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 September 30, 2022

OR

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

For the transition period from __________ to __________.

Commission File No. 001-36276

ULTRAGENYX PHARMACEUTICAL INC.

(Exact name of registrant as specified in its charter)

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

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

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 October 28, 2022, the registrant had 70,105,654 shares of common stock issued and outstanding.

ULTRAGENYX PHARMACEUTICAL INC.

FORM 10-Q FOR THE QUARTER ENDED SEPTEMBER 30, 2022

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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;
- 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;
- the impact of the COVID-19 pandemic and related health measures on our business, financial condition and liquidity;
- 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;
- stagnating or worsening business and economic conditions and increasing geopolitical instability, including inflationary pressures, general economic slowdown or a recession, rising interest rates, foreign exchange rate volatility, and changes in monetary policy; 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)

	September 30, 2022	December 31, 2021
Assets		
Current assets:		
Cash and cash equivalents	$ 391,651	$ 307,584
Marketable debt securities	497,024	432,612
Accounts receivable, net	31,164	28,432
Inventory	21,849	16,231
Prepaid expenses and other current assets	70,980	71,745
Total current assets	1,012,668	856,604
Property, plant, and equipment, net	234,614	141,247
Equity investments	13,786	34,925
Marketable debt securities	107,563	258,933
Right-of-use assets	28,751	34,936
Intangible assets, net	158,401	130,788
Goodwill	44,406	44,406
Other assets	18,285	20,558
Total assets	$ 1,618,474	$ 1,522,397
Liabilities and Stockholders' Equity		
Current liabilities:		
Accounts payable	$ 23,533	$ 17,138
Accrued liabilities	189,051	145,555
Contract liabilities	2,958	7,609
Lease liabilities	11,819	11,066
Total current liabilities	227,361	181,368
Contract liabilities	—	1,467
Lease liabilities	22,865	30,904
Deferred tax liabilities	33,306	33,306
Liabilities related to the sale of future royalties	862,063	351,786
Other liabilities	4,050	1,005
Total liabilities	1,149,645	599,836
Stockholders' equity:		
Preferred stock — 25,000,000 shares authorized; nil outstanding as of September 30, 2022 and December 31, 2021	—	—
Common stock — 250,000,000 shares authorized; 70,079,777 and 69,344,998 shares issued and outstanding as of September 30, 2022 and December 31, 2021, respectively	70	69
Additional paid-in capital	3,108,170	2,997,497
Accumulated other comprehensive loss	(10,222)	(1,404)
Accumulated deficit	(2,629,189)	(2,073,601)
Total stockholders' equity	468,829	922,561
Total liabilities and stockholders' equity	$ 1,618,474	$ 1,522,397

See accompanying notes.

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

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2022	2021	2022	2021
Revenues:				
Collaboration and license	$ 52,827	$ 55,048	$ 154,328	$ 197,998
Product sales	32,503	21,950	90,019	56,809
Non-cash collaboration royalty revenue	5,373	4,649	15,634	13,210
Total revenues	90,703	81,647	259,981	268,017
Operating expenses:				
Cost of sales	8,631	4,175	23,001	12,499
Research and development	237,297	113,417	534,981	374,140
Selling, general and administrative	69,841	53,883	205,290	160,551
Total operating expenses	315,769	171,475	763,272	547,190
Loss from operations	(225,066)	(89,828)	(503,291)	(279,173)
Interest income	3,483	408	4,876	1,488
Change in fair value of equity investments	(1,626)	25,702	(21,139)	(25,963)
Non-cash interest expense on liabilities related to the sale of future royalties	(14,505)	(8,683)	(27,141)	(25,618)
Other expense	(1,105)	(415)	(1,746)	(1,277)
Loss before income taxes	(238,819)	(72,816)	(548,441)	(330,543)
Provision for income taxes	(6,287)	(182)	(7,147)	(1,024)
Net loss	$ (245,106)	$ (72,998)	$ (555,588)	$ (331,567)
Net loss per share, basic and diluted	$ (3.50)	$ (1.08)	$ (7.96)	$ (4.91)
Weighted-average shares used in computing net loss per share, basic and diluted	70,054,173	67,875,363	69,834,037	67,533,671

See accompanying notes.

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

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2022	2021	2022	2021
Net loss	$ (245,106)	$ (72,998)	$ (555,588)	$ (331,567)
Other comprehensive loss:				
Foreign currency translation adjustments	(420)	(166)	(1,211)	(348)
Unrealized loss on available-for-sale securities	(888)	(12)	(7,607)	(287)
Other comprehensive loss	(1,308)	(178)	(8,818)	(635)
Total comprehensive loss	$ (246,414)	$ (73,176)	$ (564,406)	$ (332,202)

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 June 30, 2022	70,010,398	$ 70	$ 3,071,000	$ (8,914)	$ (2,384,083)	$ 678,073
Stock-based compensation	—	—	36,096	—	—	36,096
Issuance of common stock under equity plan awards, net of tax	69,379	—	1,074	—	—	1,074
Other comprehensive loss	—	—	—	(1,308)	—	(1,308)
Net loss	—	—	—	—	(245,106)	(245,106)
Balance as of September 30, 2022	70,079,777	$ 70	$ 3,108,170	$ (10,222)	$ (2,629,189)	$ 468,829

	Common Stock		Additional Paid-In	Accumulated Other Comprehensive	Accumulated	Total Stockholders'
	Shares	Amount	Capital	Income (Loss)	Deficit	Equity
Balance as of December 31, 2021	69,344,998	$ 69	$ 2,997,497	$ (1,404)	$ (2,073,601)	$ 922,561
Stock-based compensation	—	—	101,862	—	—	101,862
Issuance of common stock under equity plan awards, net of tax	734,779	1	8,811	—	—	8,812
Other comprehensive loss	—	—	—	(8,818)	—	(8,818)
Net loss	—	—	—	—	(555,588)	(555,588)
Balance as of September 30, 2022	70,079,777	$ 70	$ 3,108,170	$ (10,222)	$ (2,629,189)	$ 468,829

	Common Stock		Additional Paid-In	Accumulated Other Comprehensive	Accumulated	Total Stockholders'
	Shares	Amount	Capital	Income (Loss)	Deficit	Equity
Balance as of June 30, 2021	67,764,950	$ 68	$ 2,850,016	$ 232	$ (1,878,145)	$ 972,171
Stock-based compensation	—	—	27,005	—	—	27,005
Issuance of common stock under equity plan awards, net of tax	197,013	—	7,674	—	—	7,674
Other comprehensive loss	—	—	—	(178)	—	(178)
Net loss	—	—	—	—	(72,998)	(72,998)
Balance as of September 30, 2021	67,961,963	$ 68	$ 2,884,695	$ 54	$ (1,951,143)	$ 933,674

	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	—	—	78,324	—	—	78,324
Issuance of common stock under equity plan awards, net of tax	1,143,443	1	33,176	—	—	33,177
Other comprehensive loss	—	—	—	(635)	—	(635)
Net loss	—	—	—	—	(331,567)	(331,567)
Balance as of September 30, 2021	67,961,963	$ 68	$ 2,884,695	$ 54	$ (1,951,143)	$ 933,674

See accompanying notes.

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

	Nine Months Ended September 30,	
	2022	2021
Operating activities:		
Net loss	$ (555,588)	$ (331,567)
Adjustments to reconcile net loss to net cash used in operating activities:		
Stock-based compensation	101,022	78,133
Acquired in-process research and development	75,234	—
Amortization of premium on marketable debt securities, net	4,349	4,499
Depreciation and amortization	13,263	9,705
Change in fair value of equity investments	21,139	25,963
Non-cash collaboration royalty revenue	(15,634)	(13,210)
Non-cash interest expense on liabilities related to the sale of future royalties	27,141	25,618
Other	564	433
Changes in operating assets and liabilities:		
Accounts receivable	(2,973)	(2,362)
Inventory	(5,496)	(2,127)
Prepaid expenses and other assets	558	(6,979)
Accounts payable, accrued, and other liabilities	52,416	1,920
Contract liabilities	(6,118)	(74,377)
Net cash used in operating activities	(290,123)	(284,351)
Investing activities:		
Purchase of property, plant, and equipment	(89,153)	(57,045)
Acquisition, net of cash acquired	(75,391)	—
Purchase of marketable debt securities	(416,161)	(917,409)
Proceeds from sale of marketable debt securities	82,966	83,318
Proceeds from maturities of marketable debt securities	407,926	583,997
Proceeds from sale of equity investments	—	43,197
Payment for intangible asset	(30,000)	—
Other	(240)	(487)
Net cash used in investing activities	(120,053)	(264,429)
Financing activities:		
Proceeds from sale of future royalties, net	490,950	—
Proceeds from the issuance of common stock from equity plan awards, net	8,812	33,177
Other	(436)	(350)
Net cash provided by financing activities	499,326	32,827
Effect of exchange rate changes on cash	(2,427)	(802)
Net increase (decrease) in cash, cash equivalents and restricted cash	86,723	(516,755)
Cash, cash equivalents and restricted cash at beginning of period	309,585	726,294
Cash, cash equivalents and restricted cash at end of period	$ 396,308	$ 209,539
Supplemental disclosures of non-cash information:		
Acquired lease liabilities arising from obtaining right-of-use assets	$ 1,168	$ 2,610
Non-cash interest expense on liabilities related to the sale of future royalties capitalized into ending property, plant and equipment	$ 7,820	$ —

See accompanying notes.

1. Organization

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

The Company is focused on the identification, acquisition, development, and commercialization of novel products for the treatment of serious rare and ultra-rare genetic diseases. The Company operates as one reportable segment. The Company has four commercially approved products.

Crysvita® (burosumab) is approved in the United States (U.S.) by the U.S. Food and Drug Administration (FDA) and 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 (U.K.), 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, Mexico, Chile, Peru, and Argentina, Crysvita is approved for treatment of XLH in adult and pediatric patients one year of age and older. Crysvita is also approved in the U.S. by the FDA and in Canada and Peru 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.

Mepsevii® (vestronidase alfa) is approved by the FDA as the first medicine for the treatment of children and adults with mucopolysaccharidosis VII (MPS VII), also known as Sly syndrome. In the EU and the U.K., Mepsevii is approved under exceptional circumstances for patients of all ages for the treatment of non-neurological manifestations of MPS VII. In Brazil, Mexico, and Japan Mepsevii is approved for the treatment of MPS VII for patients of all ages.

Dojolvi® (triheptanoin) is approved in the U.S., Canada, and Brazil for the treatment of pediatric and adult patients severely affected by long-chain fatty acid oxidation disorders (LC-FAOD).

Evkeeza® (evinacumab) is approved in the U.S. and the European Economic Area (EEA) for the treatment of homozygous familial hypercholesterolemia (HoFH). In January 2022, the Company licensed exclusive rights from Regeneron Pharmaceuticals (Regeneron) to commercialize Evkeeza® (evinacumab) outside of the U.S.

The Company also has the following ongoing clinical development programs:

- UX111 (formerly ABO-102) is an AAV9 gene therapy product candidate for the treatment of patients with Sanfilippo syndrome type A (MPS IIIA), a rare lysosomal storage disease. In May 2022, the Company announced an exclusive license agreement with Abeona Therapeutics Inc. (Abeona) for UX111 whereby the Company assumed responsibility for the UX111 program, as further described in Note 7;
- DTX401 is an adeno-associated virus 8 (AAV8) gene therapy product candidate for the treatment of patients with glycogen storage disease type Ia (GSDIa);
- DTX301 is an AAV8 gene therapy product candidate in development for the treatment of patients with ornithine transcarbamylase (OTC) deficiency, the most common urea cycle disorder;
- UX143 (setrusumab), which is subject to the Company's collaboration agreement with Mereo BioPharma 3 (Mereo), is a fully human monoclonal antibody that inhibits sclerostin, a protein that acts on a key bone-signaling pathway and inhibits the activity of bone-forming cells for the treatment of patients with osteogenesis imperfect (OI);
- GTX-102 is an antisense oligonucleotide (ASO), which the Company is developing through 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. In July 2022, the Company executed its option to acquire GeneTx as further described in Note 6;
- UX701 is an adeno-associated virus 9, (AAV9) 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. Management recognizes that the Company will likely need to raise additional capital to fully implement its business plans. Through September 30, 2022, 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 expects it will need to 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 Condensed 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 15, 2022 (Annual Report) with the U.S. Securities and Exchange Commission (the SEC).

The results of operations for the three and nine months ended September 30, 2022 are not necessarily indicative of the results to be expected for the year ending December 31, 2022. The Condensed Consolidated Balance Sheet as of December 31, 2021 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 Condensed Consolidated Financial Statements have been prepared in accordance with GAAP. The preparation of the Condensed 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 Condensed 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, revenue recognition, and liabilities 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. The following table provides a reconciliation of cash, cash equivalents, and restricted cash reported within the Condensed Consolidated Balance Sheets that sum to the total of the same such amounts shown in the Condensed Consolidated Statement of Cash Flows (in thousands):

	September 30,	
	2022	2021
Cash and cash equivalents	$ 391,651	$ 197,538
Restricted cash included in prepaid expenses and other current assets	517	10,000
Restricted cash included in other assets	4,140	2,001
Total cash, cash equivalents, and restricted cash shown in the statements of cash flows	$ 396,308	$ 209,539

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 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. There were no material credit losses recorded for receivables and available-for-sale debt securities for the three and nine months ended September 30, 2022 and 2021.

