efforts;
- the strength of marketing and distribution support and timing of market introduction of competitive products;
- publicity concerning our products or competing products and treatments; and
- sufficient third-party insurance coverage and reimbursement.

Even if a potential product displays a favorable efficacy and safety profile in nonclinical and clinical studies, market acceptance of the product will not be fully known until after it is launched. Our efforts to educate the medical community and payors on the benefits of the product candidates require significant resources and may never be successful. If our current and future products fail to achieve an adequate level of acceptance by physicians, patients, payors, and others in the medical community, we will not be able to generate sufficient revenue to become or remain profitable.

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

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

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

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

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

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

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

Risks Related to Our Intellectual Property

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Risks Related to Our Business Operations

Actual or threatened public health epidemics or outbreaks, including the ongoing COVID-19 pandemic, 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 December 2019, a new strain of novel coronavirus (COVID-19) emerged in Wuhan, Hubei Province, China. In March 2020, the World Health Organization declared COVID-19 a pandemic.

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

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

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 are currently seeking alternative sources of supply of drug product or raw materials in an attempt to avoid future potential delays in supply of product, which may result in additional expenses. 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, and in accordance with shelter-in-place direction from state and local government authorities, we have restricted access to our facilities to personnel and third parties who must perform critical activities that must be completed on-site, limited the number of such personnel that can be present at our facilities at any one time, and requested that most of our personnel work remotely, including significant limitations on access to our laboratory space. As vaccines against COVID-19 become more widely available, we plan to ease restrictions to our facilities and allow our employees 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. The magnitude of the adverse effect on our business operations will depend, in part, on the length and severity of the restrictions and other limitations on our ability to conduct our business in the ordinary course.

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

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

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

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

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

Our business strategy focuses on the development of drugs that are eligible for FDA and EU orphan drug designation. In the United States, orphan drug designation entitles a party to financial incentives such as opportunities for grant funding towards clinical study costs, tax advantages, and user-fee waivers. In addition, if a product receives the first FDA approval for the indication for which it has orphan designation, the product is entitled to orphan drug exclusivity, which means the FDA may not approve any other application to market the same drug for the same indication for a period of seven years, except in limited circumstances, such as a showing of clinical superiority over the product with orphan exclusivity or where the manufacturer is unable to assure sufficient product quantity. In the EU, orphan drug designation entitles a party to financial incentives such as reduction of fees or fee waivers and ten years of market exclusivity following drug or biological product approval. This period may be reduced to six years if the orphan drug designation criteria are no longer met, including where it is shown that the product is sufficiently profitable not to justify maintenance of market exclusivity.

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

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

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

As a result of the accounting for our acquisition of Dimension Therapeutics, Inc. (Dimension) in November 2017, we have recorded on our balance sheet intangible assets for in-process research and development (IPR&D) related to DTX301 and DTX401. Following the FDA approval of Dojolvi in June 2020, we have also recorded contract-based intangible assets related to our license from third parties for certain assets related to the product. We test the intangible assets for impairment annually during the fourth quarter and more frequently if events or changes in circumstances indicate that it is more likely than not that the asset is impaired. If the associated research and development effort is abandoned, the related assets will be written-off and we will record a noncash impairment loss on our statement of operations. We have not recorded any impairments related to our intangible assets through the end of June 30, 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 under “Item 1. Business - Government Regulation” in our Annual Report and in the Risk Factor above entitled “ – *The insurance coverage and reimbursement status of newly approved products is uncertain*” there have been and continue to be a number of legislative initiatives to contain healthcare costs and to modify the regulation of drug and biologic products. We expect that additional state and federal healthcare reform measures and regulations will be adopted in the future, including proposals to reduce the exclusivity protections provided to already approved biological products and to provide biosimilar and interchangeable biologic products an easier path to approval. Any of these measures and regulations could limit the amounts that federal and state governments will pay for healthcare products and services, result in reduced demand for our product candidates or additional pricing pressures and affect our product development, testing, marketing approvals and post-market activities.

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

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

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

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

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

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

- multiple, conflicting, and changing laws and regulations such as privacy and data regulations, transparency regulations, tax laws, export and import restrictions, employment laws, regulatory requirements, and other governmental approvals, permits, and licenses;
- introduction of new health authority requirements and/or changes in health authority expectations;
- failure by us to obtain and maintain regulatory approvals for the use of our products in various countries;
- additional potentially relevant third-party patent rights;
- complexities and difficulties in obtaining protection for, and enforcing, our intellectual property;
- difficulties in staffing and managing foreign operations;
- complexities associated with managing multiple payor reimbursement regimes, government payors, or patient self-pay systems;
- limits on our ability to penetrate international markets;
- financial risks, such as longer payment cycles, difficulty collecting accounts receivable, the impact of local and regional financial crises on demand and payment for our products, and exposure to foreign currency exchange rate fluctuations;
- natural disasters and political and economic instability, including wars, terrorism, political unrest, results of certain elections and votes, actual or threatened public health emergencies and outbreak of disease (including for example, the COVID-19 pandemic), boycotts, adoption or expansion of government trade restrictions, and other business restrictions;
- certain expenses including, among others, expenses for travel, translation, and insurance;
- regulatory and compliance risks that relate to maintaining accurate information and control over commercial operations and activities that may fall within the purview of the U.S. Foreign Corrupt Practices Act, or FCPA, its books and records provisions, or its anti-bribery provisions, including those under the U.K. Bribery Act and similar foreign laws and regulations; and
- regulatory and compliance risks relating to doing business with any entity that is subject to sanctions administered by the Office of Foreign Assets Control of the U.S. Department of the Treasury.

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

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

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

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

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 may be due to 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, may also pose a risk that sensitive data may be exposed to unauthorized persons or to the public. If a system failure or security breach occurs and interrupts our operations or the operations at one of our third-party vendors or partners, it could result in intellectual property and other proprietary or confidential information being lost or stolen or a material disruption of our drug development programs 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, any of which could materially adversely affect our business.

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

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

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

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

The value of our investments in other companies or businesses may also fluctuate significantly and impact our operating results quarter to quarter or year to year. For instance, in June 2019, we purchased 2.4 million shares of common stock of Arcturus and in May 2020, we exercised our option to purchase an additional 600,000 shares of Arcturus' common stock pursuant to the terms of our equity purchase agreement with Arcturus; we subsequently sold an aggregate of 800,000 shares in December 2020. We also purchased 7,825,797 shares of common stock of Solid in October 2020. We have elected to apply the fair value option to account for our equity investments in Arcturus and Solid. As a result, increases or decreases in the stock price of Arcturus and Solid common stock will result in accompanying changes in the fair value of our investments, and cause substantial volatility in, our operating results for the reporting period. For instance, the changes in fair value of the Arcturus and Solid investments recognized in the Consolidated Statements of Operations for the three and six months ended June 30, 2021 was a $31.0 million and a $51.7 million decrease, respectively, primarily due to the lower Arcturus and Solid stock price as of June 30, 2021 compared to the prior period. The changes in fair value of the Arcturus investment recognized in the Consolidated Statements of Operations for the three and six months ended June 30, 2020 was a $95.2 and a $102.9 million increase, respectively, primarily due to the higher Arcturus stock price as of June 30, 2020 compared to the prior period. The losses and gains in fair value of the equity investments for the three and six months ended June 30, 2021 and for the three and six months ended June 30, 2020 increased and decreased, respectively, the amount of our net loss during those periods. If the Arcturus or Solid stock price had been lower at June 30, 2021 and 2020 compared to the prior period, we would have reported an even greater net loss for the three and six months ended June 30, 2021 and for the six months ended June 30, 2020. As the fair value of our investments in Arcturus and Solid is dependent on the stock price of Arcturus and Solid, which has recently seen wide fluctuations, the value of our investments and the impact on our operating results may similarly fluctuate significantly from quarter to quarter and year to year such that period-to-period comparisons may not be a good indication of the future value of the investments and our future operating results.

Risks Related to Ownership of Our Common Stock

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

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

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

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

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

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

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

Pursuant to our 2014 Incentive Plan, or the 2014 Plan, our management is authorized to grant stock options and other equity-based awards to our employees, directors, and consultants. At June 30, 2021, 4,103,718 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 June 30, 2021, 3,956,907 shares were available for issuance under the 2014 ESPP. Through January 1, 2024, the number of shares available for issuance under the 2014 ESPP will automatically increase on January 1 of each year by the lesser of 1,200,000 shares or 1% of all shares of our capital stock outstanding as of December 31 of the prior calendar year, subject to the ability of our compensation committee to take action to reduce the size of the increase in any given year.

In February 2021, our board of directors adopted an employment inducement plan with a maximum of 500,000 shares available for grant under the plan. At June 30, 2021, 488,223 shares were available for issuance under the inducement plan. We have registered all the shares under our inducement plan. In addition, we currently plan to register the increased number of shares available under the 2014 Plan and the 2014 ESPP each year. If our board of directors elects to increase the number of shares available for future grant under the 2014 Plan, the 2014 ESPP or the inducement plan, our stockholders may experience additional dilution, which could cause our stock price to fall.

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

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

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

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

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

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

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

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

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

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

General Risk Factors

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

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

We may incur additional tax liabilities related to our operations.

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

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

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

Litigation may substantially increase our costs and harm our business.

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

Item 2. *Unregistered Sales of Equity Securities and Use of Proceeds*

None.

Item 3. ***Defaults Upon Senior Securities***

None.

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

Not applicable.

Item 5. ***Other Information***

None.

Item 6. ***Exhibits***

Exhibit Number	Exhibit Description	Incorporated by Reference Form	Date	Number	Furnished or Filed Herewith
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	S-3ASR	2/12/2021	4.2	
10.1#	Ultragenyx Pharmaceutical Inc. Deferred Compensation Plan				X
10.2#	Form of Non-Statutory Stock Option Agreement (Annual Grant for Directors)				X
10.3#	Form of Restricted Stock Unit Agreement (Annual Grant for Directors)				X
10.4#	Form of Non-Statutory Stock Option Agreement (Grant for New Directors)				X
10.5#	Form of Restricted Stock Unit Agreement (Grant for New Directors)				X
10.6	Open Market Sales Agreement, dated May 7, 2021, by and between Ultragenyx Pharmaceutical Inc. and Jefferies LLC	8-K	5/7/2021	1.1	
31.1	Certification of Principal Executive Officer Required Under Rule 13a-14(a) or Rule 15d-14(a) of the Exchange Act				X
31.2	Certification of Principal Financial Officer Required Under Rule 13a-14(a) or Rule 15d-14(a) of the Exchange Act				X
32.1*	Certification of Principal Executive Officer and Principal Financial Officer Required Under Rule 13a-14(b) or Rule 15d-14(b) of the Exchange Act and 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	Cover Page Interactive Data File, formatted in Inline XBRL (included in Exhibit 101).				

# Indicates management contract or compensatory plan.

† 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.

* The certification attached as Exhibit 32.1 that accompanies this Quarterly Report is furnished to, and not deemed filed with, the SEC and is not to be incorporated by reference into any filing of the Registrant under the Securities Act or the Exchange Act, whether made before or after the date of this Form 10-Q, irrespective of any general incorporation language contained in such filing.

SIGNATURES

Pursuant to the requirements 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.
Date: August 2, 2021	By: /s/ Emil D. Kakkis Emil D. Kakkis, M.D., Ph.D. President and Chief Executive Officer (Duly Authorized Officer)
Date: August 2, 2021	By: /s/ Mardi C. Dier Mardi C. Dier Executive Vice President and Chief Financial Officer (Principal Financial Officer)
Date: August 2, 2021	By: /s/ Theodore A. Huizenga Theodore A. Huizenga Senior Vice President and Chief Accounting Officer (Principal Accounting Officer)

ULTRAGENYX PHARMACEUTICAL INC.
DEFERRED COMPENSATION PLAN

Effective Date
June 10, 2021

Ultragenyx Pharmaceutical Inc. Deferred Compensation Plan

Ultragenyx Pharmaceutical Inc. Deferred Compensation Plan

ARTICLE I
Establishment and Purpose

Ultragenyx Pharmaceutical Inc. (the "Company") has adopted this Ultragenyx Pharmaceutical Inc. Deferred Compensation Plan, applicable to Compensation deferred under Compensation Deferral Agreements submitted on and after the Effective Date and Company Contributions credited on or after the Effective Date.

The purpose of the Plan is to attract and retain key employees and members of the Board of Directors by providing them with an opportunity to defer receipt of a portion of their salary, bonus, and other specified compensation. The Plan is not intended to meet the qualification requirements of Code Section 401(a), but is intended to meet the requirements of Code Section 409A, and shall be operated and interpreted consistent with that intent.

The Plan constitutes an unsecured promise by a Participating Employer to pay benefits in the future. Participants in the Plan shall have the status of general unsecured creditors of the Company or the Participating Employer, as applicable. Each Participating Employer shall be solely responsible for payment of the benefits attributable to services performed for it. The Plan is unfunded for Federal tax purposes and is intended to be an unfunded arrangement for eligible employees who are part of a select group of management or highly compensated employees of the Employer within the meaning of Sections 201(2), 301(a)(3) and 401(a)(1) of ERISA and non-employee members of the Board of Directors. Any amounts set aside to defray the liabilities assumed by the Company or a Participating Employer will remain the general assets of the Company or the Participating Employer and shall remain subject to the claims of the Company's or the Participating Employer's creditors until such amounts are distributed to the Participants.

ARTICLE II
Definitions

2.1 Account. Account means a bookkeeping account maintained by the Committee to record the payment obligation of a Participating Employer to a Participant as determined under the terms of the Plan. The Committee may maintain an Account to record the total obligation to a Participant and component Accounts to reflect amounts payable at different times and in different forms. Reference to an Account means any such Account established by the Committee, as the context requires. Accounts are intended to constitute unfunded obligations within the meaning of Sections 201(2), 301(a)(3) and 401(a)(1) of ERISA.

2.2 Account Balance. Account Balance means, with respect to any Account, the total payment obligation owed to a Participant from such Account as of the most recent Valuation Date.

2.3 Affiliate. Affiliate means a corporation, trade or business that, together with the Company, is treated as a single employer under Code Section 414(b) or (c).

2.4 Beneficiary. Beneficiary means a natural person, estate, or trust designated by a Participant in accordance with Section 6.5 hereof to receive payments to which a Beneficiary is entitled in accordance with provisions of the Plan.

2.5 Board of Directors. Board of Directors means, for a Participating Employer organized as a corporation, its board of directors and for a Participating Employer organized as a limited liability company, its board of managers.

2.6 Business Day. Business Day means each day on which the New York Stock Exchange is open for business.

2.7 Change in Control. Change in Control means, with respect to a Participating Employer that is organized as a corporation, any of the following events: (i) a change in the ownership of the Participating Employer, (ii) a change in the effective control of the Participating Employer, or (iii) a change in the ownership of a substantial portion of the assets of the Participating Employer.

Change in Ownership. For purposes of this Section, a change in the ownership of the Participating Employer occurs on the date on which any one person, or more than one person acting as a group, acquires ownership of stock of the Participating Employer that, together with stock held by such person or group constitutes more than 50% of the total fair market value or total voting power of the stock of the Participating Employer. The acquisition by a person or group owning more than 50% of the total fair market value or total voting power of the stock of such Participating Employer of additional shares of such Participating Employer shall not constitute a “change of the ownership” of such Participating Employer.
Change in Effective Control. A change in the effective control of the Participating Employer occurs on the date on which either: (i) a person, or more than one person acting as a group, acquires ownership of stock of the Participating Employer possessing 30% or more of the total voting power of the stock of the Participating Employer, taking into account all such stock acquired during the 12-month period ending on the date of the most recent acquisition, provided that the acquisition by a person or group owning more than 30% of the total fair market value or total voting power of the stock of such Participating Employer of additional shares of such Participating Employer shall not constitute a “change of effective control” of such Participating Employer, or (ii) a majority of the members of the Participating Employer’s Board of Directors is replaced during any 12-month period by directors whose appointment or election is not endorsed by a majority of the members of such Board of Directors prior to the date of the appointment or election, but only if no other corporation is a majority shareholder of the Participating Employer.

Change in Ownership of Substantial Portion of Assets. A change in the ownership of a substantial portion of assets occurs on the date on which any one person, or more than one person acting as a group, other than a person or group of persons that is related to the

Participating Employer, acquires assets from the Participating Employer that have a total gross fair market value equal to or more than 40% of the total gross fair market value of all of the assets of the Participating Employer immediately prior to such acquisition or acquisitions, taking into account all such assets acquired during the 12-month period ending on the date of the most recent acquisition. A transfer of assets shall not be treated as a "change in the ownership of a substantial portion of the assets" when such transfer is made to an entity that is controlled by the shareholders of the transferor corporation as determined under Treas. Reg. section 1.409A-3(i)(5)(vii)(B).

An event constitutes a Change in Control with respect to a Participant only if the Participant performs services for the Participating Employer that has experienced the Change in Control, or the Participant's relationship to the affected Participating Employer otherwise satisfies the requirements of Treasury Regulation Section 1.409A-3(i)(5)(ii).

Notwithstanding anything to the contrary herein, with respect to a Participating Employer that is a partnership or limited liability company, Change in Control means only a change in the ownership of such entity or a change in the ownership of a substantial portion of the assets of such entity, and the provisions set forth above respecting such changes relative to a corporation shall be applied by analogy. Any reference to a "majority shareholder" shall be treated as referring to a partner or member that (a) owns more than 50% of the capital and profits interest of such entity, and (b) alone or together with others is vested with the continuing exclusive authority to make management decisions necessary to conduct the business for which the partnership or limited liability company was formed.

2.8 Claimant. Claimant means a Participant or Beneficiary filing a claim under Article XI of this Plan.

2.9 Code. Code means the Internal Revenue Code of 1986, as amended from time to time.

2.10 Code Section 409A. Code Section 409A means section 409A of the Code, and regulations and other guidance issued by the Treasury Department and Internal Revenue Service thereunder.

2.11 Committee. Committee means the Company or a committee appointed by the Company to administer the Plan.

2.12 Company. Company means Ultragenyx Pharmaceutical Inc.

2.13 Company Contribution. Company Contribution means a credit by a Participating Employer to a Participant's Account(s) in accordance with the provisions of Article V of the Plan. Unless the context clearly indicates otherwise, a reference to Company Contribution shall include Earnings attributable to such contribution.

2.14 Compensation. Compensation means a Participant's salary, bonus, commission, Director fees and retainer and such other cash or equity-based compensation approved by the Committee as Compensation that may be deferred under Section 4.2 of this Plan, excluding any compensation that has been previously deferred under this Plan or any other arrangement subject to Code Section 409A and excluding any compensation that is not U.S. source income.

2.15 Compensation Deferral Agreement. Compensation Deferral Agreement means an agreement between a Participant and a Participating Employer that specifies: (i) the amount of each component of Compensation that the Participant has elected to defer to the Plan in accordance with the provisions of Article IV, and (ii) the Payment Schedule applicable to one or more Accounts.

2.16 Deferral. Deferral means a credit to a Participant's Account(s) that records that portion of the Participant's Compensation that the Participant has elected to defer to the Plan in accordance with the provisions of Article IV. Unless the context of the Plan clearly indicates otherwise, a reference to Deferrals includes Earnings attributable to such Deferrals.

2.17 Director. Director means a non-employee member of the Board of Directors of the Company.

2.18 Earnings. Earnings means an adjustment to the value of an Account in accordance with Article VII.

2.19 Effective Date. Effective Date means June 10, 2021.

2.20 Eligible Employee. Eligible Employee means an Employee who is a member of a select group of management or highly compensated employees or an independent contractor who has been notified during an applicable enrollment of his or her status as an Eligible Employee. The Committee has the discretion to determine which Employees and independent contractors are Eligible Employees for each enrollment.

2.21 Employee. Employee means a common-law employee of an Employer.

2.22 Employer. Employer means the Company and each Affiliate.

2.23 ERISA. ERISA means the Employee Retirement Income Security Act of 1974, as amended from time to time.

2.24. In-Service Account. In-Service Account means an Account established by the Committee to record the amounts payable in a future year as specified in the Participant's Compensation Deferral Agreement. In-Service Accounts are payable upon an earlier Separation from Service, as provided in Section 6.3.

2.25 Participant. Participant means an individual described in Article III.

2.26 Participating Employer. Participating Employer means the Company and each Affiliate who has adopted the Plan with the consent of the Company. Each Participating Employer shall be identified on Schedule A attached hereto.

2.27 Payment Schedule. Payment Schedule means the date as of which payment of an Account will commence and the form in which payment of such Account will be made under the terms of a payment election in effect for such Account under the terms of this Plan.

2.28 Performance-Based Compensation. Performance-Based Compensation means Compensation where the amount of, or entitlement to, the Compensation is contingent on the satisfaction of pre-established organizational or individual performance criteria relating to a performance period of at least 12 consecutive months. Organizational or individual performance criteria are considered pre-established if established in writing by not later than 90 days after the commencement of the period of service to which the criteria relate, provided that the outcome is substantially uncertain at the time the criteria are established. Performance-Based Compensation shall not include any Compensation payable upon the Participant's death or disability (as defined in Treas. Section 1.409A-1(e)) without regard to the satisfaction of the performance criteria.

2.29 Plan. Plan means "Ultragenyx Pharmaceutical Inc. Deferred Compensation Plan" as documented herein and as may be amended from time to time hereafter. However, to the extent permitted or required under Code Section 409A, the term Plan may in the appropriate context also means a portion of the Plan that is treated as a single plan under Treas. Reg. Section 1.409A-1(c), or the Plan or portion of the Plan and any other nonqualified deferred compensation plan or portion thereof that is treated as a single plan under such section.

2.30 Plan Year. Plan Year means January 1 through December 31.

2.31 Separation Account. Separation Account means an Account established by the Committee in accordance with a Participant's Compensation Deferral Agreement to record Deferrals allocated to such Account by the Participant and which are payable upon the Participant's Separation from Service as set forth in Section 6.3. A Participant is limited to one Separation Account per Plan Year.

2.32 Separation from Service. Separation from Service means an Employee's termination of employment with the Employer and all Affiliates.

Except in the case of an Employee on a bona fide leave of absence as provided below, an Employee is deemed to have incurred a Separation from Service if the Employer and the Employee reasonably anticipated that the level of services to be performed by the Employee after a date certain would be reduced to 20% or less of the average services rendered by the Employee during the immediately preceding 36-month period (or the total period of employment, if less than 36 months), disregarding periods during which the Employee was on a bona fide leave of absence.

An Employee who is absent from work due to military leave, sick leave, or other bona fide leave of absence shall incur a Separation from Service on the first date immediately following the later of: (i) the six month anniversary of the commencement of the leave, or (ii) the expiration of the Employee's right, if any, to reemployment under statute or contract.

If a Participant ceases to provide services as an Employee and begins providing services as an independent contractor for the Employer, a Separation from Service shall occur only if the parties anticipate that the level of services to be provided as an independent contractor are such that a Separation from Service would have occurred if the Employee had continued to provide services at that level as an Employee. If, in accordance with the preceding sentence, no Separation from Service occurs as of the date the individual's employment status changes, a Separation from Service shall occur thereafter only upon the 12-month anniversary of the date all contracts with the Employer have expired, provided the Participant does not perform services for the Employer during that time.

For purposes of determining whether a Separation from Service has occurred, the Employer means the Employer as defined in Section 2.22 of the Plan, except that in applying Code sections 1563(a)(1), (2) and (3) for purposes of determining whether another organization is an Affiliate of the Company under Code Section 414(b), and in applying Treasury Regulation Section 1.414(c)-2 for purposes of determining whether another organization is an Affiliate of the Company under Code Section 414(c), "at least 50 percent" shall be used instead of "at least 80 percent" each place it appears in those sections.

The Committee specifically reserves the right to determine whether a sale or other disposition of substantial assets to an unrelated party constitutes a Separation from Service with respect to a Participant providing services to the seller immediately prior to the transaction and providing services to the buyer after the transaction.

2.33 Specified Date Account. Specified Date Account means an Account established by the Committee to record the amounts payable in a future year as specified in the Participant's Compensation Deferral Agreement. Specified Date Accounts are excluded from any Separation from Service payments under Section 6.3.

2.34 Substantial Risk of Forfeiture. Substantial Risk of Forfeiture has the meaning specified in Treas. Reg. Section 1.409A-1(d).