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 Condensed 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 in certain territories to RPI Finance Trust (RPI), an affiliate of Royalty Pharma, and to OCM LS23 Holdings LP, an investment vehicle for Ontario Municipal Employees Retirement System (OMERS) as further described in Note 8. The Company records the royalty revenue from the net sales of Crysvita in the applicable territories on a prospective basis as non-cash royalty revenue in the Condensed Consolidated Statements of Operations over the term of the applicable 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):

	September 30, 2022			
	Level 1	Level 2	Level 3	Total
Money market funds	$ 357,285	$ —	$ —	$ 357,285
Certificate of deposits and time deposits	—	29,100	—	29,100
Corporate bonds	—	380,957	—	380,957
Commercial paper	—	82,137	—	82,137
Asset-backed securities	—	—	—	-
U.S. Government Treasury and agency securities	19,081	90,758	—	109,839
Debt securities in government-sponsored entities	—	15,747	—	15,747
Investments in Arcturus and Solid common stock	11,061	—	—	11,061
Other	—	4,063	—	4,063
Total	$ 387,427	$ 602,762	$ —	$ 990,189

	December 31, 2021			
	Level 1	Level 2	Level 3	Total
Money market funds	$ 266,765	$ —	$ —	$ 266,765
Certificate of deposits and time deposits	—	16,000	—	16,000
Corporate bonds	—	349,691	—	349,691
Commercial paper	—	187,624	—	187,624
Asset-backed securities	—	41,245	—	41,245
U.S. Government Treasury and agency securities	—	87,435	—	87,435
Debt securities in government-sponsored entities	—	19,549	—	19,549
Investments in Arcturus and Solid common stock	32,200	—	—	32,200
Other	—	942	—	942
Total	$ 298,965	$ 702,486	$ —	$ 1,001,451

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):

	September 30, 2022			
		Gross Unrealized		
	Amortized Cost	Gains	Losses	Estimated Fair Value
Money market funds	$ 357,285	$ —	$ —	$ 357,285
Certificates of deposit and time deposits	29,100	—	—	29,100
Corporate bonds	388,158	—	(7,201)	380,957
Commercial paper	82,137	—	—	82,137
Asset-backed securities	—	—	—	—
U.S. Government Treasury and agency securities	111,248	8	(1,417)	109,839
Debt securities in government-sponsored entities	16,027	—	(280)	15,747
Total	$ 983,955	$ 8	$ (8,898)	$ 975,065

	December 31, 2021			
		Gross Unrealized		
	Amortized Cost	Gains	Losses	Estimated Fair Value
Money market funds	$ 266,765	$ —	$ —	$ 266,765
Certificates of deposit and time deposits	16,000	—	—	16,000
Corporate bonds	350,667	3	(979)	349,691
Commercial paper	187,624	—	—	187,624
Asset-backed securities	41,282	1	(38)	41,245
U.S. Government Treasury and agency securities	87,642	1	(208)	87,435
Debt securities in government-sponsored entities	19,612	—	(63)	19,549
Total	$ 969,592	$ 5	$ (1,288)	$ 968,309

At September 30, 2022, the remaining contractual maturities of available-for-sale securities were less than three years. There have been no significant realized gains or losses on available-for-sale securities for the three and nine months ended September 30, 2022 and 2021. The unrealized losses on the Company's investments in marketable debt securities were caused by interest rate increases. At September 30, 2022, thirty corporate bond securities with an aggregate fair value of $77.7 million and an aggregate unrealized loss of $1.7 million were in a loss position for more than twelve months. The contractual terms of these investments do not permit the issuers to settle the securities at a price less than the par value. Accordingly, it is expected that the securities will not be settled at a price less than the amortized cost basis of these investments. The Company does not intend to sell the investments and it is not more likely than not that the Company will be required to sell the investments before recovery of their amortized cost basis.

Inventory

Inventory consists of the following (in thousands):

	September 30, 2022	December 31, 2021
Work-in-process	$ 15,777	$ 10,504
Finished goods	6,072	5,727
Total inventory	$ 21,849	$ 16,231

Accrued Liabilities

Accrued liabilities consist of the following (in thousands):

	September 30, 2022	December 31, 2021
Research, clinical study, and manufacturing expenses	$ 61,921	$ 40,880
Payroll and related expenses	67,197	62,591
Other	59,933	42,084
Total accrued liabilities	$ 189,051	$ 145,555

5. Revenue

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

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2022	2021	2022	2021
Collaboration and license revenue:				
Crysvita collaboration revenue in profit-share territory	$ 51,348	$ 42,971	$ 148,121	$ 120,987
Crysvita royalty revenue in European territory	—	16	—	244
Daiichi Sankyo	1,479	12,061	6,207	76,767
Total collaboration and license revenue	52,827	55,048	154,328	197,998
Product sales:				
Crysvita	13,184	7,378	34,980	16,150
Mepsevii	6,045	3,918	15,839	12,924
Dojolvi	13,274	10,654	39,200	27,735
Total product sales	32,503	21,950	90,019	56,809
Crysvita non-cash collaboration royalty revenue	5,373	4,649	15,634	13,210
Total revenues	$ 90,703	$ 81,647	$ 259,981	$ 268,017

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

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2022	2021	2022	2021
U.S. and Canada	$ 67,012	$ 66,911	$ 196,257	$ 230,220
Europe	8,411	7,244	26,114	19,581
Latin America	14,119	7,492	36,449	18,216
Japan	1,161	—	1,161	—
Total revenues	$ 90,703	$ 81,647	$ 259,981	$ 268,017

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

	Nine Months Ended September 30, 2022	Nine Months Ended September 30, 2021
Balance of contract liabilities at beginning of period	$ (9,076)	$ (66,568)
Additions	(89)	(2,390)
Deductions	6,207	76,767
Balance of contract assets (liabilities) at end of period	$ (2,958)	$ 7,809

See Note 7 for additional details on contract liabilities activities.

The Company's largest accounts receivable balance accounted for 49% and 71% of the total accounts receivable balance as of September 30, 2022 and December 31, 2021, respectively, and was due from a collaboration partner. The accounts receivable balance from a different customer accounted for 16% and nil of the total accounts receivable balance as of September 30, 2022 and December 31, 2021, respectively.

6. GeneTx Acquisition

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, which was recorded as an in-process research and development expense. In April 2022, the parties entered into an amendment to the Unitholder Option Agreement (the "Amendment") which provided the Company with an additional, earlier option to acquire GeneTx for an option exercise price of $75.0 million based on the earlier of receipt of interim data in the Phase 1/2 study or a specified date (such option, the "Interim Option").

During the exclusive option period, GeneTx was responsible for conducting the program based on the development plan agreed upon between the parties and, subject to the terms in the Program Agreement, had the decision-making authority on all matters in connection with the research, development, manufacturing and regulatory activities with respect to the Program.

In July 2022, the Company exercised the Interim Option to acquire GeneTx and entered into a Unit Purchase Agreement (the Purchase Agreement) pursuant to which the Company purchased all the outstanding units of GeneTx. In accordance with the terms of the Purchase Agreement, the Company paid the option exercise price of $75.0 million, an additional $15.6 million to acquire the outstanding cash of GeneTx, and customary adjustments for working capital and transaction expenses of $0.6 million, for a total purchase consideration of $91.2 million. Additionally, the Company may make payments of up to $190.0 million upon the achievement of certain milestones, including up to $30.0 million in milestone payments upon achievement of the earlier of initiation of a Phase 3 clinical study or product approvals in Canada and the U.K., up to $85.0 million in additional regulatory approval milestones for the achievement of U.S. and EU product approvals, and up to $75.0 million in commercial milestone payments based on annual worldwide net product sales. In addition, the Company will also pay tiered mid- to high single-digit percentage royalties based on licensed product annual net sales. If the Company receives and resells an FDA priority review voucher (PRV) in connection with a new drug application approval, GeneTx is entitled to receive a portion of proceeds from the sale or a cash payment from the Company if the Company choses to retain the PRV.

The transaction was accounted as an asset acquisition, as substantially all of the fair value of the gross assets acquired was concentrated in a single identifiable in-process research and development intangible asset. Prior to achievement of certain development and regulatory milestones, the acquired in-process research and development intangible asset has not yet reached technological feasibility and has no alternative future use. Accordingly, the Company recorded $75.2 million, net of cash and working capital acquired, as in-process research and development expense during the three months ended September 30, 2022.

7. 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 U.S. and Canada, (the profit-share territory), and in the European Union, United Kingdom, and Switzerland, (the European territory), and the Company has the right to develop and commercialize such products in the field of orphan diseases in Mexico and Central and South America, or Latin America.

Development activities

In the field of orphan diseases, and except for ongoing studies being conducted by KKC, the Company is the lead party for development activities in the profit-share territory and in the European territory until the applicable transition date. The Company shares the costs for development activities in the profit-share territory and the European territory conducted pursuant to the development plan before the applicable transition date equally with KKC. In April 2023, which is the transition date for the profit-share territory, KKC will become the lead party and be responsible for the costs of the development activities. However, the Company will continue to share the costs of the studies commenced prior to the applicable transition date equally with KKC.

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

Collaboration revenue related to sales in profit-share territory

The Company and KKC share commercial responsibilities and profits in the profit-share territory until April 2023. Under the collaboration agreement, KKC manufactures and supplies Crysvita for commercial use in the profit-share territory and charges the Company a 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. In April 2023, commercialization responsibilities for Crysvita in the profit-share territory will transition to KKC and KKC will be responsible for the commercialization of Crysvita in the territory at and after April 2023. Thereafter, the Company will be entitled to receive a tiered double-digit revenue share from the mid-20% range up to a maximum rate of 30%.

In September 2022, the Company entered into an amendment to the collaboration agreement which clarified the scope of increased participation by KKC in support of the Company's commercial activities prior to April 2023 and granted the Company the right to continue to support KKC in commercial field activities in the U.S. through April 2024, subject to the limitations and conditions set forth in the amendment. As a result, KKC will continue to support the Company's commercial field and marketing efforts through a cost share arrangement through April 2024, subject to the limits and conditions set forth in the amendment. After April 2024, the Company's rights to promote Crysvita in the U.S. will be limited to medical geneticists and the Company will solely bear the cost of its own expenses related to the promotion of Crysvita in the profit-share territory.

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.

In July 2022, the Company sold to OMERS its right to receive 30% of the future royalty payments due to the Company based on net sales of Crysvita in the U.S. and Canada, subject to a cap, beginning in April 2023, as further described in Note 8.

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 8. 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.

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

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2022	2021	2022	2021
Company's share of revenue in profit-share territory	$ 51,348	$ 42,971	$ 148,121	$ 120,987
Royalty revenue in European territory	—	16	—	244
Non-cash royalty revenue in European territory	5,373	4,649	15,634	13,210
Total	$ 56,721	$ 47,636	$ 163,755	$ 134,441

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 $13.2 million and $35.0 million for the three and nine months ended September 30, 2022, respectively, and $7.4 million and $16.2 million for the three and nine months ended September 30, 2021, 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 its 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 September 30,		Nine Months Ended September 30,	
	2022	2021	2022	2021
Research and development	$ 3,830	$ 5,161	$ 12,770	$ 16,517
Selling, general and administrative	8,365	8,005	26,510	23,076
Total	$ 12,195	$ 13,166	$ 39,280	$ 39,593

Collaboration receivable and payable

The Company had accounts receivable from KKC in the amount of $15.2 million and $20.2 million from profit-share revenue and royalties and other receivables recorded in prepaid expenses and other current assets of $3.2 million and $16.0 million and accrued liabilities of $5.1 million and $2.3 million from commercial and development activity reimbursements, as of September 30, 2022 and December 31, 2021, respectively.

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 Pinnacle PCL™ producer cell line platform (Pinnacle PCL Platform), and HEK293 transient transfection manufacturing technology platforms for AAV-based gene therapy products.

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

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 Pinnacle PCL Platform and HEK293 transient transfection manufacturing technology platform together with the initial technical assistance and technology transfer services, which was completed in the first quarter of 2022, 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 September 30, 2022, the Company has determined that the total transaction price of the License Agreement was $183.4 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 $5.7 million estimated reimbursement amount for delivering the license and technology services. Total revenue recognized under the license agreement through September 30, 2022 was $180.4 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 was recognized over an initial period which was completed during the first quarter of 2022, 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 is being recognized on a straight-line basis over the remaining technology transfer period, which ends in March 2023, as it is expected that Daiichi Sankyo will receive and consume the benefits consistently throughout the period. Royalties from commercial sales will be accounted for as revenue upon achievement of such sales, assuming all other revenue recognition criteria are met.

The Company recognized $1.5 million and $6.2 million for the three and nine months ended September 30, 2022, respectively, and $12.1 million and $76.8 million for the three and nine months ended September 30, 2021, respectively, in revenue related to this arrangement. Accordingly, the Company recorded $3.0 million and $9.1 million of contract liabilities, net, as of September 30, 2022 and December 31, 2021, respectively. The Company recorded an accounts receivable related to the above agreements of nil and $0.1 million as of September 30, 2022 and December 31, 2021, respectively.

Mereo

In December 2020, the Company entered into a License and Collaboration Agreement with 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 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 (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 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.

Regeneron

In January 2022, the Company announced a collaboration with Regeneron to commercialize Evkeeza for HoFH outside of the U.S. Evkeeza is approved in the U.S., where it is marketed by Regeneron, and in the EEA as a first-in-class therapy for use together with diet and other low-density lipoprotein-cholesterol- lowering therapies to treat adults and adolescents aged 12 years and older with HoFH. Pursuant to the terms of the agreement, the Company received the rights to develop, commercialize and distribute the product for HoFH in countries outside of the U.S. The Company may be obligated to pay up to $63.0 million in future milestone payments, contingent upon the achievement of certain regulatory and sales milestones. The Company will share in certain costs for global trials led by Regeneron and also has the right to opt into other potential indications, including an exclusive right to negotiate a separate agreement with Regeneron to collaborate on the development and commercialization outside of the U.S. of Regeneron's investigational antibody for the treatment of fibrodysplasia ossificans progressiva (FOP). The Company's option to negotiate an agreement for the treatment of FOP expired in July 2022.

The collaboration agreement is within the scope of ASC 808 which provides guidance on the presentation and disclosure of collaborative arrangements. As the Company would be the principal in future sale transactions with the customer, the Company will recognize product sales and cost of sales in the period the related sale occurs and the related revenue recognition criteria are met. Under the collaboration agreement, Regeneron will supply the product and will charge the Company a transfer price from the low 20% range up to 40% on net sales, which will be recognized as cost of sales in the Company's Statement of Operations.

Upon closing of the transaction in January 2022, the Company paid Regeneron a $30.0 million upfront payment. As the upfront payment was related to the Company's usage of intellectual property related to Evkeeza for HoFH, the upfront payment was recorded on the Consolidated Balance Sheet as an intangible asset, which is being amortized over its useful life of 10.5 years.

The Company recorded costs of goods sold of $0.7 million and $2.1 million for the three and nine months ended September 30, 2022, respectively, related to the amortization of the intangible asset. Further, the Company reimbursed Regeneron for certain development costs of $2.5 million and $4.3 million for the three and nine months ended September 30, 2022, respectively. No revenue was recorded for Evkeeza for the three and nine months ended September 30, 2022.

Abeona

In May 2022, the Company announced an exclusive License Agreement for the AAV gene therapy for UX111 with Abeona for the treatment of MPS IIIA. Under the terms of the agreement, the Company assumed responsibility for the UX111 program and in return, Abeona is eligible to receive tiered royalties of up to 10% on net sales and commercial milestone payments of up to $30.0 million following regulatory approval of the product. Additionally, the Company entered into an Assignment and Assumption Agreement with Abeona to transfer and assign to the Company the exclusive license agreement between Nationwide Children's Hospital (NCH) and Abeona for certain rights related to UX111. Under this agreement, NCH is eligible to receive from the Company up to $1.0 million in development and regulatory milestones as well as royalties in the low single-digits of net sales.

The Company is obligated to pay Abeona certain prior development costs and other transition costs related to UX111. Prior to product regulatory approval, all consideration paid to Abeona represents rights to potential future benefits associated with Abeona's in-process research and development activities, which have not reached technological feasibility and have no alternative future use. Accordingly, the value of the acquired intellectual property rights and clinical inventory as well as prior development costs and transition costs amounting to $0.8 million and $2.9 million were recorded as research and development expense for the three and nine months ended September 30, 2022, respectively.

Bayer

In October 2022, the Collaboration and License Agreement for DTX201 with Bayer was terminated and all licensed rights to DTX201 have reverted back to the Company. The Company also obtained rights to all necessary data and information to further develop DTX201 or another hemophilia A program through a royalty free, worldwide, sublicensable, perpetual license.

Other Arrangements

The Company has also entered into several collaborations and/or licensing arrangements in prior periods. Except as disclosed above, there have not been material changes in these arrangements as disclosed in Note 7 to the Consolidated Financial Statements in the Annual Report.