2.35 Unforeseeable Emergency. Unforeseeable Emergency means a severe financial hardship to the Participant resulting from an illness or accident of the Participant, the Participant's spouse, the Participant's dependent (as defined in Code section 152, without regard to section 152(b)(1), (b)(2), and (d)(1)(B)), or a Beneficiary; loss of the Participant's property due to casualty (including the need to rebuild a home following damage to a home not otherwise covered by insurance, for example, as a result of a natural disaster); or other similar extraordinary and unforeseeable circumstances arising as a result of events beyond the control of the Participant. The types of events which may qualify as an Unforeseeable Emergency may be limited by the Committee.

2.36 Valuation Date. Valuation Date means each Business Day.

Article III
Eligibility and Participation

3.1 Eligibility and Participation. All Eligible Employees and Directors may enroll in the Plan. Eligible Employees and Directors become Participants on the first to occur of (i) the date on which the first Compensation Deferral Agreement becomes irrevocable under Article IV, or (ii) for Eligible Employees only, the date Company Contributions are credited to an Account on behalf of an Eligible Employee.

3.2 Duration. Only Eligible Employees and Directors may submit Compensation Deferral Agreements during an enrollment period and receive Company Contributions during the Plan Year. A Participant who is no longer an Eligible Employee but has not incurred a Separation from Service will not be allowed to submit Compensation Deferral Agreements but may otherwise exercise all of the rights of a Participant under the Plan with respect to his or her Account(s). On and after a Separation from Service, a Participant shall remain a Participant as long as his or her Account Balance is greater than zero (0). All Participants, regardless of employment status, will continue to be credited with Earnings and during such time may continue to make allocation elections as provided in Section 7.4. An individual shall cease being a Participant in the Plan when his Account has been reduced to zero (0).

3.3 Rehires. An Eligible Employee who Separates from Service and who subsequently resumes performing services as an Employee in the same calendar year (regardless of eligibility) will have his or her Compensation Deferral Agreement for such year, if any, reinstated, but his or her eligibility to participate in the Plan in years subsequent to the year of rehire shall be governed by the provisions of Section 3.1.

Article IV
Deferrals

4.1 Deferral Elections, Generally.

(a) An Eligible Employee or Director may make an initial election to defer Compensation by submitting a Compensation Deferral Agreement during the enrollment periods established by the Committee and in the manner specified by the Committee, but in any event, in accordance with Section 4.2. Unless an earlier date is specified in the Compensation Deferral Agreement, deferral elections with respect to a Compensation source (such as salary, bonus or other Compensation) become irrevocable on the latest date applicable to such Compensation source under Section 4.2.

(b) A Compensation Deferral Agreement that is not timely filed with respect to a service period or component of Compensation, or that is submitted by a Participant who Separates from Service prior to the latest date such agreement would become irrevocable under Section 409A, shall be considered null and void and shall not take effect with respect to such item of Compensation. The Committee may modify or revoke any Compensation Deferral Agreement prior to the date the election becomes irrevocable under the rules of Section 4.2.

(c) The Committee may permit different deferral amounts for each component of Compensation and may establish a minimum or maximum deferral amount for each such component. Unless otherwise specified by the Committee in the Compensation Deferral Agreement, Participants may defer a minimum of 5% up to a maximum of 75% of their base compensation and a minimum of 5% up to a maximum of 100% of bonus, commissions, or other Compensation earned during a Plan Year.

(d) Deferrals of cash Compensation shall be calculated with respect to the gross cash Compensation payable to the Participant prior to any deductions or withholdings, but shall be reduced by the Committee as necessary so as not to exceed 100% of the cash Compensation of the Participant remaining after deduction of all required income and employment taxes, required employee benefit deductions, deferrals to 401(k) plans and other deductions required by law. Changes to payroll withholdings that affect the amount of Compensation being deferred to the Plan shall be allowed only to the extent permissible under Code Section 409A.

(e) The Eligible Employee or Director shall specify on his or her Compensation Deferral Agreement the amount of Deferrals and whether to allocate Deferrals to a Separation Account or to one or more Specified Date Accounts or In-Service Accounts.

4.2 <u>Timing Requirements for Compensation Deferral Agreements</u>.

(a) *Initial Eligibility.* The Committee may permit an Eligible Employee or Director to defer Compensation earned in the first year of eligibility. The Compensation Deferral Agreement must be filed within 30 days after attaining Eligible Employee or Director status and becomes irrevocable not later than the 30th day.

A Compensation Deferral Agreement filed under this paragraph applies to Compensation earned after the date that the Compensation Deferral Agreement becomes irrevocable.

(b) *Prior Year Election.* Except as otherwise provided in this Section 4.2, the Committee may permit an Eligible Employee or Director to defer Compensation by filing a Compensation Deferral Agreement no later than December 31 of the year prior to the year in which the Compensation to be deferred is earned. A Compensation Deferral Agreement filed under this paragraph shall become irrevocable with respect to such Compensation not later than the December 31 filing deadline.

(c) *Performance-Based Compensation.* The Committee may permit an Eligible Employee or Director to defer Compensation which qualifies as Performance-Based Compensation by filing a Compensation Deferral Agreement no later than the date that is six months before the end of the applicable performance period, provided that:

(i) the Participant performs services continuously from the later of the beginning of the performance period or the date the performance criteria are established through the date the Compensation Deferral Agreement is submitted; and

(ii) the Compensation is not readily ascertainable as of the date the Compensation Deferral Agreement is filed.

Any election to defer Performance-Based Compensation that is made in accordance with this paragraph and that becomes payable as a result of the Participant's death or disability (as defined in Treas. Reg. Section 1.409A-1(e)) or upon a change in control (as defined in Treas. Reg. Section 1.409A-3(i)(5)) prior to the satisfaction of the performance criteria, will be void unless it would be considered timely under another rule described in this Section.

(d) *Certain Forfeitable Rights.* With respect to a legally binding right to a payment in a subsequent year that is subject to a forfeiture condition requiring the Participant's continued services for a period of at least 12 months from the date the Participant obtains the legally binding right, the Committee may permit an Eligible Employee or Director to defer such Compensation by filing a Compensation Deferral Agreement on or before the 30th day after the legally binding right to the Compensation accrues, provided that the Compensation Deferral Agreement is submitted at least 12 months in advance of the earliest date on which the forfeiture condition could lapse. The Compensation Deferral Agreement described in this paragraph becomes irrevocable not later than such 30th day. If the forfeiture condition applicable to the payment lapses before the end of such 12-month period as a result of the Participant's death or disability (as defined in Treas. Reg. Section 1.409A-3(i)(4)) or upon a change in control (as defined in Treas. Reg. Section 1.409A-3(i)(5)), the Compensation Deferral Agreement will be void unless it would be considered timely under another rule described in this Section.

(e) *"Evergreen" Deferral Elections.* The Committee, in its discretion, may provide that Compensation Deferral Agreements will continue in effect for subsequent years or performance periods by communicating that intention to Participants in writing prior to the date Compensation Deferral Agreements become irrevocable under this Section 4.2. An evergreen Compensation Deferral Agreement may be revoked or modified in writing prospectively by the Participant or the Committee with respect to Compensation for which such election remains revocable under this Section 4.2.

A Compensation Deferral Agreement is deemed to be revoked for subsequent years if the Participant is not an Eligible Employee or Director as of the last permissible date for making elections under this Section 4.2 or if the Compensation Deferral Agreement is cancelled in accordance with Section 4.6.

4.3 Allocation of Deferrals. A Compensation Deferral Agreement may allocate Deferrals to a Separation Account for the Plan Year or to one or more Specified Date Accounts or In-Service Accounts. The Committee may, in its discretion, establish in a written communication during enrollment a minimum deferral period for the establishment of a Specified Date Account or In-Service Account (for example, the second Plan Year following the year Compensation is first allocated to such Account). In the event a Participant's Compensation Deferral Agreement allocates a component of Compensation to a Specified Date Account or In-Service Account that commences payment in the year such Compensation is earned or an earlier year, the Compensation Deferral Agreement shall be deemed to allocate the Deferral to the Participant's Specified Date Account or In-Service Account (consistent with the type of Account designated in the Participant's Compensation Deferral Agreement) having the next earliest payment year. If the Participant has no other Specified Date Account or In-Service Account, the Committee will establish and allocate the Deferral to a Specified Date Account or In-Service Account (consistent with the type of Account designated in the Participant's Compensation Deferral Agreement) payable in the fifth calendar year following the Plan Year in which the applicable Compensation is earned.

4.4 Deductions from Pay. The Committee has the authority to determine the payroll practices under which any component of Compensation subject to a Compensation Deferral Agreement will be deducted from a Participant's Compensation.

4.5 Vesting. Participant Deferrals of cash Compensation shall be 100% vested at all times. Deferrals of awards of Compensation subject to vesting shall become vested in accordance with the provisions of the underlying award.

4.6 Cancellation of Deferrals. The Committee may cancel a Participant's Deferrals: (i) for the balance of the Plan Year in which an Unforeseeable Emergency occurs, and (ii) during periods in which the Participant is unable to perform the duties of his or her position or any substantially similar position due to a mental or physical impairment that can be expected to result in death or last for a continuous period of at least six months, provided cancellation occurs by the later of the end of the taxable year of the Participant or the 15th day of the third month following the date the Participant incurs the disability (as defined in this paragraph (ii)).

Article V
Company Contributions

5.1 Discretionary Company Contributions. A Participating Employer may, from time to time in its sole and absolute discretion, credit discretionary Company Contributions in the form of matching, profit sharing or other contributions to any Eligible Employee in any amount determined by the Participating Employer. Company Contributions are credited to the Eligible Employee's Separation Account for the Plan Year for which such contribution is made.

Make-Up Matching Contribution. Company Contributions may take the form of "make-up" matching contributions, at the same matching contribution rate provided under the Company 401(k) plan with respect to Deferrals that reduce 401(k) plan compensation below the limitation set forth in Code Section 401(a)(17).

Supplemental Matching Contribution. Company Contributions may take the form of "supplemental" matching contributions, at the same contribution rate provided under the Company 401(k) plan with respect to compensation deferred above the compensation limit set forth in Code Section 401(a)(17).

Discretionary Company Contribution. Discretionary Company Contributions are credited at the sole discretion of the Participating Employer and the fact that a discretionary Company Contribution is credited in one year shall not obligate the Participating Employer to continue to make such Company Contributions in subsequent years.

5.2 Vesting. Company Contributions vest according the schedule specified by the Committee on or before the time the contributions are made. Make-up and supplemental matching contributions vest at the same rate as matching contributions under the Company 401(k) plan.

Deferrals of equity-based Compensation will vest as provided under the terms of the applicable award.

All Company Contributions become 100% vested if, while employed by an Employer, a Participant dies, a Participant becomes disabled, his or her Employer experiences a change in control as determined by the Company or the Participant attains age 65.

Article VI
Payments from Accounts

6.1 General Rules. A Participant's Accounts become payable upon the first to occur of the payment events applicable to such Account under Sections 6.2 through 6.7.

Payment events and Payment Schedules elected by the Participant shall be set forth in a valid Compensation Deferral Agreement that establishes the Account to which such elections apply in accordance with Article IV or in a valid modification election applicable to such Account as described in Section 6.10.

Payment amounts are based on Account Balances as of the last Valuation Date of the month next preceding the month actual payment is made.

6.2 Specified Date Accounts and In-Service Accounts.

Commencement. Payment is made or begins in the year designated by the Participant for each Specified Date or In-Service Account.

Form of Payment. Payment of a Specified Date Account will be made in a lump sum, unless the Participant elected to receive such Account in the form of a designated number of annual installments up to 15 years.

Payment of an In-Service Account will be made in a lump sum, unless the Participant elected to receive such Account in the form of a designated number of annual installments up to five years.

Effect of Earlier Separation from Service. The time and form of payment of Specified Date Accounts is unaffected by an earlier Separation from Service. The unpaid Account Balance of an In-Service Account is paid in a lump sum following the Participant's Separation from Service, as set forth in Section 6.3.

6.3 Separation from Service. Upon a Participant's Separation from Service other than death, the Participant is entitled to receive his or her vested Separation Accounts and the unpaid vested Account Balances of any In-Service Accounts.

Commencement. All Accounts payable hereunder commence payment in the calendar year next following the calendar year in which Separation from Service occurs, provided that a Participant may elect to commence payment from any Separation Account in a later year.

Notwithstanding the foregoing, payment to a Participant who is a "specified employee" as defined in Code Section 409A(a)(2)(B) will be made or commence no earlier than the seventh month following his or her Separation from Service.