Under the financial terms of these arrangements, the Company may be required to make payments upon achievement of developmental, regulatory, and commercial milestones, which could be significant. Future milestone payments, if any, will be reflected in the Condensed Consolidated Statements of Operations upon the occurrence of the contingent event. In addition, the Company may be required to pay royalties on future sales if products related to these arrangements are commercialized. The payment of these amounts, however, is contingent upon the occurrence of various future events, which have a high degree of uncertainty of occurrence.

As described in the Annual Report, in connection with the Company's collaborations with Solid and Arcturus, the Company holds certain equity interests in each entity. The changes in the fair value of the Company's equity investments in the common stock of Solid and Arcturus were as follows (in thousands):

	Common stock
As of December 31, 2020	$ 154,756
Change in fair value	(42,713)
Sale of shares	(79,843)
December 31, 2021	32,200
Change in fair value	(21,139)
September 30, 2022	$ 11,061

8. Liabilities 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 (KKC Collaboration Agreement). 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.

In July 2022, the Company entered into a Royalty Purchase Agreement with OMERS. Pursuant to the agreement, OMERS paid $500.0 million to the Company in consideration for the right to receive 30% of the future royalty payments due to the Company from KKC based on net sales of Crysvita in the U.S. and Canada under the terms of the KKC Collaboration Agreement. The calculation of royalty payments to OMERS will be based on net sales of Crysvita beginning in April 2023 and will expire upon the earlier of the date on which aggregate payments received by OMERS equals $725.0 million or the date the final royalty payment is made to the Company under the KKC Collaboration Agreement.

Proceeds from these transactions were recorded as liabilities (liabilities related to sale of future royalties on the Consolidated Balance Sheets). The Company amortizes $320.0 million and $500.0 million, net of transaction costs of $5.8 million and $9.1 million for RPI and OMERS, respectively, using the effective interest method over the estimated life of the applicable arrangement. In order to determine the amortization of the liabilities, the Company is required to estimate the total amount of future royalty payments to be received by the Company and paid to RPI and OMERS, subject to the capped amount, over the life of the arrangements. The excess of future estimated royalty payments (subject to the capped amount), over the $314.2 million and $491.0 million, respectively, of net proceeds, is recorded as non-cash interest expense over the life of the arrangements. Consequently, the Company estimates an imputed interest on the unamortized portion of the liabilities and records interest expense relating to the transactions. The Company records the royalty revenue arising from the net sales of Crysvita in the applicable territories as non-cash royalty revenue in the Consolidated Statements of Operations over the term of the arrangements.

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 liabilities and the effective interest rate. The Company’s effective annual interest rate was approximately 9.6% and 8.3%, for RPI and OMERS, respectively, as of September 30, 2022.

There are a number of factors that could materially affect the amount and timing of royalty payments from KKC in the applicable 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, macroeconomic and inflationary pressures, the introduction of competing products, pricing for reimbursement in various 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 sales of Crysvita are made in currencies other than USD, and other events or circumstances that could result in reduced royalty payments from 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 the relevant territories 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 arrangements.

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

	RPI	OMERS	Liabilities related to the sale of future royalties
December 31, 2020	$ 335,665	$ —	$ 335,665
Non-cash collaboration royalty revenue	(17,951)	—	(17,951)
Non-cash interest expense	34,072	—	34,072
December 31, 2021	351,786	—	351,786
Net proceeds from sale of future royalties in July 2022	—	490,950	490,950
Non-cash collaboration royalty revenue	(15,634)	—	(15,634)
Non-cash interest expense	26,247	8,714	34,961
September 30, 2022	$ 362,399	$ 499,664	$ 862,063

9. 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 September 30, 2022, there were 2,034,566 shares reserved under the 2014 Plan for the future issuance of equity awards, 4,640,287 shares reserved under the 2014 Employee Stock Purchase Plan, and 322,697 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 September 30,		Nine Months Ended September 30,	
	2022	2021	2022	2021
Cost of sales	$ 225	$ 160	$ 730	$ 762
Research and development	20,251	15,366	57,588	43,949
Selling, general and administrative	15,285	11,464	42,695	33,719
Total stock-based compensation expense	$ 35,761	$ 26,990	$ 101,013	$ 78,430

10. Net Loss Per Share

Basic net loss per share has been computed by dividing the net loss by the weighted-average number of shares of common stock outstanding during the period. Diluted net loss per share is calculated by dividing net loss by the weighted-average number of shares of common stock and potential dilutive securities outstanding during the period.

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

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2022	2021	2022	2021
Options to purchase common stock, restricted stock units, and performance stock units	11,969,532	8,287,010	11,114,822	8,287,394
Employee stock purchase plan	44,649	30,196	15,047	16,923
	12,014,181	8,317,206	11,129,869	8,304,317

11. Equity Transactions

In May 2021, the Company entered into an Open Market Sale Agreement with Jefferies LLC, (Jefferies), pursuant to which the Company may offer and sell shares of the Company's common stock having an aggregate offering proceeds up to $350.0 million, from time to time, in at-the-market (ATM) offerings through Jefferies. As of September 30, 2022, the Company has sold 1,050,372 shares under the arrangement resulting in net proceeds of approximately $78.9 million. No shares were sold under the arrangement for the three and nine months ended September 30, 2022.

12. Related Party Transaction

In July 2022, the Company entered into an agreement with a non-profit foundation in which two of the Company's board members, including the Company's Chief Executive Officer, are also board members of the foundation, whereby a $1.0 million contribution will be paid out to the foundation over a four-year period, beginning in third quarter of 2022, to support rare disease education and awareness. As a result, the Company recorded $0.3 million as research and development expense for this agreement for the three and nine months ended September 30, 2022.

13. Accumulated Other Comprehensive Loss

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

	September 30, 2022	December 31, 2021
Foreign currency translation adjustments	$ (1,332)	$ (121)
Unrealized loss on available-for-sale securities	(8,890)	(1,283)
Total accumulated other comprehensive loss	$ (10,222)	$ (1,404)

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 Condensed 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, 2021 ("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.

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 Evkeeza® (evinacumab) and UX143 in clinical development:

- Crysvita is an antibody administered via subcutaneous injection that targets fibroblast growth factor 23 (FGF23), developed for the treatment of XLH, a rare, hereditary, progressive, and lifelong musculoskeletal disorder characterized by renal phosphate wasting caused by excess FGF23 production. There are approximately 48,000 patients with XLH in the developed world, including approximately 36,000 adults and 12,000 children. Crysvita is the only approved treatment that addresses the underlying cause of XLH. Crysvita is approved in the U.S. and Canada for the treatment of XLH in adult and pediatric patients six months of age and older. In the European Union, or the EU, and the United Kingdom, Crysvita is approved for the treatment of XLH with radiographic evidence of bone disease in children one year of age and older, adolescents, and adults. In Brazil, Colombia, Mexico, Chile, Peru, and Argentina, 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 U.S, Canada, and Peru 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 U.S. for the treatment of children and adults with MPS VII. In the EU and the United Kingdom, Mepsevii is approved under exceptional circumstances for the treatment of non-neurological manifestations of MPS VII for patients of all ages. In Italy, Mepsevii received reimbursement approval for the treatment of pediatric and adult patients with MPS VII. In Brazil, Mexico, and Japan, Mepsevii is approved for the treatment of MPS VII for patients of all ages.

- Evkeeza is a fully human monoclonal antibody that binds to and blocks the function of angiopoietin-like 3 (ANGPTL3), a protein that plays a key role in lipid metabolism. Evkeeza is an approved therapy for the treatment of homozygous familial hypercholesterolemia, or HoFH, a rare inherited condition. HoFH occurs when two copies of the familial hypercholesterolemia (FH)-causing genes are inherited, one from each parent, resulting in dangerously high levels (>400 mg/dL) of LDL-C, or bad cholesterol. Patients with HoFH are at risk for premature atherosclerotic disease and cardiac events as early as their teenage years. Evkeeza is approved in the U.S., where it is marketed by our partner Regeneron Pharmaceuticals (Regeneron), and the European Economic Area (EEA) as a first-in-class therapy for use together with diet and other low-density lipoprotein-cholesterol (LDL-C) lowering therapies to treat adults and adolescents aged 12 years and older with HoFH. There are approximately 3,000 to 5,000 patients with HoFH in countries outside of the U.S.

- UX143 (setrusumab) is a fully human monoclonal antibody that inhibits sclerostin, a protein that acts on a key bone-signaling pathway by inhibiting the activity of bone-forming cells and promoting bone resorption. Setrusumab is being studied for the treatment of osteogenesis imperfecta (OI) and has received orphan drug designation from the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA), rare pediatric disease designation from the FDA, and was accepted into the EMA's Priority Medicines program (PRIME). Setrusumab is subject to our collaboration agreement with Mereo Biopharma 3 (Mereo), and the lead clinical asset in our bone endocrinology franchise. There are an estimated 60,000 patients in the developed world affected by 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 U.S. 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 received marketing authorization from the Brazilian Health Regulatory Agency (ANVISA) and are in the process of seeking reimbursement approval. There are approximately 8,000 to 14,000 patients in the developed world with LC-FAOD.

Our clinical-stage gene therapy pipeline includes UX111, DTX401, DTX301, and UX701:

- UX111 (formerly ABO-102) is an adeno-associated virus 9, or AAV9, gene therapy product candidate for the treatment of patients with Sanfilippo syndrome type A (MPS IIIA), a rare lysosomal storage disease with no approved treatment that primarily affects the central nervous system (CNS). There are approximately 3,000 to 5,000 patients in the developed world affected by Sanfilippo syndrome type A. The UX111 program has received Regenerative Medicine Advanced Therapy (RMAT), Fast Track, Rare Pediatric Disease, and Orphan Drug designations in the U.S., and PRIME and Orphan Medicinal Product designations in the EU.
- 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 the EMA. The DTX401 program has received RMAT, Fast Track, and Orphan Drug designations in the U.S., and PRIME and Orphan Medicinal Product designations in the EU.
- 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 U.S. and in the EU and Fast Track Designation in the U.S.
- 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 has received Orphan Drug Designation in the U.S. and in the 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 has received Fast Track designation, Orphan Drug Designation and Rare Pediatric Disease Designation from the FDA.
- 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 has received Orphan Drug Designation in the U.S. and in the 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						
Evkeeza® (evinacumab)[3]	Fully human monoclonal antibody	HoFH						
UX143 (setrusumab)[4]	Fully human monoclonal antibody	OI						Ph2/3 dosing update and Ph3 transition
Small Molecules								
Dojolvi® (triheptanoin)	Substrate replacement	LC-FAOD						
AAV Gene Therapy								
UX111	AAV9 Gene Therapy	MPS IIIA						Regulatory update
DTX401	AAV8 Gene Therapy	GSDIa						Ongoing enrollment of Ph3
DTX301	AAV8 Gene Therapy	OTC						Ongoing enrollment of Ph3
UX701	AAV9 Gene Therapy	Wilson						Ongoing enrollment of Stage 1
Nucleic Acid								
GTX-102	Antisense Oligonucleotide	Angelman Syndrome						Ongoing enrollment of Ph1/2
UX053	mRNA	GSDIII						Ph1/2 single ascending dose data

1: IND submitted or expected to be submitted within the near term
2: In collaboration with Kyowa Kirin Company
3: Ex-US collaboration with Regeneron Pharmaceuticals
4: In collaboration with Mereo BioPharma

Recent Developments - Clinical Product Candidates

GTX-102 for the treatment of Angelman Syndrome

In July 2022, we exercised our option to acquire GeneTx Biotherapeutics LLC (GeneTx) and closed on the acquisition for an option exercise price of $75.0 million plus net working capital adjustments and transaction expenses of $0.6 million and future milestone and royalty payments as further described above in Note 6.

In July 2022, we also provided an interim data update on patients treated in Canada, the U.K., and the U.S. under each region's amended protocol for the phase 1/2 study of GTX-102. As of the data cut-off for this update, a total of 11 patients had reached at least the Day 128 evaluation, with three patients reaching the Day 170 Pre-Maintenance Dose (PMD) evaluation. We evaluated patients across various clinical measurements, including AS Change Scale, AS Severity Scale, the Bayley Scales of Infant and Toddler Development (Bayley-4), the Vineland-3 adaptive behavior scale, and the Observed Reported Communication Ability (ORCA). Early and some changes in statistically, significant quantitative measures appear to show a dose-dependent effect that will require continued follow-up of these patients in the maintenance phase.

As of the date of this filing, 13 patients have received cumulative doses of 20 mg or higher, and 14 patients have over 132 days of exposure to treatment, which was the minimum cumulative dose and maximum exposure after the first dose that led to the lower extremity weakness seen in the five patients treated in the U.S. under the original study protocol in 2020. As of the date of this filing, there have been no treatment-related serious adverse events of any type or adverse events related to lower extremity weakness observed to date in these patients. No clinically-significant elevations of cerebrospinal fluid protein level have been observed as of the date of this filing. Two of the five patients treated in the U.S. under the original protocol in 2020 have now restarted treatment in Canada and have received two or more doses with no treatment-related serious adverse events of any type or adverse events related to lower extremity weakness observed in these patients to date.

Dosing in the U.K. and Canada is ongoing under a protocol amendment approved in May 2022 to add dose-selection cohorts at incrementally higher starting doses based on age, followed by two, larger expansion cohorts (n = 20) in each age range. Discussions with the FDA to harmonize the three regions are currently ongoing.

We currently expect to begin enrollment of the expansion cohorts in the first half of 2023. We also expect to provide the next data update when we have substantive data on a larger number of patients in the program.

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

In September 2022, DTX401 was granted PRIME designation by the EMA. This designation will enable early and more frequent interactions with the agency and places DTX401 on an expedited review pathway.

We are currently enrolling and dosing patients in the Phase 3 GlucoGene study of DTX401. The Phase 3 study has a 48-week primary efficacy analysis period and we plan to enroll approximately 50 patients eight years of age and older, randomized 1:1 to DTX401 (1.0 x 10^13 GC/kg dose) or placebo. The primary endpoint is the reduction in oral glucose replacement with cornstarch while maintaining glucose control. The last patient is expected to be enrolled in the baseline screening phase of the Phase 3 study of DTX401 around the end of the year.

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

We continue to be in the process of initiating the Phase 3 *Enh3ance* study that will include a 64-week primary efficacy analysis period and plan to enroll approximately 50 patients 12 years of age and older, randomized 1:1 to DTX301 (1.7 x 10^13 GC/kg dose) or placebo. The co-primary endpoints are the percentage of patients who achieve a response as measured by discontinuation or reduction in baseline disease management and the 24-hour plasma ammonia levels. The first patients in the U.S. are expected to enter an approximate 4-to 8-week baseline screening period around the end of 2022, after which they are expected to receive a single dose of DTX301 or placebo.

UX701 for the treatment of Wilson Disease

We are currently enrolling and dosing patients with Wilson disease in the first stage of the *Cyprus2+* study of UX701.