Form of Payment. Each Separation Account will be paid in a single lump sum, unless the Participant elected to receive such Account in a designated number of annual installments up to 15 years.

All In-Service Accounts will be paid in a single lump sum.

6.4 Change in Control. A Participant who experiences a Separation from Service within 18 months following a Change in Control will receive all of his or her unpaid Accounts in a single lump sum commencing in the calendar year next following the year in which Separation from Service occurs, regardless of any other elections he or she may have made with respect to any Account.

Notwithstanding any other provision of this Section 6.4, payment of any Account to a Participant who is a "specified employee" as defined in Code Section 409A(a)(2)(B) will commence no earlier than the seventh month following his or her Separation from Service.

6.5 Death. Notwithstanding anything to the contrary in this Article VI, upon the death of the Participant (regardless of whether such Participant is an Employee at the time of death), all remaining vested Account Balances shall be paid to his or her Beneficiary in a single lump sum no later than December 31 of the calendar year following the year of the Participant's death.

(a) *Designation of Beneficiary in General*. The Participant shall designate a Beneficiary in the manner and on such terms and conditions as the Committee may prescribe. No such designation shall become effective unless filed with the Committee during the Participant's lifetime. Any designation shall remain in effect until a new designation is filed with the Committee; provided, however, that in the event a Participant designates his or her spouse as a Beneficiary, such designation shall be automatically revoked upon the dissolution of the marriage unless, following such dissolution, the Participant submits a new designation naming the former spouse as a Beneficiary. A Participant may from time to time change his or her designated Beneficiary without the consent of a previously-designated Beneficiary by filing a new designation with the Committee.

(b) *No Beneficiary*. If a designated Beneficiary does not survive the Participant, or if there is no valid Beneficiary designation, amounts payable under the Plan upon the death of the Participant shall be paid to the Participant's spouse, or if there is no surviving spouse, then to the duly appointed and currently acting personal representative of the Participant's estate.

6.6 Unforeseeable Emergency. A Participant who experiences an Unforeseeable Emergency may submit a written request to the Committee to receive payment of all or any portion of his or her vested Accounts. If the emergency need cannot be relieved by cessation of Deferrals to the Plan, the Committee may approve an emergency payment therefrom not to exceed the amount reasonably necessary to satisfy the need, taking into account the additional compensation that is available to the Participant as the result of cancellation of deferrals to the Plan, including amounts necessary to pay any taxes or penalties that the Participant reasonably anticipates will result from the payment. The amount of the emergency payment shall be subtracted from the Separation Accounts and then from the Specified Date Accounts, starting with the Account having the latest commencement date until fully distributed, then continuing in this manner with the next latest Account until the full amount of the distribution is made. Emergency payments shall be paid in a single lump sum within the 90-day period following the date the payment is approved by the Committee. The Committee may specify that Deferrals will be distributed before any Company Contributions.

6.7 Administrative Cash-Out of Small Balances. Notwithstanding anything to the contrary in this Article VI, the Committee may at any time and without regard to whether a payment event has occurred, direct in writing an immediate lump sum payment of the Participant's Accounts if the balance of such Accounts, combined with any other amounts required to be treated as deferred under a single plan pursuant to Code Section 409A, does not exceed the applicable dollar amount under Code Section 402(g)(1)(B), provided any other such aggregated amounts are also distributed in a lump sum at the same time.

6.8 Acceleration of or Delay in Payments. Notwithstanding anything to the contrary in this Article VI, the Committee, in its sole and absolute discretion, may elect to accelerate the time or form of payment of an Account, provided such acceleration is permitted under Treas. Reg. Section 1.409A-3(j)(4). The Committee may also, in its sole and absolute discretion, delay the time for payment of an Account, to the extent permitted under Treas. Reg. Section 1.409A-2(b)(7).

6.9 Rules Applicable to Installment Payments. If a Payment Schedule specifies installment payments, payments will be made beginning as of the payment commencement date for such installments and shall continue to be made in each subsequent payment period until the number of installment payments specified in the Payment Schedule has been paid. The amount of each installment payment shall be determined by dividing (a) by (b), where (a) equals the Account Balance as of the last Valuation Date in the month preceding the month of payment and (b) equals the remaining number of installment payments. For purposes of Section 6.10, installment payments will be treated as a single payment. If an Account is payable in installments, the Account will continue to be credited with Earnings in accordance with Article VII hereof until the Account is completely distributed.

6.10 Modifications to Payment Schedules. A Participant may modify the Payment Schedule elected by him or her with respect to a Specified Date Account or In-Service Account described in Section 6.2 and with respect to a Separation Account under Section 6.3, consistent with the permissible Payment Schedules available to such Account under Section 6.2 or 6.3 as is applicable. At the time and manner specified by the Committee, a Participant may modify the Payment Schedule of any Separation Account and Specified Date Account payable under Section 6.5, consistent with the forms of payment permissible for each such Account under Sections 6.2 and 6.3, as is applicable. Any such modification must comply with the requirements of this Section 6.10.

(a) *Time of Election*. The modification election must be submitted to the Committee not less than 12 months prior to the date payments would have commenced under the Payment Schedule in effect prior to modification (the "Prior Election").

(b) *Date of Payment under Modified Payment Schedule*. The date payments are to commence under the modified Payment Schedule must be no earlier than five years after the date payment would have commenced under the Prior Election. Under no circumstances may a modification election result in an acceleration of payments in violation of Code Section 409A. If the Participant modifies only the form, and not the commencement date for payment, payments shall commence on the fifth anniversary of the date payment would have commenced under the Prior Election.

(c) *Irrevocability; Effective Date*. A modification election is irrevocable when filed and becomes effective 12 months after the filing date.

(d) *Effect on Accounts*. An election to modify a Payment Schedule is specific to the Account or payment event to which it applies, and shall not be construed to affect the Payment Schedules or payment events of any other Accounts.

Article VII

Valuation of Account Balances; Investments

7.1 Valuation. Deferrals shall be credited to appropriate Accounts on the date such Compensation would have been paid to the Participant absent the Compensation Deferral Agreement. Valuation of Accounts shall be performed under procedures approved by the Committee.

7.2 Earnings Credit. Each Account will be credited with Earnings on each Business Day, based upon the Participant's investment allocation among a menu of investment options selected in advance by the Committee, in accordance with the provisions of this Article VII ("investment allocation").

7.3 Investment Options. Investment options will be determined by the Committee. The Committee, in its sole discretion, shall be permitted to add or remove investment options from the Plan menu from time to time, provided that any such additions or removals of investment options shall not be effective with respect to any period prior to the effective date of such change.

7.4 Investment Allocations. A Participant's investment allocation constitutes a deemed, not actual, investment among the investment options comprising the investment menu. At no time shall a Participant have any real or beneficial ownership in any investment option included in the investment menu, nor shall the Participating Employer or any trustee

acting on its behalf have any obligation to purchase actual securities as a result of a Participant's investment allocation. A Participant's investment allocation shall be used solely for purposes of adjusting the value of a Participant's Account Balances.
A Participant shall specify an investment allocation for each of his Accounts in accordance with procedures established by the Committee. Allocation among the investment options must be designated in increments of 1%. The Participant's investment allocation will become effective on the same Business Day or, in the case of investment allocations received after a time specified by the Committee, the next Business Day.

A Participant may change an investment allocation on any Business Day, both with respect to future credits to the Plan and with respect to existing Account Balances, in accordance with procedures adopted by the Committee. Changes shall become effective on the same Business Day or, in the case of investment allocations received after a time specified by the Committee, the next Business Day, and shall be applied prospectively.

7.5 Unallocated Deferrals and Accounts. If the Participant fails to make an investment allocation with respect to an Account, such Account shall be invested in an investment option, the primary objective of which is the preservation of capital, as determined by the Committee.

7.6 Company Stock. Deferred restricted stock units will be credited as such, based on the deferred portion of units awarded to the Participant under the terms of the Company's equity compensation plan. Fractional units will be rounded down to the next whole unit.

If Company stock is offered as an investment option, amounts allocated to or from Company stock will be converted from cash to units or units to cash as is applicable. Each unit will be equal in value to one share of Company common stock based on the closing price of the Company's common stock on the day the allocation instructions from the Participant are effective.

Each deferred restricted stock unit will be paid in the form of one share of Company stock. A Participant may not allocate restricted stock units to another investment option under the Plan.

Dividend equivalents will be credited as provided in the equity compensation plan and treated as Earnings for purposes of determining the time and form of payment from the Plan.

7.7 Valuations Final After 180 Days. The Participant shall have 180 days following the Valuation Date on which the Participant failed to receive the full amount of Earnings and to file a claim under Article XI for the correction of such error.

ARTICLE VIII
Administration

8.1 Plan Administration. This Plan shall be administered by the Committee which shall have discretionary authority to make, amend, interpret and enforce all appropriate rules and regulations for the administration of this Plan and to utilize its discretion to decide or resolve any and all questions, including but not limited to eligibility for benefits and interpretations of this Plan and its terms, as may arise in connection with the Plan. Claims for benefits shall be filed with the Committee and resolved in accordance with the claims procedures in Article XI.

8.2 Administration Upon Change in Control. Upon a change in control affecting the Company, the Committee, as constituted immediately prior to such change in control, shall continue to act as the Committee. The Committee, by a vote of a majority of its members, shall have the authority (but shall not be obligated) to appoint an independent third party to act as the Committee. For purposes of this Section 8.2, a “change in control” means a change in control within the meaning of the rabbi trust agreement associated with the Plan or if no such definition is provided, the term shall have the meaning under Code Section 409A.

Upon such change in control, the Company may not remove the Committee or its members, unless a majority of Participants and Beneficiaries with Account Balances consent to the removal and replacement of the Committee. Notwithstanding the foregoing, the Committee shall not have authority to direct investment of trust assets under any rabbi trust described in Section 10.2.

The Participating Employers shall, with respect to the Committee identified under this Section: (i) pay all reasonable expenses and fees of the Committee, (ii) indemnify the Committee (including individuals serving as Committee members) against any costs, expenses and liabilities including, without limitation, attorneys’ fees and expenses arising in connection with the performance of the Committee’s duties hereunder, except with respect to matters resulting from the Committee’s gross negligence or willful misconduct, and (iii) supply full and timely information to the Committee on all matters related to the Plan, any rabbi trust, Participants, Beneficiaries and Accounts as the Committee may reasonably require.

8.3 Withholding. The Participating Employer shall have the right to withhold from any payment due under the Plan (or with respect to any amounts credited to the Plan) any taxes required by law to be withheld in respect of such payment (or credit). Withholdings with respect to amounts credited to the Plan shall be deducted from Compensation that has not been deferred to the Plan.

8.4 Indemnification. The Participating Employers shall indemnify and hold harmless each employee, officer, director, agent or organization, to whom or to which are delegated duties, responsibilities, and authority under the Plan or otherwise with respect to administration of the Plan, including, without limitation, the Committee, its delegates and its agents, against all claims, liabilities, fines and penalties, and all expenses reasonably incurred by or imposed upon him or it (including but not limited to reasonable attorney fees) which arise as a result of his or its actions or failure to act in connection with the operation and administration of the Plan to the extent lawfully allowable and to the extent that such claim, liability, fine, penalty, or expense is not paid for by liability insurance purchased or paid for by the Participating Employer. Notwithstanding the foregoing, the Participating Employer shall not indemnify any person or organization if his or its actions or failure to act are due to gross negligence or willful misconduct or for any such amount incurred through any settlement or compromise of any action unless the Participating Employer consents in writing to such settlement or compromise.

8.5 Delegation of Authority. In the administration of this Plan, the Committee may, from time to time, employ agents and delegate to them such administrative duties as it sees fit, and may from time to time consult with legal counsel who shall be legal counsel to the Company.

8.6 Binding Decisions or Actions. The decision or action of the Committee in respect of any question arising out of or in connection with the administration, interpretation and application of the Plan and the rules and regulations thereunder shall be final and conclusive and binding upon all persons having any interest in the Plan.

Article IX
Amendment and Termination

9.1 Amendment and Termination. The Company may at any time and from time to time amend the Plan or may terminate the Plan as provided in this Article IX. Each Participating Employer may also terminate its participation in the Plan.

9.2 Amendments. The Company, by action taken by its Board of Directors, may amend the Plan at any time and for any reason, provided that any such amendment shall not reduce the vested Account Balances of any Participant accrued as of the date of any such amendment or restatement (as if the Participant had incurred a voluntary Separation from Service on such date). The Board of Directors of the Company may delegate to the Committee the authority to amend the Plan without the consent of the Board of Directors for the purpose of: (i) conforming the Plan to the requirements of law; (ii) facilitating the administration of the Plan; (iii) clarifying provisions based on the Committee’s interpretation of the Plan documents; and (iv) making such other amendments as the Board of Directors may authorize. No amendment is needed to revise the list of Participating Employers set forth on Schedule A attached hereto.

9.3 Termination. The Company, by action taken by its Board of Directors, may terminate the Plan and pay Participants and Beneficiaries their Account Balances in a single lump sum at any time, to the extent and in accordance with Treas. Reg. Section 1.409A-3(j)(4)(ix).

9.4 Accounts Taxable Under Code Section 409A. The Plan is intended to constitute a plan of deferred compensation that meets the requirements for deferral of income taxation under

Code Section 409A. The Committee, pursuant to its authority to interpret the Plan, may sever from the Plan or any Compensation Deferral Agreement any provision or exercise of a right that otherwise would result in a violation of Code Section 409A.

ARTICLE X
Informal Funding

10.1 General Assets. Obligations established under the terms of the Plan may be satisfied from the general funds of the Participating Employers, or a trust described in this Article X. No Participant, spouse or Beneficiary shall have any right, title or interest whatever in assets of the Participating Employers. Nothing contained in this Plan, and no action taken pursuant to its provisions, shall create or be construed to create a trust of any kind, or a fiduciary relationship, between the Participating Employers and any Employee, spouse, or Beneficiary. To the extent that any person acquires a right to receive payments hereunder, such rights are no greater than the right of an unsecured general creditor of the Participating Employer.

10.2 Rabbi Trust. A Participating Employer may, in its sole discretion, establish a grantor trust, commonly known as a rabbi trust, as a vehicle for accumulating assets to pay benefits under the Plan. Payments under the Plan may be paid from the general assets of the Participating Employer or from the assets of any such rabbi trust. Payment from any such source shall reduce the obligation owed to the Participant or Beneficiary under the Plan.

If a rabbi trust is in existence upon the occurrence of a “change in control”, as defined in such trust, the Participating Employer shall, upon such change in control, and on each anniversary of the change in control, contribute in cash or liquid securities such amounts as are necessary so that the value of assets after making the contributions exceed 125% of the total value of all Account Balances.

ARTICLE XI
Claims

11.1 Filing a Claim. Any controversy or claim arising out of or relating to the Plan shall be filed in writing with the Committee which shall make all determinations concerning such claim. Any claim filed with the Committee and any decision by the Committee denying such claim shall be in writing and shall be delivered to the Participant or Beneficiary filing the claim (the “Claimant”). Notice of a claim for payments shall be delivered to the Committee within 90 days of the latest date upon which the payment could have been timely made in accordance with the terms of the Plan and Code Section 409A, and if not paid, the Participant or Beneficiary must file a claim under this Article XI not later than 180 days after such latest date. If the Participant or Beneficiary fails to file a timely claim, the Participant forfeits any amounts to which he or she may have been entitled to receive under the claim.

(a) *In General.* Notice of a denial of benefits (other than claims based on disability) will be provided within 90 days of the Committee's receipt of the Claimant's claim for benefits. If the Committee determines that it needs additional time to review the claim, the Committee will provide the Claimant with a notice of the extension before the end of the initial 90-day period. The extension will not be more than 90 days from the end of the initial 90-day period and the notice of extension will explain the special circumstances that require the extension and the date by which the Committee expects to make a decision.

(b) *Disability Benefits.* Notice of denial of claims based on disability will be provided within 45 days of the Committee's receipt of the Claimant's claim for disability benefits. If the Committee determines that it needs additional time to review the disability claim, the Committee will provide the Claimant with a notice of the extension before the end of the initial 45-day period. If the Committee determines that a decision cannot be made within the first extension period due to matters beyond the control of the Committee, the time period for making a determination may be further extended for an additional 30 days. If such an additional extension is necessary, the Committee shall notify the Claimant prior to the expiration of the initial 30-day extension. Any notice of extension shall indicate the circumstances necessitating the extension of time, the date by which the Committee expects to furnish a notice of decision, the specific standards on which such entitlement to a benefit is based, the unresolved issues that prevent a decision on the claim and any additional information needed to resolve those issues. A Claimant will be provided a minimum of 45 days to submit any necessary additional information to the Committee. In the event that a 30-day extension is necessary due to a Claimant's failure to submit information necessary to decide a claim, the period for furnishing a notice of decision shall be tolled from the date on which the notice of the extension is sent to the Claimant until the earlier of the date the Claimant responds to the request for additional information or the response deadline.

(c) *Contents of Notice.* If a claim for benefits is completely or partially denied, notice of such denial shall be in writing. Any electronic notification shall comply with the standards imposed by Department of Labor Regulation 29 CFR 2520.104b-1(c)(1)(i), (iii), and (iv). The notice of denial shall set forth the specific reasons for denial in plain language. The notice shall: (i) cite the pertinent provisions of the Plan document, and (ii) explain, where appropriate, how the Claimant can perfect the claim, including a description of any additional material or information necessary to complete the claim and why such material or information is necessary. The claim denial also shall include an explanation of the claims review procedures and the time limits applicable to such procedures, including the right to appeal the decision, the deadline by which such appeal must be filed and a statement of the Claimant's right to bring a civil action under Section 502(a) of ERISA following an adverse decision on appeal and the specific date by which such a civil action must commence under Section 11.4.

In the case of a complete or partial denial of a disability benefit claim, the notice shall provide such information and shall be communicated in the manner required under applicable Department of Labor regulations.

11.2 Appeal of Denied Claims. A Claimant whose claim has been completely or partially denied shall be entitled to appeal the claim denial by filing a written appeal with a committee designated to hear such appeals (the “Appeals Committee”). A Claimant who timely requests a review of the denied claim (or his or her authorized representative) may review, upon request and free of charge, copies of all documents, records and other information relevant to the denial and may submit written comments, documents, records and other information relating to the claim to the Appeals Committee. All written comments, documents, records, and other information shall be considered “relevant” if the information: (i) was relied upon in making a benefits determination, (ii) was submitted, considered or generated in the course of making a benefits decision regardless of whether it was relied upon to make the decision, or (iii) demonstrates compliance with administrative processes and safeguards established for making benefit decisions. The review shall take into account all comments, documents, records, and other information submitted by the Claimant relating to the claim, without regard to whether such information was submitted or considered in the initial benefit determination. The Appeals Committee may, in its sole discretion and if it deems appropriate or necessary, decide to hold a hearing with respect to the claim appeal.

(a) *In General.* Appeal of a denied benefits claim (other than a disability benefits claim) must be filed in writing with the Appeals Committee no later than 60 days after receipt of the written notification of such claim denial. The Appeals Committee shall make its decision regarding the merits of the denied claim within 60 days following receipt of the appeal (or within 120 days after such receipt, in a case where there are special circumstances requiring extension of time for reviewing the appealed claim). If an extension of time for reviewing the appeal is required because of special circumstances, written notice of the extension shall be furnished to the Claimant prior to the commencement of the extension. The notice will indicate the special circumstances requiring the extension of time and the date by which the Appeals Committee expects to render the determination on review. The review will take into account comments, documents, records and other information submitted by the Claimant relating to the claim without regard to whether such information was submitted or considered in the initial benefit determination.

(b) *Disability Benefits.* Appeal of a denied disability benefits claim must be filed in writing with the Appeals Committee no later than 180 days after receipt of the written notification of such claim denial. The review shall be conducted in accordance with applicable Department of Labor regulations.

The Appeals Committee shall make its decision regarding the merits of the denied claim within 45 days following receipt of the appeal (or within 90 days after such receipt, in a case where there are special circumstances requiring extension of time for reviewing the appealed claim). If an extension of time for reviewing the appeal is required because of special circumstances, written notice of the extension shall be furnished to the Claimant prior to the commencement of the extension. The notice will indicate the special circumstances requiring the extension of time and the date by which the Appeals Committee expects to render the determination on review. Following its review of any additional information submitted by the Claimant, the Appeals Committee shall render a decision on its review of the denied claim.

(c) *Contents of Notice.* If a benefits claim is completely or partially denied on review, notice of such denial shall be in writing. Any electronic notification shall comply with the standards imposed by Department of Labor Regulation 29 CFR 2520.104b-1(c)(1)(i), (iii), and (iv). Such notice shall set forth the reasons for denial in plain language.

The decision on review shall set forth: (i) the specific reason or reasons for the denial, (ii) specific references to the pertinent Plan provisions on which the denial is based, (iii) a statement that the Claimant is entitled to receive, upon request and free of charge, reasonable access to and copies of all documents, records, or other information relevant (as defined above) to the Claimant's claim, and (iv) a statement of the Claimant's right to bring an action under Section 502(a) of ERISA, following an adverse decision on review and the specific date by which such a civil action must commence under Section 11.4.

For the denial of a disability benefit, the notice will also include such additional information and be communicated in the manner required under applicable Department of Labor regulations.

11.3 Claims Appeals Upon Change in Control. Upon a change in control, the Appeals Committee, as constituted immediately prior to such change in control, shall continue to act as the Appeals Committee. The Company may not remove any member of the Appeals Committee, but may replace resigning members if 2/3rds of the members of the Board of Directors of the Company and a majority of Participants and Beneficiaries with Account Balances consent to the replacement. For purposes of this Section 11.3, a "change in control" means a change in control within the meaning of the rabbi trust agreement associated with the Plan or if no such definition is provided, the term shall have the meaning under Code Section 409A.

The Appeals Committee shall have the exclusive authority at the appeals stage to interpret the terms of the Plan and resolve appeals under the Claims Procedure.

Each Participating Employer shall, with respect to the Committee identified under this Section: (i) pay its proportionate share of all reasonable expenses and fees of the Appeals

Committee, (ii) indemnify the Appeals Committee (including individual committee members) against any costs, expenses and liabilities including, without limitation, attorneys' fees and expenses arising in connection with the performance of the Appeals Committee hereunder, except with respect to matters resulting from the Appeals Committee's gross negligence or willful misconduct, and (iii) supply full and timely information to the Appeals Committee on all matters related to the Plan, any rabbi trust, Participants, Beneficiaries and Accounts as the Appeals Committee may reasonably require.

11.4 Legal Action. A Claimant may not bring any legal action, including commencement of any arbitration, relating to a claim for benefits under the Plan unless and until the Claimant has followed the claims procedures under the Plan and exhausted his or administrative remedies under Sections 11.1 and 11.2. No such legal action may be brought more than 12 months following the notice of denial of benefits under Section 11.2, or if no appeal is filed by the applicable appeals deadline, twelve (12) months following the appeals deadline.

If a Participant or Beneficiary prevails in a legal proceeding brought under the Plan to enforce the rights of such Participant or any other similarly situated Participant or Beneficiary, in whole or in part, the Participating Employer shall reimburse such Participant or Beneficiary for all legal costs, expenses, attorneys' fees and such other liabilities incurred as a result of such proceedings. If the legal proceeding is brought in connection with a change in control as defined in Section 11.3, the Participant or Beneficiary may file a claim directly with the trustee for reimbursement of such costs, expenses and fees. For purposes of the preceding sentence, the amount of the claim shall be treated as if it were an addition to the Participant's or Beneficiary's Account Balance and will be included in determining the Participating Employer's trust funding obligation under Section 10.2.

11.5 Discretion of Appeals Committee. All interpretations, determinations and decisions of the Appeals Committee with respect to any claim shall be made in its sole discretion, and shall be final and conclusive.

11.6 Arbitration.

(a) *Prior to Change in Control.* If, prior to a change in control as defined in Section 11.3, any claim or controversy between a Participating Employer and a Participant or Beneficiary is not resolved through the claims procedure set forth in Article XI, such claim shall be submitted to and resolved exclusively by expedited binding arbitration by a single arbitrator. Arbitration shall be conducted in accordance with the following procedures:

The complaining party shall promptly send written notice to the other party identifying the matter in dispute and the proposed remedy. Following the giving of such notice, the parties shall meet and attempt in good faith to resolve the matter. In the event the parties are unable to resolve the matter within 21 days, the parties shall meet and attempt in good faith to select a single arbitrator acceptable to both parties. If a single arbitrator is not selected by mutual consent within ten Business Days following the giving of the written notice of dispute, an arbitrator shall be selected from a list of nine persons each of whom shall be an attorney who is either engaged in the active practice of law or recognized arbitrator and who, in either event, is experienced in serving as an arbitrator in disputes between employers and employees, which list shall be provided by the main office of either JAMS, the American Arbitration Association ("AAA") or the Federal Mediation and Conciliation Service. If, within three Business Days of the parties' receipt of such list, the parties are unable to agree on an arbitrator from the list, then the parties shall each strike names alternatively from the list, with the first to strike being determined by the flip of a coin. After each party has had four strikes, the remaining name on the list shall be the arbitrator. If such person is unable to serve for any reason, the parties shall repeat this process until an arbitrator is selected.