During the first stage of the study, the safety and efficacy of up to three dose levels of UX701 will be evaluated over the course of 52 weeks and a dose will be selected for further evaluation in stage 2. The sequential doses to be evaluated are 5.0 x 10^12 GC/kg, 1.0 x 10^13 GC/kg, and 2.0 x 10^13 GC/kg. A protocol amendment for stage 1 has been approved that removes the use of placebo from this stage of the study. In stage 2, a new cohort of patients will be randomized 2:1 to receive the selected dose of UX701 or placebo. The primary safety and efficacy analyses will be conducted at Week 52 of stage 2. The primary efficacy endpoints are change in 24-hour urinary copper concentration and percent reduction in standard of care medication by Week 52. After the initial 52-week study period, we expect that all patients will receive long term follow up in stage 3.

Completion of Stage 1 enrollment is expected in mid-2023 with data on safety and initial signs of clinical activity expected around the end of 2023 or early 2024.

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

We are currently dosing patients in a pediatric and young adult Phase 2/3 study. The objective of the Phase 2/3 study will first focus on determining an effective dose based on increases in collagen production using serum P1NP levels and an acceptable safety profile. A protocol amendment for the Phase 2 study will remove the placebo arm and continue evaluating the same two dose levels of setrusumab as in the original protocol. We currently expect to complete enrollment in this portion of the study in early 2023. Data from the Phase 2 study and determination of the Phase 3 dose is currently expected mid-2023. Following determination of the dose, we intend to adapt the study into a pivotal Phase 3 stage, evaluating fracture reduction over an estimated 15 to 24 months as the primary endpoint, subject to regulatory review. Separately, we currently plan to initiate a Phase 2 study of patients under age five with OI in the first half of 2023.

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

We are dosing patients in a Phase 1/2 study of UX053 for the treatment of GSDIII and we currently expect preliminary data from Part 1 of the study in the first half of 2023.

Other Developments

Partial sale of North America Crysvita royalty

In July 2022, we sold 30% of our royalty interest in Crysvita in the U.S. and Canada beginning in April 2023 to Ontario Municipal Employees Retirement System (OMERS) for $500.0 million, subject to a cap of $725.0 million.

Amendment to Collaboration Agreement with KKC

In September 2022, we entered into an amendment to the collaboration agreement which clarified the scope of increased participation by KKC in support of our commercial activities prior to April 2023 and granted us the right to continue to support KKC in commercial field activities in the U.S. through April 2024, subject to the limitations and conditions set forth in the amendment. As a result, KKC will continue to support our commercial field and marketing efforts through a cost share arrangement through April 2024, subject to the limits and conditions set forth in the amendment. After April 2024, our rights to promote Crysvita in the U.S. will be limited to medical geneticists and we will solely bear the cost of our own expenses related to the promotion of Crysvita in the profit-share territory.

Financial Operations Overview

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

We have incurred net losses in each year since inception. Our net loss was $245.1 million and $555.6 million for the three and nine months ended September 30, 2022, respectively, and $73.0 million and $331.6 million for the three and nine months ended September 30, 2021, respectively. Net loss for the three and nine months ended September 30, 2022 included losses of $1.6 million and $21.1 million, respectively, resulting from changes in fair value of our investments in Arcturus Therapeutics Holdings Inc. (Arcturus) and Solid Biosciences Inc. (Solid) equity securities. In the three and nine months ended September 30, 2021, we had included a gain of $25.7 million and a loss of $26.0 million, respectively, resulting from changes in the fair value of our investments in Arcturus and Solid. 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 and nine months ended September 30, 2022 our total revenues were $90.7 million and $260.0 million, respectively, compared to $81.6 million and $268.0 million for the three and nine months ended September 30, 2021, respectively. Revenues for the three and nine months ended September 30, 2022 included $1.5 million and $6.2 million, respectively, from our collaboration and license agreement with Daiichi Sankyo Co., Ltd. (Daiichi Sankyo), as compared to $12.1 million and $76.8 million for the three and nine months ended September 30, 2021, respectively. The decrease in collaboration revenue with Daiichi Sankyo was partially offset 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 September 30, 2022, we had $996.2 million in available cash, cash equivalents, and marketable debt securities.

Critical Accounting Estimates

Our management's discussion and analysis of our financial condition and results of operations is based on our Condensed Consolidated Financial Statements, which have been prepared in accordance with U.S. generally accepted accounting principles, or GAAP. The preparation of these Condensed 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 nine months ended September 30, 2022, 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 nine months ended September 30, 2022 to the three and nine months ended September 30, 2021:

Revenue (dollars in thousands)

	Three Months Ended September 30, 2022	Three Months Ended September 30, 2021	Dollar Change	% Change
Collaboration and license revenue:				
Crysvita collaboration revenue in profit-share territory	$ 51,348	$ 42,971	$ 8,377	19 %
Crysvita royalty revenue in European territory	—	16	(16)	-100 %
Daiichi Sankyo	1,479	12,061	(10,582)	-88 %
Total collaboration and license revenue	52,827	55,048	(2,221)	-4 %
Product sales:				
Crysvita	13,184	7,378	5,806	79 %
Mepsevii	6,045	3,918	2,127	54 %
Dojolvi	13,274	10,654	2,620	25 %
Total product sales	32,503	21,950	10,553	48 %
Crysvita non-cash collaboration royalty revenue	5,373	4,649	724	16 %
Total revenues	$ 90,703	$ 81,647	$ 9,056	11 %

	Nine Months Ended September 30, 2022	Nine Months Ended September 30, 2021	Dollar Change	% Change
Collaboration and license revenue:				
Crysvita collaboration revenue in profit-share territory	$ 148,121	$ 120,987	$ 27,134	22 %
Crysvita royalty revenue in European territory	—	244	(244)	-100 %
Daiichi Sankyo	6,207	76,767	(70,560)	-92 %
Total collaboration and license revenue	154,328	197,998	(43,670)	-22 %
Product sales:				
Crysvita	34,980	16,150	18,830	117 %
Mepsevii	15,839	12,924	2,915	23 %
Dojolvi	39,200	27,735	11,465	41 %
Total product sales	90,019	56,809	33,210	58 %
Crysvita non-cash collaboration royalty revenue	15,634	13,210	2,424	18 %
Total revenues	$ 259,981	$ 268,017	$ (8,036)	-3 %

For the three and nine months ended September 30, 2022, our share of Crysvita collaboration revenue in the profit-share territory increased by $8.4 million and $27.1 million, respectively, as compared to the same periods in 2021. The increase primarily reflects the continuing increase in demand for Crysvita due to an increase in the number of patients on therapy.

In March 2020, we executed a license agreement with Daiichi Sankyo. For the three and nine months ended September 30, 2022, the collaboration and license revenue from this arrangement decreased by $10.6 million and $70.6 million, respectively, as compared to the same periods in 2021. The decrease was due to completion of the technology transfer as of March 31, 2022.

The increase in product sales of $10.6 million and $33.2 million for the three and nine months ended September 30, 2022, respectively, compared to the same periods in 2021 was primarily due to an increase in demand for Crysvita in Latin America due to an increase in the number of patients on therapy, continued momentum from the commercial launch of Dojolvi in the U.S., continued increase in demand for our other approved products, and an increase in sales of our products under our named patient program in certain countries.

The increase in Crysvita non-cash collaboration royalty revenue of $0.7 million and $2.4 million for the three and nine months ended September 30, 2022, respectively, compared to the same periods in 2021 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 September 30, 2022	Three Months Ended September 30, 2021	Dollar Change	% Change
Cost of sales	$ 8,631	$ 4,175	$ 4,456	107 %

	Nine Months Ended September 30, 2022	Nine Months Ended September 30, 2021	Dollar Change	% Change
Cost of sales	$ 23,001	$ 12,499	$ 10,502	84 %

Cost of sales increased by $4.5 million and $10.5 million for the three and nine months ended September 30, 2022, respectively, compared to the same periods in 2021. The increase was due to increased demand for our approved products and amortization of the intangible asset for Evkeeza from our license agreement with Regeneron. The increase in cost of sales was also impacted by excess inventory write-downs of $0.3 million and $1.6 million recorded for the three and nine months ended September 30, 2022, compared to nil and $1.7 million recorded for the three and nine months ended September 30, 2021, respectively.

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, acquisition, and milestone fees include any significant expenses related to strategic licensing agreements and acquisitions. 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 September 30, 2022	Three Months Ended September 30, 2021	Dollar Change	% Change
Commercial programs	$ 24,923	$ 12,696	$ 12,227	96 %
Clinical programs:				
Gene therapy programs	34,498	28,039	6,459	23 %
Nucleic acid and other biologic programs	26,325	13,137	13,188	100 %
Translational research	22,486	16,101	6,385	40 %
Upfront license, acquisition, and milestone fees	75,234	—	75,234	100 %
Infrastructure	17,672	14,748	2,924	20 %
Stock-based compensation	20,251	15,366	4,885	32 %
Other research and development	15,908	13,330	2,578	19 %
Total research and development expenses	$ 237,297	$ 113,417	$ 123,880	109 %

	Nine Months Ended September 30,		Dollar	%
	2022	2021	Change	Change
Commercial programs	$ 54,266	$ 38,998	$ 15,268	39 %
Clinical programs:				
Gene therapy programs	110,521	79,136	31,385	40 %
Nucleic acid and other biologic programs	68,651	32,732	35,919	110 %
Translational research	64,128	45,361	18,767	41 %
Upfront license, acquisition, and milestone fees	75,234	50,000	25,234	50 %
Infrastructure	51,739	43,984	7,755	18 %
Stock-based compensation	57,588	43,949	13,639	31 %
Other research and development	52,854	39,980	12,874	32 %
Total research and development expenses	$ 534,981	$ 374,140	$ 160,841	43 %

Total research and development expenses increased $123.9 million and $160.8 million for the three and nine months ended September 30, 2022, respectively, compared to the same periods in 2021. The change in research and development expenses was primarily due to:

- for commercial programs, an increase of $12.2 million and $15.3 million for the three and nine months ended September 30, 2022, respectively, primarily related to collaborative cost sharing with Regeneron for Evkeeza and increased R&D personnel allocations to commercial programs;
- for gene therapy programs, an increase of $6.5 million and $31.4 million for the three and nine months ended September 30, 2022, respectively, primarily related to increases in clinical manufacturing and clinical trial expenses for the DTX401 and DTX301 Phase 3 programs and the in-licensing of the UX111 program from Abeona Therapeutics;
- for nucleic acid and other biologic programs, an increase of $13.2 million and $35.9 million for the three and nine months ended September 30, 2022, respectively, primarily related to the addition of clinical trial and manufacturing expenses related to UX053, following its IND approval in March 2021; increased clinical trial and manufacturing expenses related to the continued progress of the UX143 program in collaboration with Mereo; and clinical and other development expenses related to the continued progress of the GTX-102 program;
- for translational research, an increase of $6.4 million and $18.8 million for the three and nine months ended September 30, 2022, respectively, primarily related to IND-enabling development costs for multiple research projects;
- for upfront license, acquisition, and milestone fees, an increase of $75.2 million and $25.2 million for the three and nine months ended September 30, 2022, respectively, due to $75.2 million recognized from the GeneTx acquisition during the three and nine months ended September 30, 2022, as compared to nil and $50.0 million recognized from the upfront fee for the Mereo license for the three and nine months ended September 30, 2021;
- for infrastructure, an increase of $2.9 million and $7.8 million for the three and nine months ended September 30, 2022, respectively, primarily related to increased expenses for support of our clinical and research program pipeline, expansion of laboratory space, depreciation of laboratory-related leasehold improvements and equipment, and IT-related expenses;
- for stock-based compensation, an increase of $4.9 million and $13.6 million for the three and nine months ended September 30, 2022, respectively, primarily related to the increases in employee headcount; and
- for other research and development expenses, an increase of $2.6 million and $12.9 million for the three and nine months ended September 30, 2022, respectively, primarily related to increased staffing to support internal manufacturing, increased travel, and increased administrative and general support.

We expect our annual research and development expenses to moderate 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 September 30, 2022	Three Months Ended September 30, 2021	Dollar Change	% Change
Selling, general and administrative	$ 69,841	$ 53,883	$ 15,958	30 %

	Nine Months Ended September 30, 2022	Nine Months Ended September 30, 2021	Dollar Change	% Change
Selling, general and administrative	$ 205,290	$ 160,551	$ 44,739	28 %

Selling, general and administrative expenses increased by $16.0 million and $44.7 million for the three and nine months ended September 30, 2022, respectively, compared to the same periods in 2021. 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 moderate in the future to support our approved products and multiple clinical-stage product candidates.

Interest Income (dollars in thousands)

	Three Months Ended September 30, 2022	Three Months Ended September 30, 2021	Dollar Change	% Change
Interest income	$ 3,483	$ 408	$ 3,075	754 %

	Nine Months Ended September 30, 2022	Nine Months Ended September 30, 2021	Dollar Change	% Change
Interest income	$ 4,876	$ 1,488	$ 3,388	228 %

Interest income increased by $3.1 million and $3.4 million, for the three and nine months ended September 30, 2022, respectively, compared to the same periods in 2021, primarily due to increases in interest rates and higher average marketable debt securities balances.

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

	Three Months Ended September 30, 2022	Three Months Ended September 30, 2021	Dollar Change	% Change
Change in fair value of equity investments	$ (1,626)	$ 25,702	$ (27,328)	-106 %

	Nine Months Ended September 30, 2022	Nine Months Ended September 30, 2021	Dollar Change	% Change
Change in fair value of equity investments	$ (21,139)	$ (25,963)	$ 4,824	-19 %

For the three and nine months ended September 30, 2022, we recorded a net decrease in the fair value of our equity investments of $1.6 million and $21.1 million, respectively, due to unrealized losses on our investments in Arcturus common stock of $0.5 million and $11.1 million during the three and nine months ended September 30, 2022, respectively, and unrealized losses on our investments in Solid common stock of $1.1 million and $10.0 million during the three and nine months ended September 30, 2022, respectively.

For the three months ended September 30, 2021, we recorded a net increase in fair value of equity investments of $25.7 million. The fair value of our investment in Arcturus common stock increased by $35.6 million during the period, which included a realized gain on the sale of a portion of common stock for net proceeds of $43.2 million. This increase was partially offset by a $9.9 million decrease in fair value of our investment in Solid common stock, resulting in a net increase of $25.7 million.

For the nine months ended September 30, 2021, we recorded a net decrease in fair value of equity investments of $26.0 million. The fair value of our investment in Arcturus common stock increased by $14.7 million during the period, which included a realized gain on the sale of a portion of common stock for net proceeds of $43.2 million. The increase was offset by $40.6 million decrease in fair value of our investment in Solid common stock resulting in a net decrease of $26.0 million.

Given the historic volatility of the publicly traded stock price of Arcturus and Solid, the fair value adjustments of our equity investments may be subject to wide fluctuations which may have a significant impact on our earnings in future periods.

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

	Three Months Ended September 30, 2022	Three Months Ended September 30, 2021	Dollar Change	% Change
Non-cash interest expense on liabilities related to the sale of future royalties	$ (14,505)	$ (8,683)	$ (5,822)	67%

	Nine Months Ended September 30, 2022	Nine Months Ended September 30, 2021	Dollar Change	% Change
Non-cash interest expense on liabilities related to the sale of future royalties	$ (27,141)	$ (25,618)	$ (1,523)	6%

The non-cash interest expense on liabilities related to the sale of future royalties increased by $5.8 million and $1.5 million for the three and nine months ended September 30, 2022, respectively, compared to the same periods in 2021. This was primarily due to the partial sale of North American Crysvita royalty to OMERS in July 2022, which resulted in an increase in liabilities related to the sale of future royalties by $491.0 million and higher interest expense, partially offset by the capitalization of interest related to the construction-in-progress for the gene therapy manufacturing plant. To the extent 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 Expense (dollars in thousands)

	Three Months Ended September 30, 2022	Three Months Ended September 30, 2021	Dollar Change	% Change
Other expense	$ (1,105)	$ (415)	$ (690)	166%

	Nine Months Ended September 30, 2022	Nine Months Ended September 30, 2021	Dollar Change	% Change
Other expense	$ (1,746)	$ (1,277)	$ (469)	37%

Other expense increased by $0.7 million and $0.5 million, respectively, for the three and nine months ended September 30, 2022, compared to the same periods in 2021. These changes were primarily due to fluctuations in foreign exchange rates.

Provision for Income Taxes (dollars in thousands)

	Three Months Ended September 30, 2022	Three Months Ended September 30, 2021	Dollar Change	% Change
Provision for income taxes	$ (6,287)	$ (182)	$ (6,105)	*

* not meaningful

	Nine Months Ended September 30, 2022	Nine Months Ended September 30, 2021	Dollar Change	% Change
Provision for income taxes	$ (7,147)	$ (1,024)	$ (6,123)	598%

The provision for income taxes increased by $6.1 million for the three and nine months ended September 30, 2022, compared to the same periods in 2021. Beginning in 2022, the Tax Cuts and Jobs Act of 2017 eliminated the right to deduct research and development expenditures for tax purposes in the period the expenses were incurred and instead requires all U.S. and foreign research and development expenditures to be amortized over five and fifteen tax years, respectively. Due to this required capitalization of research and development expenditures and the significant taxable income generated as a result of our sale of royalties in July 2022, we have recorded a one-time discrete tax expense of $5.9 million for the three and nine months ended September 30, 2022. The discrete tax expense is for state taxes we anticipate paying as a result of statutory limitations on our ability to offset expected taxable income with net operating loss carry forwards in certain states. We realized no benefit for current year losses due to a full valuation allowance against the U.S. net deferred tax assets.

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 September 30, 2022, we had $996.2 million in available cash, cash equivalents, and marketable debt securities. We believe that our existing capital resources will be sufficient to fund our projected operating requirements for at least the next twelve months. Our cash, cash equivalents, and marketable debt securities are held in a variety of deposit accounts, interest-bearing accounts, corporate bond securities, commercial paper, U.S government securities, asset-backed securities, debt securities in government-sponsored entities, and money market funds. Cash in excess of immediate requirements is invested with a view toward liquidity and capital preservation, and we seek to minimize the potential effects of concentration and credit risk.

In May 2021, we entered into an Open Market Sale Agreement with Jefferies LLC, (Jefferies), pursuant to which we may offer and sell shares of our common stock having an aggregate offering proceeds up to $350.0 million, from time to time, in at-the-market (ATM) offerings through Jefferies. As of September 30, 2022, net proceeds from shares sold under the arrangement were approximately $78.9 million. No shares were sold under this arrangement for the three and nine months ended September 30, 2022. In July 2022, we received net proceeds of $491.0 million from the sale of certain future royalties to OMERS.

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

	Nine Months Ended September 30,	
	2022	2021
Cash used in operating activities	$ (290,123)	$ (284,351)
Cash used in investing activities	(120,053)	(264,429)
Cash provided by financing activities	499,326	32,827
Effect of exchange rate changes on cash	(2,427)	(802)
Net increase (decrease) in cash, cash equivalents and restricted cash	$ 86,723	$ (516,755)

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 nine months ended September 30, 2022 was $290.1 million and primarily reflected a net loss of $555.6 million and $15.6 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 $101.0 million for stock-based compensation, $75.2 million for acquired in-process research and development expense, $4.3 million for the amortization of the premium paid on purchased marketable debt securities, $13.3 million for depreciation and amortization, $21.1 million for a change in fair value of equity investments in Arcturus and Solid, and $27.1 million for non-cash interest incurred on the liabilities related to the sale of future royalties to RPI and OMERS. Cash used in operating activities also reflected a $3.0 million decrease due to an increase in accounts receivable primarily related to order timing, a $5.5 million decrease due to an increase in inventory primarily for Mepsevii and Dojolvi, and a decrease of $6.1 million in contract liabilities, net, related to the revenue recognized from the license agreements with Daiichi Sankyo, offset by a $52.4 million increase in accounts payable, accrued liabilities, and other liabilities primarily due to timing of payments and receipt of invoices, as well as an increase in manufacturing accruals and income taxes payable, partially offset by the payout of the 2021 annual bonuses, and a $0.6 million increase due to a net decrease in prepaid expenses and other assets.

Cash used in operating activities for the nine months ended September 30, 2021 was $284.4 million and primarily reflected a net loss of $331.6 million and $13.2 million for non-cash collaboration royalty revenues related to the sale of future royalties to RPI, offset by non-cash charges of $78.1 million for stock-based compensation, $4.5 million for the amortization of the premium paid on purchased marketable debt securities, $9.7 million for depreciation and amortization, $26.0 million for a change in fair value of equity investments in Arcturus and Solid, and $25.6 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 $2.4 million decrease due to an increase in accounts receivable primarily related to higher revenues, a $2.1 million decrease due to an increase in inventory for Dojolvi, a $7.0 million decrease due to an increase in prepaid expenses and other current assets primarily due to an increase in prepaid subscriptions, prepaid manufacturing and prepaid insurance, and a decrease of $74.4 million in contract liabilities, net, related to the revenue recognized from the license agreements with Daiichi Sankyo, offset by a $1.9 million increase in accounts payable, accrued liabilities, and other liabilities primarily due to an increase in accruals related to the construction of the gene therapy manufacturing plant, partially offset by a decrease in accrued bonus due to the payout of the 2020 annual bonuses.

Cash Used in Investing Activities

Cash used in investing activities for the nine months ended September 30, 2022 was $120.1 million and was primarily related to purchases of property, plant, and equipment of $89.2 million, primarily related to purchases for our gene therapy manufacturing plant, the acquisition of GeneTx of $75.4 million, net of cash acquired, purchases of marketable debt securities of $416.2 million, and the payment to Regeneron for an intangible asset of $30.0 million, offset by proceeds from the sale of marketable debt securities of $83.0 million and maturities of marketable debt securities of $407.9 million.

Cash used in investing activities for the nine months ended September 30, 2021 was $264.4 million and was primarily related to purchases of property, plant, and equipment of $57.0 million and purchases of marketable debt securities of $917.4 million, offset by proceeds from the sale of marketable debt securities of $83.3 million, maturities of marketable debt securities of $584.0 million, and proceeds from the sale of equity investments of $43.2 million.

Cash Provided by Financing Activities

Cash provided by financing activities for the nine months ended September 30, 2022 was $499.3 million and was primarily comprised of $491.0 million in net proceeds from the partial sale of future North America Crysvita royalties to OMERS and $8.8 million in net proceeds from the issuance of common stock pursuant to equity plan awards.

Cash provided by financing activities for the nine months ended September 30, 2021 was $32.8 million and was primarily comprised of $33.2 million in net proceeds from the issuance of common stock pursuant to 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, including future milestone payments thereunder, 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 "Risk Factors – Risks Related to Our Business Operations;" and
- the terms and timing of any collaborative, licensing, marketing, distribution, acquisition, 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, royalty sales, 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

Material contractual obligations arising in the normal course of business primarily consist of operating and finance leases, manufacturing and service contract obligations, and building construction and improvement agreements.

Future minimum lease payments under non-cancellable leases as of September 30, 2022, were approximately $62.2 million, of which $13.7 million are due within one year.

Manufacturing and service contract obligations primarily relate to manufacturing of inventory for our approved products. As of September 30, 2022, we had obligations of approximately $31.0 million, of which $26.7 million are due within one year.

Building construction and improvement agreements relate to the construction and fit-out of the Company's leased properties. As of September 30, 2022, we had obligations of approximately $9.9 million, of which $0.1 million are expected to be due within one year.

We generally expect to satisfy these commitments with cash on hand and cash provided by operating activities. The terms of certain of our licenses, royalties, development and collaboration agreements, as well as other research and development activities, require us to pay potential future milestone payments based on product development success. The amount and timing of such obligations are unknown or uncertain.

Off-Balance Sheet Arrangements

We have not engaged in any off-balance sheet arrangements, as contemplated by 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 investments held in Arcturus and Solid were $7.4 million and $3.7 million as of September 30, 2022, respectively. A hypothetical 10 percent decrease in the market price for our equity investments in Arcturus and Solid as of September 30, 2022 would decrease the fair value by $0.7 million and $0.4 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 September 30, 2022, we had cash, cash equivalents, and marketable debt securities totaling $996.2 million, compared to $999.1 million as of December 31, 2021, 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 continue to 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 September 30, 2022 or December 31, 2021. To date, we have not experienced a loss of principal on any of these investments and as of September 30, 2022, 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, the macro-economic environment, inflation, or global political instability 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 and nine months ended September 30, 2022, 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 Condensed 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 September 30, 2022. 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 the quarter ended September 30, 2022, 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 to need to raise additional capital to fund our activities.
- Clinical drug development is a lengthy, complex, and expensive process with uncertain outcomes.
- If we do not achieve our projected development goals in the time frames we announce and expect, we may experience delays in commercialization of our products and other adverse effects.
- We may experience difficulty in enrolling patients, which could delay or prevent clinical studies of our product candidates.
- The regulatory approval processes of the FDA and comparable foreign authorities are lengthy and inherently unpredictable.
- Our product candidates may cause undesirable or serious side effects that could delay or prevent their regulatory approval or result in other negative consequences.
- We face a multitude of manufacturing risks, particularly with respect to our gene therapy and mRNA product candidates.
- Our products will remain subject to regulatory scrutiny even if we obtain regulatory approval.
- Product liability lawsuits against us could cause us to incur substantial liabilities.
- We may not realize the full commercial potential of our product candidates if we are unable to source and develop effective biomarkers.
- We rely on third parties to conduct our nonclinical and clinical studies and perform other tasks for us.
- We are dependent on KKC for the clinical and commercial supply of Crysvita for all major markets and for the development and commercialization of Crysvita in certain major markets.
- We rely on third parties to manufacture our products and product candidates.
- The loss of, or failure to supply by, any of any of our single-source suppliers for our drug substance and drug product could adversely affect our business.
- The actions of distributors and specialty pharmacies could affect our ability to sell or market products profitably.
- A competitor could misappropriate or disclose our trade secrets.
- Our revenue may be adversely affected if the market opportunities for our products and product candidates are smaller than expected.
- Our competitors may develop therapies that are similar, more advanced, or more effective than ours.
- We may not successfully manage expansion of our company, including building an integrated commercial organization.
- Our exclusive rights to promote Crysvita in the U.S. and Canada will transition back to KKC.
- Commercial success of our products depends on the degree of market acceptance by physicians, patients, third-party payors, and others in the medical community.
- We face uncertainty related to insurance coverage and reimbursement status of our newly approved products.
- If we, or our third-party partners, are unable to maintain effective proprietary rights for our products or product candidates, we may not be able to compete effectively.
- Claims of intellectual property infringement may prevent or delay our development and commercialization efforts.
- We may not be successful in obtaining or maintaining necessary rights to our product candidates through acquisitions and in-licenses.
- We may face competition from biosimilars of our biologics product and product candidates or from generic versions of our small-molecule product and product candidates, which may result in a material decline in sales of affected products.
- We could lose license rights that are important to our business if we fail to comply with our obligations in the agreements under which we license intellectual property and other rights from third parties.

- We may become involved in lawsuits to protect or enforce our patents or the patents of our licensors, or be subject to claims that challenge the inventorship or ownership of our patents.
- Changes in U.S. patent law could diminish the value of patents in general, thereby impairing our ability to protect our products.
- We may not be able to protect our intellectual property rights throughout the world.
- The ongoing COVID-19 pandemic has impacted our operations and could materially and adversely affect our business and operating results.
- We have no experience as a company developing or operating a manufacturing facility.
- Our success depends in part on our ability to retain our President and Chief Executive Officer and other qualified personnel.
- Our revenue may be impacted if we fail to obtain or maintain orphan drug exclusivity for our products.
- Our operating results may be adversely impacted if our intangible assets become impaired.
- We may not be successful in identifying, licensing, developing, or commercializing additional product candidates, or we may fail to capitalize on opportunities that may be more profitable.
- We may fail to comply with laws and regulations or changes in laws and regulations could adversely affect our business.
- We are exposed to risks related to international expansion of our business outside of the U.S.
- Our business may be adversely affected in the event of computer system failures or security breaches.
- We or our third-party partners may be adversely affected by earthquakes or other serious natural disasters that are not adequately protected by business continuity and disaster recovery plans.
- We may incur various costs and expenses and risks related to acquisition of companies or products or strategic transactions.
- The market price of our common stock is highly volatile.
- Future sales and issuances of our common stock could dilute the percentage ownership of our current stockholders and result in a decline in stock price.
- We do not intend to pay dividends on our common stock so any returns will be limited to the value of our stock.
- Provisions in our amended and restated certificate of incorporation and by-laws, as well as provisions of Delaware law, could make it more difficult for a third party to acquire us or increase the cost of acquiring us or could limit our stockholders' ability to obtain a favorable judicial forum for disputes with us or our directors, officers or employees.
- We face general risks related to our ability to maintain effective internal controls over financial reporting, additional tax liabilities related to our operations, our ability to use our net operating loss carryforwards and costs of litigation.

Risks Related to Our Financial Condition and Capital Requirements

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

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

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

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

We have limited experience in generating revenue from product sales.

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

- obtaining regulatory and marketing approvals with broad indications for product candidates for which we complete clinical studies;
- developing a sustainable and scalable manufacturing process for our products and any approved product candidates and establishing and maintaining supply and manufacturing relationships with third parties that can conduct the processes and provide adequate (in amount and quality) product supply to support market demand for our products and product candidates, if approved;

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

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

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

As of September 30, 2022, our available cash, cash equivalents, and marketable debt securities were $996.2 million. We expect we will need additional capital to continue to commercialize our products, and to develop and obtain regulatory approval for, and to commercialize, all of our product candidates. In addition, our operating plans may change as a result of many factors that may currently be unknown to us, and we may need to seek additional funds sooner than planned. Our future funding requirements will depend on many factors, including but not limited to:

- the scope, rate of progress, results, and cost of our clinical studies, nonclinical testing, and other related activities;
- the cost of manufacturing clinical and commercial supplies of our products and product candidates;
- the cost of creating additional infrastructure, including facilities and systems, such as our GMP gene therapy manufacturing plant;
- the number and characteristics of the product candidates that we pursue;
- the cost, timing, and outcomes of regulatory approvals;
- the cost and timing of establishing and operating our international subsidiaries;
- the cost and timing of establishing and operating field forces, marketing, and distribution capabilities;
- the cost and timing of other activities needed to commercialize our products; and
- the terms and timing of any collaborative, licensing, acquisition, and other arrangements that we may establish, including any required milestone, royalty, and reimbursements or other payments thereunder.