Unless the parties agree otherwise, within 60 days of the selection of the arbitrator, a hearing shall be conducted before such arbitrator at a time and a place agreed upon by the parties. In the event the parties are unable to agree upon the time or place of the arbitration, the time and place shall be designated by the arbitrator after consultation with the parties. Within 30 days of the conclusion of the arbitration hearing, the arbitrator shall issue an award, accompanied by a written decision explaining the basis for the arbitrator's award.

In any arbitration hereunder, the Participating Employer shall pay all administrative fees of the arbitration and all fees of the arbitrator, except that the Participant or Beneficiary may, if he/she/it wishes, pay up to one-half of those amounts. Each party shall pay its own attorneys' fees, costs, and expenses, unless the arbitrator orders otherwise. The prevailing party in such arbitration, as determined by the arbitrator, and in any enforcement or other court proceedings, shall be entitled, to the extent permitted by law, to reimbursement from the other party for all of the prevailing party's costs (including but not limited to the arbitrator's compensation), expenses, and attorneys' fees. The arbitrator shall have no authority to add to or to modify this Plan, shall apply all applicable law, and shall have no lesser and no greater remedial authority than would a court of law resolving the same claim or controversy. The arbitrator shall, upon an appropriate motion, dismiss any claim without an evidentiary hearing if the party bringing the motion establishes that it would be entitled to summary judgment if the matter had been pursued in court litigation.

The parties shall be entitled to discovery as follows: Each party may take no more than three depositions. The Participating Employer may depose the Participant or Beneficiary plus two other witnesses, and the Participant or Beneficiary may depose the Participating Employer, pursuant to Rule 30(b)(6) of the Federal Rules of Civil Procedure, plus two other witnesses. Each party may make such reasonable document discovery requests as are allowed in the discretion of the arbitrator.

The decision of the arbitrator shall be final, binding, and non-appealable, and may be enforced as a final judgment in any court of competent jurisdiction.

This arbitration provision of the Plan shall extend to claims against any parent, subsidiary, or affiliate of each party, and, when acting within such capacity, any officer, director, shareholder, Participant, Beneficiary, or agent of any party, or of any of the above, and shall apply as well to claims arising out of state and federal statutes and local ordinances as well as to claims arising under the common law or under this Plan.

Notwithstanding the foregoing, and unless otherwise agreed between the parties, either party may apply to a court for provisional relief, including a temporary restraining order or preliminary injunction, on the ground that the arbitration award to which the applicant may be entitled may be rendered ineffectual without provisional relief.

Any arbitration hereunder shall be conducted in accordance with the Federal Arbitration Act: provided, however, that, in the event of any inconsistency between the rules and procedures of the Act and the terms of this Plan, the terms of this Plan shall prevail.

If any of the provisions of this Section 11.6(a) are determined to be unlawful or otherwise unenforceable, in the whole part, such determination shall not affect the validity of the remainder of this section and this section shall be reformed to the extent necessary to carry out its provisions to the greatest extent possible and to insure that the resolution of all conflicts between the parties, including those arising out of statutory claims, shall be resolved by neutral, binding arbitration. If a court should find that the provisions of this Section 11.6(a) are not absolutely binding, then the parties intend any arbitration decision and award to be fully admissible in evidence in any subsequent action, given great weight by any finder of fact and treated as determinative to the maximum extent permitted by law.

The parties do not agree to arbitrate any putative class action or any other representative action. The parties agree to arbitrate only the claims(s) of a single Participant or Beneficiary.

(b) *Upon Change in Control.* Upon a change in control as defined in Section 11.3, Section 11.6(a) shall not apply and any legal action initiated by a Participant or Beneficiary to enforce his or her rights under the Plan may be brought in any court of competent jurisdiction. Notwithstanding the Appeals Committee’s discretion under Sections 11.3 and 11.5, the court shall apply a de novo standard of review to any prior claims decision under Sections 11.1 through 11.3 or any other determination made by the Company, its Board of Directors, a Participating Employer, the Committee, or the Appeals Committee.

Article XII
General Provisions

12.1 Assignment. No interest of any Participant, spouse or Beneficiary under this Plan and no benefit payable hereunder shall be assigned as security for a loan, and any such purported assignment shall be null, void and of no effect, nor shall any such interest or any such benefit be subject in any manner, either voluntarily or involuntarily, to anticipation, sale, transfer, assignment or encumbrance by or through any Participant, spouse or Beneficiary. Notwithstanding anything to the contrary herein, however, the Committee has the discretion to make payments to an alternate payee in accordance with the terms of a domestic relations order (as defined in Code Section 414(p)(1)(B)).

The Company may assign any or all of its liabilities under this Plan in connection with any restructuring, recapitalization, sale of assets or other similar transactions affecting a Participating Employer without the consent of the Participant.

12.2 No Legal or Equitable Rights or Interest. No Participant or other person shall have any legal or equitable rights or interest in this Plan that are not expressly granted in this Plan. Participation in this Plan does not give any person any right to be retained in the service of the Participating Employer. The right and power of a Participating Employer to dismiss or discharge an Employee is expressly reserved. The Participating Employers make no representations or warranties as to the tax consequences to a Participant or a Participant's beneficiaries resulting from a deferral of income pursuant to the Plan.

12.3 No Employment Contract. Nothing contained herein shall be construed to constitute a contract of employment between an Employee and a Participating Employer.

12.4 Notice. Any notice or filing required or permitted to be delivered to the Committee under this Plan shall be delivered in writing, in person, or through such electronic means as is established by the Committee. Notice shall be deemed given as of the date of delivery or, if delivery is made by mail, as of the date shown on the postmark on the receipt for registration or certification. Written transmission shall be sent by certified mail to:

ULTRAGENYX PHARMACEUTICAL INC.
60 LEVERONI COURT
NOVATO, CALIFORNIA 94949
ATTN: HUMAN RESOURCES

Any notice or filing required or permitted to be given to a Participant under this Plan shall be sufficient if in writing or hand-delivered, or sent by mail to the last known address of the Participant.

12.5 Headings. The headings of Sections are included solely for convenience of reference, and if there is any conflict between such headings and the text of this Plan, the text shall control.

12.6 Invalid or Unenforceable Provisions. If any provision of this Plan shall be held invalid or unenforceable, such invalidity or unenforceability shall not affect any other provisions hereof and the Committee may elect in its sole discretion to construe such invalid or unenforceable provisions in a manner that conforms to applicable law or as if such provisions, to the extent invalid or unenforceable, had not been included.

12.7 Lost Participants or Beneficiaries. Any Participant or Beneficiary who is entitled to a benefit from the Plan has the duty to keep the Committee advised of his or her current mailing address. If benefit payments are returned to the Plan or are not presented for payment after a reasonable amount of time, the Committee shall presume that the payee is missing. The Committee, after making such efforts as in its discretion it deems reasonable and appropriate to locate the payee, shall stop payment on any uncashed checks and may discontinue making future payments until contact with the payee is restored. If the Committee is unable to locate the Participant or Beneficiary within five years of the date payment is scheduled to be made, then the Participant Account will be forfeited; provided that a Participant's Account shall not be credited with Earnings following the first anniversary of such date on which payment is to be made; and further provided, however, that such benefit shall be reinstated, without further adjustment for interest, if a valid claim is made by or on behalf of the Participant or Beneficiary for all or part of the forfeited benefit.

12.8 Facility of Payment to a Minor. If a distribution is to be made to a minor, or to a person who is otherwise incompetent, then the Committee may, in its discretion, make such distribution: (i) to the legal guardian, or if none, to a parent of a minor payee with whom the payee maintains his or her residence, or (ii) to the conservator or committee or, if none, to the person having custody of an incompetent payee. Any such distribution shall fully discharge the Committee, the Company, and the Plan from further liability on account thereof.

12.9 Governing Law. To the extent not preempted by ERISA and the Code, the laws of the State of California shall govern the construction and administration of the Plan.

12.10 Compliance With Code Section 409A; No Guarantee. This Plan is intended to be administered in compliance with Code Section 409A and each provision of the Plan shall be interpreted consistent with Code Section 409A. Although intended to comply with Code Section 409A, this Plan shall not constitute a guarantee to any Participant or Beneficiary that the Plan in form or in operation will result in the deferral of federal or state income tax liabilities or that the Participant or Beneficiary will not be subject to the additional taxes imposed under Section 409A. No Employer shall have any legal obligation to a Participant with respect to taxes imposed under Code Section 409A

[Signature page follows.]

IN WITNESS WHEREOF, the undersigned executed this Plan as of the 15th day of June, 2021, to be effective as of the Effective Date.

Ultragenyx Pharmaceutical Inc.

By: Emil D. Kakkis, M.D., Ph.D. (Print Name)

Its: President and Chief Executive Officer (Title)

/s/ Emil D. Kakkis, M.D., Ph.D. ________ (Signature)

Schedule A

Participating Employers

Ultragenyx Pharmaceutical Inc.

Exhibit 10.2

Name:	
Number of Shares of Stock subject to Stock Option:	
Price Per Share:	
Date of Grant:	
Vesting Start Date:	

ULTRAGENYX PHARMACEUTICAL INC.
2014 INCENTIVE PLAN

NON-STATUTORY STOCK OPTION AGREEMENT (DIRECTORS)

This agreement (this "Agreement") evidences a stock option granted by Ultragenyx Pharmaceutical Inc. (the "Company") to the undersigned (the "Optionee") pursuant to and subject to the terms of the Ultragenyx Pharmaceutical Inc. 2014 Incentive Plan (as amended from time to time, the "Plan"), which is incorporated herein by reference.

1.Grant of Stock Option. The Company grants to the Optionee on the date set forth above (the "Date of Grant") an option (the "Stock Option") to purchase, on the terms provided herein and in the Plan, up to the number of shares of Stock set forth above (the "Shares") with an exercise price per Share as set forth above, in each case subject to adjustment pursuant to Section 7(b) of the Plan in respect of transactions occurring after the date hereof.

The Stock Option evidenced by this Agreement is a non-statutory option (that is, an option that does not qualify as an incentive stock option under Section 422 of the Code) and is granted to the Optionee in connection with the Optionee's employment by or service to the Company and its qualifying subsidiaries. For purposes of the immediately preceding sentence, "qualifying subsidiary" means a subsidiary of the Company as to which the Company has a "controlling interest" as described in Treas. Regs. §1.409A-1(b)(5)(iii)(E)(1).

2.Meaning of Certain Terms. Except as otherwise defined herein, all capitalized terms used herein have the same meaning as in the Plan. The following terms have the following meanings:

(a)"Beneficiary" means, in the event of the Optionee's death, the beneficiary named in the written designation (in form acceptable to the Administrator) most recently filed with the Administrator by the Optionee prior to the Optionee's death and not subsequently revoked, or, if there is no such designated beneficiary, the executor or administrator of the Optionee's estate. An effective beneficiary designation will be treated as having been revoked only upon receipt by the Administrator, prior to the Optionee's death, of an instrument of revocation in form acceptable to the Administrator.

(b)"Option Holder" means the Optionee or, if as of the relevant time the Stock Option has passed to a Beneficiary, the Beneficiary.

3.Vesting; Method of Exercise; Treatment of the Stock Option Upon Cessation of Employment.

(a)Vesting. As used herein with respect to the Stock Option or any portion thereof, the term "vest" means to become exercisable and the term "vested" as applied to any outstanding Stock Option means that the Stock Option is then exercisable, subject in each case to the terms of the Plan. Unless earlier terminated, forfeited, relinquished or expired, the Stock Option will vest as to all of the Shares initially subject to the Stock Option on the earlier of (i) the first anniversary of the Date of Grant or (ii) the date of the Company's annual meeting of stockholders first held after the Date of Grant. Notwithstanding the foregoing, Shares subject to the Stock Option shall not vest on any vesting date unless the Optionee has remained in continuous Employment from the Date of Grant through such vesting date.