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

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

Risks Related to the Discovery and Development of Our Product Candidates

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

Before obtaining marketing approval from regulatory authorities for the sale of our product candidates, we must conduct extensive clinical studies to demonstrate the safety and efficacy of the product candidates in humans. Clinical testing is expensive, complex, time consuming, and uncertain as to outcome. We cannot guarantee that any clinical studies will be conducted as planned or completed on schedule, if at all. A failure of one or more clinical studies can occur at any stage of testing, and our future clinical studies may not be successful. Product candidates that have shown promising results in early-stage clinical studies may still suffer significant setbacks or fail in subsequent clinical studies. The safety or efficacy results generated to date in clinical studies do not ensure that later clinical studies will demonstrate similar results. Further, we have, and may in the future, expect to continue to report preliminary or interim data from our clinical trials. Preliminary or interim data from our clinical trials are subject to the risk that one or more of the clinical outcomes may materially change as patient enrollment continues and/or more patient data become available. Such data may show initial evidence of clinical benefit, but as patients continue to be assessed and more patient data become available, there is a risk that any therapeutic effects are no longer durable in patients and/or decrease over time or cease entirely. As a result, preliminary or interim data should be considered carefully and with caution until the final data are available. Results from investigator-sponsored studies or compassionate-use studies may not be confirmed in company-sponsored studies or may negatively impact the prospects for our programs. Additionally, given the nature of the rare diseases we are seeking to treat, we often have to devise newly-defined endpoints to be tested in our studies, which can lead to some subjectivity in interpreting study results and could result in regulatory agencies not agreeing with the validity of our endpoints, or our interpretation of the clinical data, and therefore delaying or denying approval. Given the illness of the patients in our studies and the nature of their rare diseases, we may also be required or choose to conduct certain studies on an open-label basis. We have in the past, and may in the future elect to review interim clinical data at multiple time points during the studies, which could introduce bias into the study results and potentially result in denial of approval.

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

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

- delays or failures in generating sufficient preclinical, toxicology, or other *in vivo* or *in vitro* data to support the initiation or continuation of human clinical studies or filings for regulatory approval;
- failure to demonstrate a starting dose for our product candidates in the clinic that might be reasonably expected to result in a clinical benefit;

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

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

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

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

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

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

Each of the conditions for which we plan to evaluate our current product candidates is a rare genetic disease. Accordingly, there are limited patient pools from which to draw for clinical studies. For example, we estimate that approximately 6,000 patients worldwide suffer from GSDIa, for which DTX401 is being studied, and these all may not be treatable if they are immune to the AAV viral vector.

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

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

Our future success is dependent on our ability to successfully commercialize our products and develop, obtain regulatory approval for, and then successfully commercialize one or more product candidates. We are not permitted to market or promote any of our product candidates before we receive regulatory approval from the FDA or comparable foreign regulatory authorities. We have only obtained regulatory approval for three products that we have developed, and it is possible that none of our existing product candidates or any product candidates we may seek to develop in the future will ever obtain regulatory approval. Further, as the clinical trial requirements of regulatory authorities and the criteria these regulators use to determine the safety and efficacy of a product candidate vary substantially according to the type, complexity, novelty and intended use and market of the product candidates, the regulatory approval process for novel product candidates, such as our gene therapy product candidates, can be more expensive and take longer than for other product candidates, leading to fewer product approvals. To date, very few gene therapy products have received regulatory approval in the U.S. or Europe. The regulatory framework and oversight over development of gene therapy products has evolved and may continue to evolve in the future. Within the FDA, the Center for Biologics Evaluation and Research (CBER) regulates gene therapy products. Within the CBER, the review of gene therapy and related products is consolidated in the Office of Cellular, Tissue and Gene Therapies, and the FDA has established the Cellular, Tissue and Gene Therapies Advisory Committee to advise CBER on its reviews. The CBER works closely with the National Institutes of Health (NIH). The FDA and the NIH have published guidance with respect to the development and submission of gene therapy protocols. For example, in January 2020, the FDA issued final guidance to set forth the framework for the development, review and approval of gene therapies. The final guidance pertains to the development of gene therapies for the treatment of specific disease categories, including rare diseases, and to manufacturing and long-term follow up issues relevant to gene therapy, among other topics. At the same time the FDA issued new draft guidance describing the FDA's approach for determining whether two gene therapy products were the same or different for the purpose of assessing orphan drug exclusivity; the draft guidance was finalized by the FDA in September 2021.

To obtain regulatory approval in the U.S. and other jurisdictions, we must comply with numerous and varying requirements regarding safety, efficacy, chemistry, manufacturing and controls, clinical studies (including good clinical practices), commercial sales, pricing, and distribution of our product candidates, as described 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;
- the FDA may be delayed in responding to our applications or submissions due to competing priorities or limited resources, including as a result of the COVID-19 pandemic;
- failure of our nonclinical or clinical development to comply with an agreed upon Pediatric Investigational Plan (PIP), which details the designs and completion timelines for nonclinical and clinical studies and is a condition of marketing authorization in the EU; and
- the approval policies or regulations of regulatory authorities may significantly change in a manner rendering our clinical data insufficient for approval.

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

This lengthy and uncertain approval process, as well as the unpredictability of the clinical and nonclinical studies, may result in our failure to obtain regulatory approval to market any of our product candidates, or delayed regulatory approval.

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

Undesirable side effects caused by our product candidates could cause us or regulatory authorities to interrupt, delay, or halt clinical studies or further development, and could result in a more restrictive label, the delay or denial of regulatory approval by the FDA or other comparable foreign authorities, or a Risk Evaluation and Mitigation Strategy, or REMS, plan, which could include a medication guide outlining the risks of such side effects for distribution to patients, restricted distribution, a communication plan for healthcare providers, and/or other elements to assure safe use. Our product candidates are in development and the safety profile has not been established. Further, as one of the goals of Phase 1 and/or 2 clinical trials is to identify the highest dose of treatment that can be safely provided to study participants, adverse side effects, including serious adverse effects, have occurred in certain studies as a result of changes to the dosing regimen during such studies and may occur in future studies. Results of our studies or investigator-sponsored trials could reveal a high and unacceptable severity and prevalence of these or other side effects. In such an event, our studies could be suspended or terminated, and the FDA or comparable foreign regulatory authorities could order us to cease further development of or deny or withdraw approval of our product candidates for any or all targeted indications.

Additionally, notwithstanding our prior or future regulatory approvals for our product candidates, if we or others later identify undesirable side effects caused by such products, a number of potentially significant negative consequences could result, including but not limited to:

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

Any of these events could prevent us from achieving or maintaining market acceptance of the particular product candidate, if approved.

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

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

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

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

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

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

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

Our products and any product candidates that are approved in the future remain subject to ongoing regulatory requirements for manufacturing, labeling, packaging, storage, distribution, advertising, promotion, sampling, record-keeping, conduct of post-marketing studies, and submission of safety, efficacy, and other post-market information, including both federal and state requirements in the U.S. and requirements of comparable foreign regulatory authorities, as described in “Item 1. Business – Government Regulation” of 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, material, testing method or standard is relied upon for commercial production. Switching manufacturers, materials, test methods or standards may involve substantial costs and may result in a delay in our desired clinical and commercial timelines. Accordingly, we and others with whom we work are required continue to expend time, money, and effort in all areas of regulatory compliance, including manufacturing, production, and quality control.

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

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

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

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

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

We face an inherent risk of product liability exposure related to the testing of our approved products and product candidates in human clinical trials, as well as in connection with commercialization of our current and future products. If we cannot successfully defend ourselves against claims that any of our approved products or product candidates caused injuries, we could incur substantial liabilities. There can be no assurance that our product liability insurance, which provides coverage in the amount of $15.0 million per incident and $15.0 million in the aggregate, will be sufficient in light of our current or planned clinical programs. We may not be able to maintain insurance coverage at a reasonable cost or in sufficient amounts to protect us against losses due to liability, or losses may exceed the amount of insurance that we carry. A product liability claim or series of claims brought against us could cause our stock price to decline and, if judgments exceed our insurance coverage, could adversely affect our results of operations and business. In addition, regardless of merit or eventual outcome, product liability claims may result in impairment of our business reputation, withdrawal of clinical study participants, costs due to related litigation, distraction of management's attention from our primary business, initiation of investigations by regulators, substantial monetary awards to patients or other claimants, the inability to commercialize our product candidates, and decreased demand for our product candidates, if approved for commercial sale.

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

We are developing companion diagnostic tests to identify the right patients for certain of our product candidates and to monitor response to treatment. In certain cases, diagnostic tests may need to be developed as companion diagnostics and regulatory approval obtained in order to commercialize some product candidates. We currently use and expect to continue to use biomarkers to identify the right patients for certain of our product candidates. We may also need to develop predictive biomarkers in the future. We can offer no assurances that any current or future potential biomarker will in fact prove predictive, be reliably measured, or be accepted as a measure of efficacy by the FDA or other regulatory authorities. In addition, our success may depend, in part, on the development and commercialization of companion diagnostics. We also expect the FDA will require the development and regulatory approval of a companion diagnostic assay as a condition to approval of our gene therapy product candidates. There has been limited success to date industrywide in developing and commercializing these types of companion diagnostics. Development and manufacturing of companion diagnostics is complex and there are limited manufacturers with the necessary expertise and capability. Even if we are able to successfully develop companion diagnostics, we may not be able to manufacture the companion diagnostics at a cost or in quantities or on timelines necessary for use with our product candidates. To be successful, we need to address a number of scientific, technical and logistical challenges. We are currently working with a third party to develop companion diagnostics, however, we have little experience in the development and commercialization of diagnostics and may not ultimately be successful in developing and commercializing appropriate diagnostics to pair with any of our product candidates that receive marketing approval. We rely on third parties for the automation, characterization and validation, of our bioanalytical assays, companion diagnostics and the manufacture of its critical reagents.

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

Risks Related to our Reliance on Third Parties

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

We acquire most of the drug substances and drug products for our products and product candidates from single sources. If any single source supplier breaches an agreement with us, or terminates the agreement in response to an alleged breach by us or otherwise becomes unable or unwilling to fulfill its supply obligations, we would not be able to manufacture and distribute the product or product candidate until a qualified alternative supplier is identified, which could significantly impair our ability to commercialize such product or delay the development of such product candidate. For example, the drug substance and drug product for Crysvita are made by KKC pursuant to our license and collaboration agreement with KKC. The drug substance and drug product for Mepsevii are currently manufactured by Rentschler under a commercial supply and services agreement, accompanying purchase orders, and other agreements. Pharmaceutical-grade drug substance for Dojolvi is manufactured by IOI Oleo pursuant to a supply agreement, and the drug product for Dojolvi is prepared by Haupt Pharma AG, pursuant to a master services agreement. Single source suppliers are also used for our gene therapy programs. We cannot provide assurances that identifying alternate sources, if available at all, and establishing relationships with such sources would not result in significant expense or delay in the commercialization of our products or the development of our product candidates. Additionally, we may not be able to enter into supply arrangements with an alternative supplier on commercially reasonable terms or at all. The terms of any new agreement may also be less favorable or more costly than the terms we have with our current supplier. A delay in the commercialization of our products or the development of our product candidates or having to enter into a new agreement with a different third party on less favorable terms than we have with our current suppliers could have a material adverse impact upon on our business.

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

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

Risks Related to Commercialization of Our Products and Product Candidates

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

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

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

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

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

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

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

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

Our exclusive rights to promote Crysvita in the U.S. and Canada will transition back to KKC.

Pursuant to the terms of our collaboration and license agreement with KKC, or the collaboration agreement, we have the sole right to promote Crysvita in the U.S. and Canada, or the profit-share territory, for a specified period of time, with KKC increasingly participating in the promotion of the product until the transition date of April 2023, which is the fifth anniversary of the commercial launch of the product in the U.S. At the transition date, commercialization responsibilities for Crysvita in the profit-share territory will transition to KKC whereby KKC will be responsible for the commercialization of the product in the territory at and after the transition date. In September 2022, we entered into an amendment to the collaboration agreement which clarified the scope of increased participation by KKC in support of our commercial activities prior to April 2023 and granted us the right to continue to support KKC in commercial field activities in the U.S. through April 2024, subject to the limitations and conditions set forth in the amendment. As a result, KKC will continue to support our commercial field and marketing efforts through a cost share arrangement through April 2024, subject to the limits and conditions set forth in the amendment. After April 2024, our rights to promote Crysvita in the U.S. will be limited to medical geneticists and we are solely responsible for the costs of our own expenses related to the promotion of Crysvita in the profit-share territory. The transition of responsibilities to KKC requires significant effort and may result in the diversion of management's attention to transition activities. We may also encounter unexpected difficulties or incur unexpected costs in connection with such transition activities. Further, we cannot assure that we will have adequate commercial activity to support our North America field force and other aspects of our commercial infrastructure in the territory after April 2024 and we may fail to retain members of our field teams due to such uncertainties. Collaboration with KKC may not result in a seamless transition of responsibilities for KKC to promote the product in the profit-share territory after the transition date and the commercial success of Crysvita in the profit-share territory after the transition date will depend on, among other things, the efforts and allocation of resources of KKC.

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

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

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

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

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

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

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

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

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

Risks Related to Our Intellectual Property

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

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

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

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

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

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

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

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

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

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

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

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

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

In addition to the protection afforded by patents, we rely on trade secret protection and confidentiality agreements to protect proprietary know-how that is not patentable or that we elect not to patent, processes for which patents are difficult to enforce and any other elements of our products or product candidate discovery and development processes that involve proprietary know-how, information, or technology that is not covered by patents. However, trade secrets can be difficult to protect. The confidentiality agreements entered into with our employees, consultants, scientific advisors, contractors and other third parties that we rely on in connection with the development, manufacture and commercialization of our products may not be sufficient to protect our proprietary technology and processes, which increase the risk that such trade secrets may become known by our competitors or may be inadvertently incorporated into the technology of others.

The physical security of our premises and physical and electronic security of our information technology systems may not preserve the integrity and confidentiality of our data and trade secrets. These individuals, organizations and systems, agreements or security measures may be breached, and we may not have adequate remedies for any breach. In addition, our trade secrets may otherwise become known or be independently discovered by competitors.

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

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

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

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

We are aware of certain U.S. and foreign patents owned by third parties that a court might construe to be valid and relevant to one or more of our gene therapy product candidates, certain methods that may be used in their manufacture, or certain formulations comprising one or more of our gene therapy candidates. We are also aware of certain U.S. and foreign patents owned by third parties that relate to anti-sclerostin antibodies and their use, and which a court might construe to be valid and relevant to setrusumab. We are additionally aware of certain U.S. and foreign patents owned by third parties that relate to nucleic acid-containing lipid particles or to certain mRNA modifications, and which a court might construe to be valid and relevant to UX053. There is a risk that one or more of these third parties may choose to engage in litigation with us to enforce or to otherwise assert their patent rights against us. Even if we believe such claims are without merit, a court of competent jurisdiction could hold that one or more of these patents is valid, enforceable, and infringed, in which case the owners of any such patents may be able to block our ability to commercialize a product candidate unless we obtained a license under the applicable patents, or until such patents expire. However, such a license may not be available on commercially reasonable terms or at all.