(b)Exercise of the Stock Option. No portion of the Stock Option may be exercised until such portion vests. Each election to exercise any vested portion of the Stock Option will be subject to the terms and conditions of the Plan and shall be in writing, signed by the Option Holder (or in such other form as is acceptable to the Administrator). Each such written exercise election must be received by the Company at its principal office or by such other party as the Administrator may prescribe and be accompanied by payment in full as provided in the Plan. The exercise price may be paid (i) by cash or check acceptable to the Administrator, (ii) to the extent permitted by the Administrator, through a broker-assisted cashless exercise program acceptable to the Administrator, (iii) by such other means, if any, as may be acceptable to the Administrator, or (iv) by any combination of the foregoing permissible forms of payment. In the event that the Stock Option is exercised by a person other than the Optionee, the Company will be under no obligation to deliver shares hereunder unless and until it is satisfied as to the authority of the Option Holder to exercise the Stock Option and compliance with applicable securities laws. The latest date on which the Stock Option or any portion thereof may be exercised will be the 10th anniversary of the Date of Grant (the "Final Exercise Date"); provided, however, if at such time the Optionee is prohibited by applicable law or written Company policy applicable to similarly situated employees or directors from engaging in any open-market sales of Stock, the Final Exercise Date will be automatically extended to thirty (30) days following the date the Optionee is no longer prohibited from engaging in such open-market sales. If the Stock Option is not exercised by the Final Exercise Date the Stock Option or any remaining portion thereof will thereupon immediately terminate.

(c)Treatment of the Stock Option Upon Cessation of Employment. If the Optionee's Employment ceases, the Stock Option, to the extent not already vested will be immediately forfeited, and any vested portion of the Stock Option that is then outstanding will be treated as follows:

(i)Subject to clauses (ii) and (iii) below and Section 4 of this Agreement, the Stock Option, to the extent vested immediately prior to the cessation of the Optionee's Employment, will remain exercisable until the earlier of (A) the date that is 24 months following the date of such cessation of Employment, or (B) the Final Exercise Date, and except to the extent previously exercised as permitted by this Section 3(c)(i) will thereupon immediately terminate.

(ii)Subject to clauses (iii) below and Section 4 of this Agreement, the Stock Option, to the extent vested immediately prior to the cessation of the Optionee's Employment due to death, will remain exercisable until the earlier of (A) the first anniversary of the Optionee's death or (B) the Final Exercise Date, and except to the extent previously exercised as permitted by this Section 3(c)(ii) will thereupon immediately terminate.

(iii)If the Optionee's Employment is terminated by the Company and its subsidiaries in connection with an act or failure to act constituting Cause (as the Administrator, in its sole discretion, may determine), or such termination occurs in circumstances that in the determination of the Administrator would have entitled the Company and its subsidiaries to terminate the Optionee's Employment for Cause, the Stock Option (whether or not vested) will immediately terminate and be forfeited upon such termination.

4.Forfeiture; Recovery of Compensation.

(a)The Administrator may cancel, rescind, withhold or otherwise limit or restrict the Stock Option at any time if the Optionee is not in compliance with all applicable provisions of this Agreement and the Plan.

(b)By accepting the Stock Option, the Optionee expressly acknowledges and agrees that his or her rights, and those of any permitted transferee of the Stock Option, under the Stock Option to any Stock acquired under the Stock Option or proceeds from the disposition thereof, are subject to Section 6(a)(5) of the Plan (including any successor provision). Nothing in the preceding sentence shall be construed as limiting the general application of Section 8 of this Agreement.

5.Transfer of Stock Option. The Stock Option may not be transferred except as expressly permitted under Section 6(a)(3) of the Plan.

6.Withholding. The Optionee shall be responsible for satisfying and paying all taxes arising from or due in connection with the Option, its exercise or a disposition of Shares acquired upon exercise of the Option. The Company shall have no liability or obligation related to the foregoing.

7.Effect on Service. Neither the grant of the Stock Option, nor the issuance of Shares upon exercise of the Stock Option, will give the Optionee any right to be retained in the employ or service of the Company or any of its Affiliates, affect the right of the Company or any of its Affiliates to discharge or discipline such Optionee at any time, or affect any right of such Optionee to terminate his or her Employment at any time.

8.Provisions of the Plan. This Agreement is subject in its entirety to the provisions of the Plan, which are incorporated herein by reference. A copy of the Plan as in effect on the Date of Grant has been furnished to the Optionee. By exercising all or any part of the Stock Option, the Optionee agrees to be bound by the terms of the Plan and this Agreement. In the event of any conflict between the terms of this Agreement and the Plan, the terms of the Plan shall control.

9.Acknowledgements. The Optionee acknowledges and agrees that (a) this Agreement may be executed in two or more counterparts, each of which shall be an original and all of which together shall constitute one and the same instrument, (b) this agreement may be executed and exchanged using facsimile, portable document format (PDF) or electronic signature, which, in each case, shall constitute an original signature for all purposes hereunder and (c) such signature by the Company will be binding against the Company and will create a legally binding agreement when this Agreement is countersigned by the Optionee.

[The remainder of this page is intentionally left blank]

IN WITNESS WHEREOF, the Company has caused this Agreement to be executed by its duly authorized officer.

ULTRAGENYX PHARMACEUTICAL INC.

By: ____________________________
Name: Emil Kakkis
Title:Chief Executive Officer
Dated:

Acknowledged and Agreed:

By_______________________

Exhibit 10.3

Name:	
Number of Restricted Stock Units subject to Award:	
Date of Grant:	

ULTRAGENYX PHARMACEUTICAL INC.
2014 INCENTIVE PLAN

RESTRICTED STOCK UNIT AGREEMENT (DIRECTORS)

This agreement (this "Agreement") evidences an award (the "Award") of restricted stock units (the "Restricted Stock Units") granted by Ultragenyx Pharmaceutical Inc. (the "Company") to the undersigned (the "Grantee") pursuant to and subject to the terms of the Ultragenyx Pharmaceutical Inc. 2014 Incentive Plan (as amended from time to time, the "Plan"), which is incorporated herein by reference.

1. Grant of Restricted Stock Units. The Company grants to the Grantee on the date set forth above (the "Date of Grant") an award consisting of the right to receive on the terms provided herein and in the Plan, one share of Stock with respect to each Restricted Stock Unit forming part of the Award, in each case, subject to adjustment pursuant to Section 7(b) of the Plan in respect of transactions occurring after the date hereof.

2. Meaning of Certain Terms. Except as otherwise defined herein, all capitalized terms used herein have the same meaning as in the Plan.

3. Vesting. Unless earlier terminated, forfeited, relinquished or expired, the Restricted Stock Units shall vest as follows: all of the underlying shares shall vest on the earlier of (i) the first anniversary of the Date of Grant or (ii) the date of the Company's annual meeting of stockholders first held after the Date of Grant.

4. Delivery of Stock. The Company shall deliver to the Grantee as soon as practicable upon the vesting of the Restricted Stock Units or any portion thereof, but in all events no later than March 15th of the year following the year in which such Restricted Stock Units vest, one share of Stock with respect to each such vested Restricted Stock Unit, subject to the terms of the Plan and this Agreement.

5. Dividends; Other Rights. The Award shall not be interpreted to bestow upon the Grantee any equity interest or ownership in the Company or any Affiliate prior to the date on which the Company delivers shares of Stock to the Grantee (if any). The Grantee is not entitled to vote any shares of Stock by reason of the granting of this Award or to receive or be credited with any dividends declared and payable on any share of Stock prior to the date on which any such share is delivered to the Grantee hereunder. The Grantee shall have the rights of a shareholder only as to those shares of Stock, if any, that are actually delivered under this Award.

6. Forfeiture; Recovery of Compensation.

(a) The Administrator may cancel, rescind, withhold or otherwise limit or restrict the Award at any time if the Grantee is not in compliance with all applicable provisions of this Agreement and the Plan.

(b) By accepting the Award the Grantee expressly acknowledges and agrees that his or her rights, and those of any permitted transferee of the Award, under the Award to any Stock acquired under the Award or proceeds from the disposition thereof, are subject to Section 6(a)(5) of the Plan (including any successor provision). Nothing in the preceding sentence shall be construed as limiting the general application of Section 10 of this Agreement.

7. Nontransferability. Neither the Award nor the Restricted Stock Units may be transferred except as expressly permitted under Section 6(a)(3) of the Plan.

8. Certain Tax Matters.

(a) The Grantee shall be responsible for satisfying and paying all taxes arising from or due in connection with the Restricted Stock Units or with the shares of Stock issued upon vesting of the Restricted Stock Units. The Company shall have no liability or obligation related to the foregoing.

(b) The Grantee expressly acknowledges that because this Award consists of an unfunded and unsecured promise by the Company to deliver Stock in the future, subject to the terms hereof, it is not possible to make a so-called "83(b) election" with respect to the Award.

9. Effect on Service. Neither the grant of the Award, nor the issuance of Shares upon vesting of the Award, will give the Grantee any right to be retained in the employ or service of the Company or any of its Affiliates, affect the right of the Company or any of its Affiliates to discharge or discipline such Grantee at any time, or affect any right of such Grantee to terminate his or her Employment at any time.

10. Provisions of the Plan. This Agreement is subject in its entirety to the provisions of the Plan, which are incorporated herein by reference. A copy of the Plan as in effect on the Date of Grant has been furnished to the Grantee. By accepting the Award, the Grantee agrees to be bound by the terms of the Plan and this Agreement. In the event of any conflict between the terms of this Agreement and the Plan, the terms of the Plan shall control.

11. Acknowledgments. The Grantee acknowledges and agrees that (a) this Agreement may be executed in two or more counterparts, each of which shall be an original and all of which together shall constitute one and the same instrument, (b) this agreement may be executed and exchanged using facsimile, portable document format (PDF) or electronic signature, which, in each case, shall constitute an original signature for all purposes hereunder and (c) such signature by the Company will be binding against the Company and will create a legally binding agreement when this Agreement is countersigned by the Grantee.

[The remainder of this page is intentionally left blank.]

IN WITNESS WHEREOF, the Company has caused this Agreement to be executed by its duly authorized officer.

ULTRAGENYX PHARMACEUTICAL INC.

By: ______________________________
Name: Emil Kakkis
Title: Chief Executive Officer
Dated:

Acknowledged and Agreed:

By______________________

[Signature Page to Restricted Stock Unit Agreement]

Exhibit 10.4

Name:	
Number of Shares of Stock subject to Stock Option:	
Price Per Share:	
Date of Grant:	
Vesting Start Date:	

ULTRAGENYX PHARMACEUTICAL INC.
2014 INCENTIVE PLAN

NON-STATUTORY STOCK OPTION AGREEMENT (DIRECTORS)

This agreement (this "Agreement") evidences a stock option granted by Ultragenyx Pharmaceutical Inc. (the "Company") to the undersigned (the "Optionee") pursuant to and subject to the terms of the Ultragenyx Pharmaceutical Inc. 2014 Incentive Plan (as amended from time to time, the "Plan"), which is incorporated herein by reference.

1.Grant of Stock Option. The Company grants to the Optionee on the date set forth above (the "Date of Grant") an option (the "Stock Option") to purchase, on the terms provided herein and in the Plan, up to the number of shares of Stock set forth above (the "Shares") with an exercise price per Share as set forth above, in each case subject to adjustment pursuant to Section 7(b) of the Plan in respect of transactions occurring after the date hereof.

The Stock Option evidenced by this Agreement is a non-statutory option (that is, an option that does not qualify as an incentive stock option under Section 422 of the Code) and is granted to the Optionee in connection with the Optionee's employment by or service to the Company and its qualifying subsidiaries. For purposes of the immediately preceding sentence, "qualifying subsidiary" means a subsidiary of the Company as to which the Company has a "controlling interest" as described in Treas. Regs. §1.409A-1(b)(5)(iii)(E)(1).

2.Meaning of Certain Terms. Except as otherwise defined herein, all capitalized terms used herein have the same meaning as in the Plan. The following terms have the following meanings:

(a)"Beneficiary" means, in the event of the Optionee's death, the beneficiary named in the written designation (in form acceptable to the Administrator) most recently filed with the Administrator by the Optionee prior to the Optionee's death and not subsequently revoked, or, if there is no such designated beneficiary, the executor or administrator of the Optionee's estate. An effective beneficiary designation will be treated as having been revoked only upon receipt by the Administrator, prior to the Optionee's death, of an instrument of revocation in form acceptable to the Administrator.

(b)"Option Holder" means the Optionee or, if as of the relevant time the Stock Option has passed to a Beneficiary, the Beneficiary.

3.Vesting; Method of Exercise; Treatment of the Stock Option Upon Cessation of Employment.

(a)Vesting. As used herein with respect to the Stock Option or any portion thereof, the term "vest" means to become exercisable and the term "vested" as applied to any outstanding Stock Option means that the Stock Option is then exercisable, subject in each case to the terms of the Plan. Unless earlier terminated, forfeited, relinquished or expired, the Stock Option will vest as to 1/36th of the Shares initially subject to the Stock Option monthly, so that the Stock Option will fully vest on the third (3rd) anniversary of the Date of Grant. Notwithstanding the foregoing, Shares subject to the Stock Option shall not vest on any vesting date unless the Optionee has remained in continuous Employment from the Date of Grant through such vesting date.

(b)Exercise of the Stock Option. No portion of the Stock Option may be exercised until such portion vests. Each election to exercise any vested portion of the Stock Option will be subject to the terms and conditions of the Plan and shall be in writing, signed by the Option Holder (or in such other form as is acceptable to the Administrator). Each such written exercise election must be received by the Company at its principal office or by such other party as the Administrator may prescribe and be accompanied by payment in full as provided in the Plan. The exercise price may be paid (i) by cash or check acceptable to the Administrator, (ii) to the extent permitted by the Administrator, through a broker-assisted cashless exercise program acceptable to the Administrator, (iii) by such other means, if any, as may be acceptable to the Administrator, or (iv) by any combination of the foregoing permissible forms of payment. In the event that the Stock Option is exercised by a person other than the Optionee, the Company will be under no obligation to deliver shares hereunder unless and until it is satisfied as to the authority of the Option Holder to exercise the Stock Option and compliance with applicable securities laws. The latest date on which the Stock Option or any portion thereof may be exercised will be the 10th anniversary of the Date of Grant (the "Final Exercise Date"); provided, however, if at such time the Optionee is prohibited by applicable law or written Company policy applicable to similarly situated employees or directors from engaging in any open-market sales of Stock, the Final Exercise Date will be automatically extended to thirty (30) days following the date the Optionee is no longer prohibited from engaging in such open-market sales. If the Stock Option is not exercised by the Final Exercise Date the Stock Option or any remaining portion thereof will thereupon immediately terminate.

(c)Treatment of the Stock Option Upon Cessation of Employment. If the Optionee's Employment ceases, the Stock Option, to the extent not already vested will be immediately forfeited, and any vested portion of the Stock Option that is then outstanding will be treated as follows:

(i)Subject to clauses (ii) and (iii) below and Section 4 of this Agreement, the Stock Option, to the extent vested immediately prior to the cessation of the Optionee's Employment, will remain exercisable until the earlier of (A) the date that is 24 months following the date of such cessation of Employment, or (B) the Final Exercise Date, and except to the extent previously exercised as permitted by this Section 3(c)(i) will thereupon immediately terminate.

(ii)Subject to clauses (iii) below and Section 4 of this Agreement, the Stock Option, to the extent vested immediately prior to the cessation of the Optionee's Employment due to death, will remain exercisable until the earlier of (A) the first anniversary of the Optionee's death or (B) the Final Exercise Date, and except to the extent previously exercised as permitted by this Section 3(c)(ii) will thereupon immediately terminate.

(iii)If the Optionee's Employment is terminated by the Company and its subsidiaries in connection with an act or failure to act constituting Cause (as the Administrator, in its sole discretion, may determine), or such termination occurs in circumstances that in the determination of the Administrator would have entitled the Company and its subsidiaries to terminate the Optionee's Employment for Cause, the Stock Option (whether or not vested) will immediately terminate and be forfeited upon such termination.

4.Forfeiture; Recovery of Compensation.

(a)The Administrator may cancel, rescind, withhold or otherwise limit or restrict the Stock Option at any time if the Optionee is not in compliance with all applicable provisions of this Agreement and the Plan.

(b)By accepting the Stock Option, the Optionee expressly acknowledges and agrees that his or her rights, and those of any permitted transferee of the Stock Option, under the Stock Option to any Stock acquired under the Stock Option or proceeds from the disposition thereof, are subject to Section 6(a)(5) of the Plan (including any successor provision). Nothing in the preceding sentence shall be construed as limiting the general application of Section 8 of this Agreement.

5.Transfer of Stock Option. The Stock Option may not be transferred except as expressly permitted under Section 6(a)(3) of the Plan.

6.Withholding. The Optionee shall be responsible for satisfying and paying all taxes arising from or due in connection with the Option, its exercise or a disposition of Shares acquired upon exercise of the Option. The Company shall have no liability or obligation related to the foregoing.

7.Effect on Service. Neither the grant of the Stock Option, nor the issuance of Shares upon exercise of the Stock Option, will give the Optionee any right to be retained in the employ or service of the Company or any of its Affiliates, affect the right of the Company or any of its Affiliates to discharge or discipline such Optionee at any time, or affect any right of such Optionee to terminate his or her Employment at any time.

8.Provisions of the Plan. This Agreement is subject in its entirety to the provisions of the Plan, which are incorporated herein by reference. A copy of the Plan as in effect on the Date of Grant has been furnished to the Optionee. By exercising all or any part of the Stock Option, the Optionee agrees to be bound by the terms of the Plan and this Agreement. In the event of any conflict between the terms of this Agreement and the Plan, the terms of the Plan shall control.

9.Acknowledgements. The Optionee acknowledges and agrees that (a) this Agreement may be executed in two or more counterparts, each of which shall be an original and all of which together shall constitute one and the same instrument, (b) this agreement may be executed and exchanged using facsimile, portable document format (PDF) or electronic signature, which, in each case, shall constitute an original signature for all purposes hereunder and (c) such signature by the Company will be binding against the Company and will create a legally binding agreement when this Agreement is countersigned by the Optionee.

[The remainder of this page is intentionally left blank]

IN WITNESS WHEREOF, the Company has caused this Agreement to be executed by its duly authorized officer.

ULTRAGENYX PHARMACEUTICAL INC.

By: ________________________________
Name: Emil Kakkis
Title:Chief Executive Officer
Dated:

Acknowledged and Agreed:

By_______________________

Exhibit 10.5

Name:	
Number of Restricted Stock Units subject to Award:	
Date of Grant:	

ULTRAGENYX PHARMACEUTICAL INC.
2014 INCENTIVE PLAN

RESTRICTED STOCK UNIT AGREEMENT (DIRECTORS)

This agreement (this "Agreement") evidences an award (the "Award") of restricted stock units (the "Restricted Stock Units") granted by Ultragenyx Pharmaceutical Inc. (the "Company") to the undersigned (the "Grantee") pursuant to and subject to the terms of the Ultragenyx Pharmaceutical Inc. 2014 Incentive Plan (as amended from time to time, the "Plan"), which is incorporated herein by reference.

1.Grant of Restricted Stock Units. The Company grants to the Grantee on the date set forth above (the "Date of Grant") an award consisting of the right to receive on the terms provided herein and in the Plan, one share of Stock with respect to each Restricted Stock Unit forming part of the Award, in each case, subject to adjustment pursuant to Section 7(b) of the Plan in respect of transactions occurring after the date hereof.

2.Meaning of Certain Terms. Except as otherwise defined herein, all capitalized terms used herein have the same meaning as in the Plan.

3.Vesting. Unless earlier terminated, forfeited, relinquished or expired, the Restricted Stock Units shall vest as follows: 1/3 of the underlying shares shall vest on each anniversary of the Date of Grant so that the Restricted Stock Units will fully vest on the third (3rd) anniversary of the Date of Grant.

4.Delivery of Stock. The Company shall deliver to the Grantee as soon as practicable upon the vesting of the Restricted Stock Units or any portion thereof, but in all events no later than March 15th of the year following the year in which such Restricted Stock Units vest, one share of Stock with respect to each such vested Restricted Stock Unit, subject to the terms of the Plan and this Agreement.

5.Dividends; Other Rights. The Award shall not be interpreted to bestow upon the Grantee any equity interest or ownership in the Company or any Affiliate prior to the date on which the Company delivers shares of Stock to the Grantee (if any). The Grantee is not entitled to vote any shares of Stock by reason of the granting of this Award or to receive or be credited with any dividends declared and payable on any share of Stock prior to the date on which any such share is delivered to the Grantee hereunder. The Grantee shall have the rights of a shareholder only as to those shares of Stock, if any, that are actually delivered under this Award.

6.Forfeiture; Recovery of Compensation.

(a)The Administrator may cancel, rescind, withhold or otherwise limit or restrict the Award at any time if the Grantee is not in compliance with all applicable provisions of this Agreement and the Plan.

(b)By accepting the Award the Grantee expressly acknowledges and agrees that his or her rights, and those of any permitted transferee of the Award, under the Award to any Stock acquired under the Award or proceeds from the disposition thereof, are subject to Section 6(a)(5) of the Plan (including any successor provision). Nothing in the preceding sentence shall be construed as limiting the general application of Section 10 of this Agreement.

7.Nontransferability. Neither the Award nor the Restricted Stock Units may be transferred except as expressly permitted under Section 6(a)(3) of the Plan.

8.Certain Tax Matters.

(a)The Grantee shall be responsible for satisfying and paying all taxes arising from or due in connection with the Restricted Stock Units or with the shares of Stock issued upon vesting of the Restricted Stock Units. The Company shall have no liability or obligation related to the foregoing.

(b)The Grantee expressly acknowledges that because this Award consists of an unfunded and unsecured promise by the Company to deliver Stock in the future, subject to the terms hereof, it is not possible to make a so-called "83(b) election" with respect to the Award.

9.Effect on Service. Neither the grant of the Award, nor the issuance of Shares upon vesting of the Award, will give the Grantee any right to be retained in the employ or service of the Company or any of its Affiliates, affect the right of the Company or any of its Affiliates to discharge or discipline such Grantee at any time, or affect any right of such Grantee to terminate his or her Employment at any time.

10.Provisions of the Plan. This Agreement is subject in its entirety to the provisions of the Plan, which are incorporated herein by reference. A copy of the Plan as in effect on the Date of Grant has been furnished to the Grantee. By accepting the Award, the Grantee agrees to be bound by the terms of the Plan and this Agreement. In the event of any conflict between the terms of this Agreement and the Plan, the terms of the Plan shall control.

11.Acknowledgments. The Grantee acknowledges and agrees that (a) this Agreement may be executed in two or more counterparts, each of which shall be an original and all of which together shall constitute one and the same instrument, (b) this agreement may be executed and exchanged using facsimile, portable document format (PDF) or electronic signature, which, in each case, shall constitute an original signature for all purposes hereunder and (c) such signature by the Company will be binding against the Company and will create a legally binding agreement when this Agreement is countersigned by the Grantee.

[The remainder of this page is intentionally left blank.]

IN WITNESS WHEREOF, the Company has caused this Agreement to be executed by its duly authorized officer.

ULTRAGENYX PHARMACEUTICAL INC.

By: ________________________________
Name: Emil Kakkis
Title:Chief Executive Officer
Dated:

Acknowledged and Agreed:

By______________________

[Signature Page to Restricted Stock Unit Agreement]

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 Quarterly Report on Form 10-Q 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 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: August 2, 2021

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

Exhibit 31.2

CERTIFICATION PURSUANT TO SECTION 302 OF THE SARBANES-OXLEY ACT OF 2002

I, Mardi C. Dier, certify that:

1. I have reviewed this Quarterly Report on Form 10-Q 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 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: August 2, 2021

/s/ Mardi C. Dier
Mardi C. Dier
Executive Vice President and Chief Financial Officer
(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 Quarterly Report of Ultragenyx Pharmaceutical Inc. (the “Company”) on Form 10-Q for the quarter ended June 30, 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 Executive Vice President and Chief Financial Officer 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: August 2, 2021	/s/ Emil D. Kakkis Emil D. Kakkis, M.D., Ph.D. President and Chief Executive Officer (Principal Executive Officer)
Dated: August 2, 2021	/s/ Mardi C. Dier Mardi C. Dier Executive Vice President and Chief Financial Officer (Principal Financial Officer)