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

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

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

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

If we are unable to successfully obtain rights to required third-party intellectual property rights or maintain the existing intellectual property rights we have, we may have to abandon development of the corresponding program.

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

Even if we are successful in achieving regulatory approval to commercialize a product candidate faster than our competitors, we may face competition from biosimilars with respect to our biological products (Crysvita, Mepsevii and Evkeeza) and our biological product candidates. In the U.S., the Biologics Price Competition and Innovation Act of 2009, or BPCI Act, was included in the Affordable Care Act and created an abbreviated approval pathway for biological products that are demonstrated to be "highly similar," or biosimilar, to or "interchangeable" with an FDA-approved biological product. The BPCI Act prohibits the FDA from approving a biosimilar or interchangeable product that references a brand biological product until 12 years after the licensure of the reference product, but permits submission of an application for a biosimilar or interchangeable product to the FDA four years after the reference product was first licensed. The BPCI Act does not prevent another company from developing a product that is highly similar to the innovative product, generating its own data, and seeking approval. The law is complex and is still being interpreted and implemented by the FDA. As a result, its ultimate impact, implementation and meaning are subject to uncertainty. Modification of the BPCI Act, or changes to the FDA's interpretation or implementation of the BPCI Act, could have a material adverse effect on the future commercial prospects for our biological products and product candidates.

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

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

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

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

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

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

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

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

In addition, we have in-licensed patents and patent applications owned by the University of Pennsylvania, relating to the AAV8 vector used in DTX301 and DTX401, and the AAV9 vector used in UX701. These patents and patent applications are licensed or sublicensed by REGENX and sublicensed to us. We do not have the right to control the prosecution of these patent applications, or the maintenance of any of these patents. In addition, under our agreement with REGENX, we do not have the first right to enforce the licensed patents, and our enforcement rights are subject to certain limitations that may adversely impact our ability to use the licensed patents to exclude others from commercializing competitive products. Moreover, REGENX and the University of Pennsylvania may have interests which differ from ours in determining whether to enforce and the manner in which to enforce such patents.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Risks Related to Our Business Operations

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

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

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

The COVID-19 pandemic has also impacted the timing of review of our submissions and may continue to do so in the future. The pandemic has also significantly impacted our commercialization efforts for our products. Illness from the more contagious omicron variant impacted the availability of certain of our field and sales medical teams and also resulted in staffing shortages at offices, clinics and hospitals, making it difficult to maintain consistent contact with our current patients or identify new patients for our commercialized products and product candidates. Further, certain of our patients may experience interruptions in insurance coverage due to job loss or change in employment status due to the economic impact from the pandemic, which would limit patient access to our products. Effects from government budgetary constraints, either in the U.S. or internationally, due to the economic impact of the pandemic, such as changes to state coverage rules under Medicaid programs in the U.S., could also impact continued insurance coverage and reimbursement for our products. Any of these events could impact our ability to commercialize our products and adversely affect our operating results and revenue.

We have experienced delays in delivery of ancillary clinical trial materials due to government-imposed mandates and other restrictions from COVID-19 and may in the future experience delays or interruptions in supply of drug product or raw materials, or incur increased costs or expenses. For instance, the Presidential Executive Order invoking the Defense Production Act of 1950 has caused certain of our third-party manufacturers or suppliers to prioritize and allocate more resources and capacity to supply materials to other companies engaged in the study or manufacture of treatments or vaccinations for COVID-19, which has resulted in delays or shortages in supply of such materials to us. Any of these events could adversely impact our clinical trial activities and our ability to meet commercial demand for our product and product candidates and result in loss of revenue. In response to these events, we continue to seek and secure alternative sources of supply of drug product or raw materials in an attempt to avoid future potential delays in supply of product, which may result in additional expenses. We have also experienced interruptions or delays in sourcing certain equipment, materials and resources, and increased costs for certain raw materials, related to construction of our gene therapy manufacturing facility as a result of COVID-19, which could delay the anticipated timing for completion of the plant or result in significant additional expenses.

We have opened our offices in the U.S. and there is the risk that employees may transmit or contract COVID-19 when they return to work onsite despite the safety protocols we have implemented. If members of our management and other key personnel in critical functions across our organization are unable to perform their duties or have limited availability due to illness from COVID-19, we may not be able to execute on our business strategy and/or our operations may be negatively impacted. Further, as our offices reopen, we have offered a significant percentage of our employees flexibility in the amount of time they work in the office. Our new office model, our vaccination policy or other workforce actions taken in response to the COVID-19 pandemic, may not meet the expectations of our workforce, which could adversely impact our ability to attract and retain certain employees.

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

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

During the fourth quarter 2020, we completed our purchase of land located in the Town of Bedford, Massachusetts for construction of our gene therapy manufacturing facility and began construction of the base building for the facility, which is currently expected to be completed in 2023. We do not have experience as a company, however, in developing a manufacturing facility and we may experience unexpected costs or delays or ultimately be unsuccessful in developing the facility or capability. We are dependent on key partners for delivery of power, electricity and other utilities to our manufacturing facility and we cannot assure that such services will be provided at the facility without interruptions, delays or unexpected costs. Further, as described in the risk factor above entitled, “Actual or threatened public health epidemics or outbreaks, including the ongoing COVID-19 pandemic, have and could again materially and adversely impact our business and operating results,” the COVID-19 pandemic has adversely impacted delivery of raw materials, and increased costs for certain materials, for construction of our facility. As we expand our commercial footprint to multiple geographies, we may establish multiple manufacturing facilities, which may lead to regulatory delays or prove costly. Even if we are successful, we cannot assure that such additional capacity will be required or that our investment will be recouped. Further, our manufacturing capabilities could be affected by cost-overruns, unexpected delays, equipment failures, lack of capacity, labor shortages, natural disasters, power failures, program failures, actual or threatened public health emergencies, and numerous other factors that could prevent us from realizing the intended benefits of our manufacturing strategy.

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

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

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

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

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

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

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

As a result of the accounting for our acquisition of Dimension Therapeutics, Inc. (Dimension) in November 2017, we have recorded on our Consolidated Balance Sheet intangible assets for in-process research and development (IPR&D) related to DTX301 and DTX401. We have also recorded contract-based intangible assets related to our license from third parties for certain assets related to Dojolvi following FDA approval of the product, in addition to the intangible asset related to our license from Regeneron for Evkeeza. 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 Condensed Consolidated Statement of Operations. We have not recorded any impairments related to our intangible assets through the end of September 30, 2022.

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

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

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

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

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

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

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

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

We are in the process of expanding our company-wide ERP system to upgrade certain existing business, operational, and financial processes related to our gene therapy manufacturing facility, which we currently expect to be completed in 2023. The ERP expansion is a complex and time-consuming project. Our results of operations could be adversely affected if we experience time delays or cost overruns during the ERP expansion process, or if the ERP system or associated process changes do not give rise to the benefits that we expect. This project has required and may continue to require investment of capital and human resources, the re-engineering of processes of our business, and the attention of many employees who would otherwise be focused on other aspects of our business. Any deficiencies in the design and implementation of the expanded ERP system could result in potentially much higher costs than we had incurred and could adversely affect our ability to develop and launch solutions, provide services, fulfill contractual obligations, file reports with the SEC in a timely manner, operate our business or otherwise affect our controls environment. Any of these consequences could have an adverse effect on our results of operations and financial condition.

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

Cybersecurity incidents, including phishing attacks and attempts to misappropriate or compromise confidential or proprietary information or sabotage enterprise IT systems are becoming increasingly frequent and more sophisticated. The information and data processed and stored in our technology systems, and those of our strategic partners, CROs, contract manufacturers, suppliers, distributors or other third parties for which we depend to operate our business, may be vulnerable to loss, damage, denial-of-service, unauthorized access or misappropriation. Data security breaches can occur as a result of malware, hacking, business email compromise, ransomware attacks, phishing or other cyberattacks directed by third parties. We, and certain of the third parties for which we depend on to operate our business, have experienced cybersecurity incidents, including third-party unauthorized access to and misappropriation of financial information. Further, risks of unauthorized access and cyber-attacks have increased as most of our personnel, and the personnel of many third-parties with which we do business, have adopted remote working arrangements as a result of the COVID-19 pandemic. Improper or inadvertent employee behavior, including data privacy breaches by employees, contractors and others with permitted access to our systems, pose a risk that sensitive data may be exposed to unauthorized persons or to the public. A system failure or security breach that interrupts our operations or the operations at one of our third-party vendors or partners could result in intellectual property and other proprietary or confidential information being lost or stolen or a material disruption of our drug development programs and commercial operations. For example, the loss of clinical trial data from ongoing or planned clinical trials could result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce the data. To the extent that any disruption or security breach results in a loss of or damage to our data or applications, loss of trade secrets or inappropriate disclosure of confidential or proprietary information, including protected health information or personal identifiable information of employees or former employees, access to our clinical data, or disruption of the manufacturing process, we could incur liability and the further development of our drug candidates could be delayed. Further, we could incur significant costs to investigate and mitigate such cybersecurity incidents. A security breach that results in the unauthorized access, use or disclosure of personal identifiable information also requires us to notify individuals, governmental authorities, credit reporting agencies, or other parties, as applicable, pursuant to privacy and security laws and regulations or other obligations. Such a security breach could harm our reputation, erode confidence in our information security measures, and lead to regulatory scrutiny and result in penalties, fines, indemnification claims, litigation and potential civil or criminal liability.

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

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

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

We may acquire or invest in businesses or products that we believe could complement or expand our business or otherwise offer growth opportunities. For example, we acquired Dimension in November 2017 and GeneTx in July 2022. 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. We may experience difficulties in assimilating the personnel, operations and products of the acquired companies, management's attention may be diverted from other business concerns and we may potentially lose key employees of the acquired company. If we are unable to successfully or timely integrate the operations of acquired companies with our business, we may incur unanticipated liabilities and be unable to realize the revenue growth, synergies and other anticipated benefits resulting from the acquisition, and our business, results of operations and financial condition could be materially and adversely affected.

The value of our investments in other companies or businesses may also fluctuate significantly and impact our operating results quarter to quarter or year to year. For instance, in June 2019, we purchased 2,400,000 shares of common stock of Arcturus and in May 2020, we exercised our option to purchase an additional 600,000 shares of Arcturus' common stock pursuant to the terms of our equity purchase agreement with Arcturus; we have subsequently sold an aggregate of 2,500,000 shares. We also purchased 7,825,797 shares of common stock of Solid in October 2020. We have elected to apply the fair value option to account for our equity investments in Arcturus and Solid. As a result, increases or decreases in the stock price of Arcturus and Solid common stock will result in accompanying changes in the fair value of our investments, and cause substantial volatility in, our operating results for the reporting period. As the fair value of our investments in Arcturus and Solid is dependent on the stock price of Arcturus and Solid, which has recently seen wide fluctuations, the value of our investments and the impact on our operating results may similarly fluctuate significantly from quarter to quarter and year to year such that period-to-period comparisons may not be a good indication of the future value of the investments and our future operating results.

Risks Related to Ownership of Our Common Stock

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

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

- adverse results or delays in preclinical or clinical studies;
- any inability to obtain additional funding;
- any delay in filing an IND, NDA, BLA, MAA, or other regulatory submission for any of our product candidates and any adverse development or perceived adverse development with respect to the applicable regulatory agency's review of that IND, NDA, BLA, MAA, or other regulatory submission;
- the perception of limited market sizes or pricing for our products and product candidates;
- decisions by our collaboration partners with respect to the indications for our products and product candidates in countries where they have the right to commercialize the products and product candidates;
- decisions by our collaboration partners regarding market access and pricing in countries where they have the right to commercialize our products and product candidates;
- failure to successfully develop and commercialize our products and product candidates;
- the level of revenue we receive from our commercialized products or from named patient sales;
- post-marketing safety issues;
- failure to maintain our existing strategic collaborations or enter into new collaborations;
- failure by us or our licensors and strategic collaboration partners to prosecute, maintain, or enforce our intellectual property rights;
- changes in laws or regulations applicable to our products;
- any inability to obtain adequate product supply for our products and product candidates or the inability to do so at acceptable prices;
- adverse regulatory decisions;
- introduction of new products, services, or technologies by our competitors;
- changes in or failure to meet or exceed financial projections or other guidance we may provide to the public;
- changes in or failure to meet or exceed the financial projections or other expectations of the investment community;
- the perception of the pharmaceutical industry or our company by the public, legislatures, regulators, and the investment community;
- the perception of the pharmaceutical industry's approach to drug pricing;
- announcements of significant acquisitions, strategic partnerships, joint ventures, or capital commitments by us, our strategic collaboration partners, or our competitors;
- the integration and performance of any businesses we have acquired or may acquire;

- disputes or other developments relating to proprietary rights, including patents, litigation matters, and our ability to obtain patent protection for our technologies;
- additions or departures of key scientific or management personnel;
- significant investigations, regulatory proceedings or lawsuits, including patent or stockholder litigation;
- securities or industry analysts' reports regarding our stock, or their failure to issue such reports;
- changes in the market valuations of similar companies;
- general market or macroeconomic conditions, including the impact from the COVID-19 pandemic;
- sales of our common stock by us or our stockholders in the future; and
- trading volume of our common stock.

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

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

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

Pursuant to our 2014 Incentive Plan, (the 2014 Plan), our management is authorized to grant stock options and other equity-based awards to our employees, directors, and consultants. At September 30, 2022, 2,034,566 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 (2014 ESPP), eligible employees can acquire shares of our common stock at a discount to the prevailing market price. At September 30, 2022, 4,640,287 shares were available for issuance under the 2014 ESPP. Through January 1, 2024, the number of shares available for issuance under the 2014 ESPP will automatically increase on January 1 of each year by the lesser of 1,200,000 shares or 1% of all shares of our capital stock outstanding as of December 31 of the prior calendar year, subject to the ability of our compensation committee to take action to reduce the size of the increase in any given year.

In February 2021, our board of directors adopted the Employment Inducement Plan (the Inducement Plan) with a maximum of 500,000 shares available for grant under the plan. At September 30, 2022, 322,697 shares were available for issuance under the Inducement Plan. If our board of directors elects to increase the number of shares available for future grant under the 2014 Plan, the 2014 ESPP, or the Inducement Plan, our stockholders may experience additional dilution, which could cause our stock price to fall.

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

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

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

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

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

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

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

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

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

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

General Risk Factors

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

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

We may incur additional tax liabilities related to our operations.

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

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

We have incurred substantial losses during our history. To the extent that we continue to generate taxable losses, unused taxable losses will, subject to certain limitations, carry forward to offset future taxable income, if any, until such unused losses expire. Under Sections 382 and 383 of the Internal Revenue Code of 1986, as amended (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 (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 and policies, 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*

		Incorporated by Reference			
Exhibit Number	**Exhibit Description**	**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*	Amendment No. 12 to Collaboration and License Agreement, effective as of September 29, 2022, between Ultragenyx Pharmaceutical Inc. and Kyowa Kirin Co., Ltd.				X
10.2#	Amendment No. 2, dated September 13, 2022, to Executive Employment Agreement by and between Ultragenyx Pharmaceutical Inc. and Emil D. Kakkis, M.D., Ph.D.				X
10.3#	Amendment, dated September 13, 2022, to Offer Letter by and between Ultragenyx Pharmaceutical Inc. and Camille Bedrosian, M.D.				X
10.4#	Amendment No. 2, dated September 13, 2022, to Offer Letter by and between Ultragenyx Pharmaceutical Inc. and Mardi C. Dier.				X
10.5#	Amendment No. 2, dated September 13, 2022, to Offer Letter by and between Ultragenyx Pharmaceutical Inc. and Thomas Kassberg.				X
10.6#	Amendment, dated September 13, 2022, to Offer Letter by and between Ultragenyx Pharmaceutical Inc. and Karah Parschauer.				X
10.7#	Amendment, dated September 13, 2022, to Offer Letter by and between Ultragenyx Pharmaceutical Inc. and Dennis Huang.				X
10.8#	Amendment No. 3, dated September 13, 2022, to Offer Letter by and between Ultragenyx Pharmaceutical Inc. and Erik Harris.				X
10.9#	Amendment, dated September 13, 2022, to Offer Letter by and between Ultragenyx Pharmaceutical Inc. and John R. Pinion II				X
10.10*	Royalty Purchase Agreement by and among Rare Delaware Inc., Ultragenyx Pharmaceutical Inc. and OCM LS23 Holdings LP dated as of July 14, 2022	10-Q	7/29/2022	10.1	
10.11*	Unit Purchase Agreement by and among Ultragenyx Pharmaceutical Inc., GeneTx Biotherapeutics LLC, the Unitholders and Deborah A. Guagliardo, dated as of July 15, 2022	10-Q	7/29/2022	10.2	
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).	

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

\# Indicates management contract or compensatory plan.

** The certification attached as Exhibit 32.1 that accompanies this 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: November 2, 2022	By:	/s/ Emil D. Kakkis Emil D. Kakkis, M.D., Ph.D. President and Chief Executive Officer (Principal Executive Officer)
Date: November 2, 2022	By:	/s/ Mardi C. Dier Mardi C. Dier Executive Vice President and Chief Financial Officer (Principal Financial Officer)
Date: November 2, 2022	By:	/s/ Theodore A. Huizenga Theodore A. Huizenga Senior Vice President and Chief Accounting Officer (Principal Accounting Officer)

Exhibit 10.1

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

AMENDMENT NO. 12 TO COLLABORATION AND LICENSE AGREEMENT

This Amendment No. 12 to the Collaboration and License Agreement, ("**Amendment**") is made and entered into by and between Kyowa Kirin Co., Ltd. (formerly, Kyowa Hakko Kirin Co., Ltd.), a company organized and existing under the laws of Japan, with an address at 1-9-2 Otemachi, Chiyoda-ku, Tokyo, 100-0004, Japan ("**KKC**") and Ultragenyx Pharmaceutical Inc., a company organized and existing under the laws of the State of Delaware, with an address at 60 Leveroni Court, Novato, California 94949, USA ("**UGNX**"). Each of KKC and UGNX shall be referred to herein as a "**Party**" and collectively, as the "**Parties**".

RECITALS

WHEREAS, KKC and UGNX entered into a Collaboration and License Agreement effective as of August 29, 2013, as amended (collectively, the "**Agreement**").

WHEREAS, with the Profit Share Territory Transition Date approaching, the Parties desire to further clarify their obligations and rights related to the Licensed Product in the Profit Share Territory before and after the Profit Share Territory Transition Date under the Agreement, including extending the rights of UGNX to Commercialize the Licensed Product in the Profit Share Territory after the Profit Share Territory Transition Date pursuant to the terms of the Agreement and the hiring and recruiting of certain UGNX sales personnel.

WHEREAS, both Parties wish to further amend the Agreement as set forth below.

AGREEMENT

NOW, THEREFORE, in consideration of the mutual covenants and premises herein contained, and for other good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, and intending to be legally bound, the Parties agree as follows:

1. Except as otherwise set forth in the applicable provision, this Amendment shall be effective as of **September 29, 2022** (the "**12th Amendment Effective Date**").

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

3. Effective as of [***], Article 1. Definitions shall be amended by the addition of the following new sections that provide as follows:

“1.1.87 “**UGNX Transferred Employee**” means any Business Employee who accepts an offer of employment from KKC or an Affiliate, and who is subsequently employed by KKC or an Affiliate on or after the Profit Share Territory Transition Date.”

4. Effective as of the 12th Amendment Effective Date, Article 1. Definitions shall be amended by the addition of the following new sections that provide as follows:

1.1.88 “**Medical Affairs Activities”** means activities designed to ensure or improve appropriate medical use of, conduct medical education of, or generate further research regarding, the Licensed Product sold in the Profit Share Territory, including by way of example but without limitation: (a) activities of medical scientific liaisons who (i) conduct service-based medical activities including providing input and assistance with consultancy meetings, recommending investigators for clinical trials and provide input in the design of such trials and other research related activities, and (ii) deliver non-promotional communications and conduct non-promotional activities including engaging in scientific exchanges and responding to unsolicited requests of medical professionals and presenting new clinical trial and other scientific information; (b) grants to support continuing medical education and other third party-medical education, symposia, or third party research; (c) support for and attendance at scientific or medical education meetings, conferences, and congresses; and (d) development, publication and dissemination of approved publications, as well as medical information services provided in response to inquiries communicated via Sales Representatives or received from third parties by letter, phone call or e-mail.

1.1.89 “**PALs”** means UGNX’s Patient Access Liaisons.

1.1.90 “**Patient Advocacy**” means a Party’s department or function that is responsible for managing interactions and collaborations with patient advocacy organizations or groups.

1.1.91 “**Ramp-Down Period**” means the period of time commencing on April 27, 2023 and expiring at the end of the day on April 26, 2024.

1.1.92 “**Ramp-Up Period**” means the period of time commencing April 27, 2022 and expiring at the end of the day on April 26, 2023.

1.1.93 “**RDL**” means UGNX’s Rare Disease Liaison.

1.1.94 “**Sales Call**” means a visit, whether in-person or virtual, by a Sales Representative to a Target to market and promote the Licensed Product for XLH or TIO.

1.1.95 “**Sales Representative**” means a pharmaceutical sales representative employed by either Party to conduct marketing or promotional efforts with respect to the Licensed Product in accordance with the terms of this Agreement.

1.1.96 “**Target**” means a healthcare professional in the U.S. who has prescribed the Licensed Product, a healthcare professional in the U.S. who has not prescribed the Licensed Product but who is known to have patients with XLH and/or a healthcare professional in the U.S. who has not prescribed the Licensed Product but who has been identified through a predictive targeting process and marketing initiatives to potentially may have patients with XLH and TIO. For clarity, “Target” excludes Medical Geneticists.

1.1.97 "**TIO**" means tumor-induced osteomalacia.

1.1.98 "**Transition Committee**" means a cross-functional, cross-party team of leaders operationalizing the transition of certain activities and the obligations and rights for the Licensed Product in the Profit Share Territory pursuant to the Transition Plan and overseeing the day-to-day activities of the transition at a high level.

1.1.99 **"UCG"** means UGNX's UltraCare Guides.

1.1.100 "**UGNX Sales Personnel**" means UGNX's Sales Representatives."

5. Effective as of the 12th Amendment Effective Date, Section 2.4.1 shall be amended by the addition of the following clause at the end of the current provision:

"including for clarity, on product packaging and Marketing Materials for the Licensed Product in the Field."

6. Effective as of the 12th Amendment Effective Date, Section 6.1.2 shall be deleted in its entirety and replaced with the following:

"6.1.2. Sales, Promotion and Marketing in the Profit Share Territory.

KKC shall book sales of the Licensed Products in the Field in the Profit Share Territory. During the first three (3) years following the First Commercial Sale in the U.S., UGNX will have the exclusive right and responsibility, and shall use Commercially Reasonable Efforts, to promote the Licensed Products in the Field in the Profit Share Territory in order to maximize sales of the Licensed Products in the Profit Share Territory. Subject to Sections 6.7.2 and 6.10, during the period commencing on the third (3rd) anniversary of the First Commercial Sale in the U.S. through the day immediately preceding the Profit Share Territory Transition Date, KKC will have the right to increasingly participate in the promotion of the Licensed Products in the Profit Share Territory [***] (i.e.[***], and UGNX shall continue to promote the Licensed Products in the Profit Share Territory and use Commercially Reasonable Efforts in assisting KKC in the transition of the promotion activities for the Licensed Products in the Profit Share Territory. UGNX shall provide information, documents (including originals or copies, as applicable) that will assist in the transition of the promotion activities for the Licensed Product as set forth in the Transition Plan and other assistance as mutually agreed between the Parties in order to allow KKC to market and promote the Licensed Products in the Profit Share Territory as of the Profit Share Territory Transition Date. During the Ramp-Down Period, KKC shall market and promote the Licensed Product in the Profit Share Territory [***] and subject to Section 6.11, UGNX shall have the right to participate in the promoting and marketing of the Licensed Product in the U.S. (including with respect to activity targeting Medical Geneticists, which right shall not be subject in any way to the limitations set forth in Section 6.11), and each of UGNX and KKC shall use Commercially Reasonable Efforts to market and promote the Licensed Product in the Field in the Profit Share Territory as permitted by this Agreement. After the expiration of the Ramp-Down Period and subject to UGNX's rights to continue to promote to Medical Geneticists, KKC will have the exclusive right, and shall use Commercially Reasonable Efforts, to market and promote the Licensed Products in the Field in the Profit Share Territory [***]. From after the Profit Share Territory Transition Date, UGNX will have the right to continue to promote the Licensed Products in the Profit Share Territory [***] using its own sales force with respect to activity targeting Medical Geneticists and UGNX shall use Commercially Reasonable Efforts to promote the Licensed Products to such key subscribers for Medical Geneticists."

7. Effective as of the 12th Amendment Effective Date, Sections 6.7.2 and 6.7.3 shall be deleted in their entirety and replaced with the following:

"6.7.2: **Ramp-Up Period in the U.S**. To the extent of the Commercialization of the Licensed Product in the United States, UGNX and KKUS each agrees to use its Commercially Reasonable Efforts to facilitate an appropriate transition of the Commercialization of the Licensed Product from UGNX to KKUS upon the Profit Share Territory Transition Date. The following activities shall occur prior to the Profit Share Territory Transition Date (or such other later date as set forth below):

(a) **Transition Committee**.

(i) As of [***], KKUS and UGNX have formed a Transition Committee, consisting of a lead representative designated by each Party (the "**Transition Committee Leaders**") and representatives from each of the cross-functional teams (collectively, the "**Workstream Leaders**"). Each Party will be free to change its representatives in the Transition Committee by giving written notice to the other Party. Unless earlier terminated or extended by mutual agreement of the Parties, the Transition Committee will remain in effect until [***]. For clarity, pursuant to Section 6.10.2(a) of this Agreement, the Canadian Transition Committee shall also be included within and part of the discussions at the Transition Committee.

(ii) The Transition Committee Leaders will meet at least [***], with in-person meetings at least [***] each [***], or more or less often as mutually agreed to by the Parties. The Workstream Leaders will meet at least [***], or more or less often as mutually agreed between the Parties.

(iii) In the event of unresolved disputes at the Transition Committee (including any cross functional team) or disputes related to transition activities for the Licensed Product in the Profit Share Territory or the Transition Plan (including disputes preventing the finalization of the Transition Plan), the matter will be promptly discussed by [***] of the Parties, with [***] for resolving any such dispute. Where [***] are unable to resolve such dispute after [***] (or such longer period of time as mutually agreed upon by the senior executives), then the matter will be referred to the JSC and Section 3.5.2 of the Agreement will apply. In the event such dispute is not resolved by the JSC, notwithstanding Section 3.5.3 of the Agreement, the dispute will be resolved in accordance with Article 16 of the Agreement.

(iv) Notwithstanding anything in the contrary in this Agreement, except to the extent otherwise mutually agreed between the Parties, the Parties shall retain the JSC through and following the Ramp-Down Period and the following subcommittees of the JSC through at least until the end of the Ramp-Down Period: the [***], [***],] [***] and [***]. After the Profit Share Territory Transition Date, KKUS will provide the JSC with [***] updates related to Commercialization of the Licensed Product in the Profit Share Territory in detail reasonably consistent with updates previously provided to the JSC for the Profit Share Territory prior to the Profit Share Territory Transition Date. After the Ramp-Down Period, both Parties shall discuss in good faith whether to continue the subcommittees of the JSC after the Ramp-Down Period. For clarity, except to the extent otherwise expressly provided otherwise, Section 3.5 (Decision-Making) of the Agreement shall continue to apply to the JSC and any such subcommittees.

(b) **Transition Plan**. The Transition Committee will develop mutually agreed plans for transition of the Licensed Product from UGNX to KKUS upon the Profit Share Territory Transition Date, including establishing critical deliverables and timelines during calendar year 2022 through April 26, 2023 in addition to responsibilities required of the Parties after such transition (the "**Transition Plan**").

The Transition Plan may be amended by the Transition Committee as needed through April 26, 2023. For clarity, pursuant to Section 6.10.2(b) of this Agreement, the plans for transition of the Licensed Product in Canada shall also be included within the Transition Plan.

(i) The Transition Plan shall include plans related to the transition of responsibilities related to functional areas identified by the Transition Committee, which may include distribution management (including distribution and inventory management), supply chain (including conversion of the national drug code (NDC) for the Licensed Product from UGNX to KKUS), government price reporting, channel account management, information technology, regulatory and reporting (including adverse experience reporting), development activities (other than those responsibilities related to the DMP which will be governed by the separate DMP Operational Plan), Medical Affairs Activities (including advisory boards, grants and sponsorships, continuing medical education programs), commercial (including sales, marketing), patient support services programs (including patient HUB), Patient Advocacy, and training and other areas of interest as determined by the Transition Committee. Without limiting the foregoing, the Transition Plan will include the obligations expressly specified in this Section 6.7.2.

(ii) Within [***] of the 12th Amendment Effective Date (or such other period as mutually determined by the Parties), the Transition Plan will be presented to the JSC for review and approval.

(iii) The Parties will use their Commercially Reasonable Efforts to implement the activities set forth in the Transition Plan pursuant to the timelines set forth in the Transition Plan to facilitate the timely transition of specified relevant functions in the Profit Share Territory by the Profit Share Territory Transition Date.

(iv) In the event UGNX is required to provide services to KKUS or KKUS requests UGNX to provide services, in each case related to the transition following the Profit Share Territory Transition Date and as mutually agreed between the Parties, [***] related to such services by UGNX, except as otherwise mutually agreed upon or to the extent such services required after the Profit Share Territory Transition Date result from [***].

(c) **Contracts**. Any contract amendments required to transfer or assign agreements between UGNX and third parties to KKUS to permit KKUS to operate under or receive the benefit of such agreements will be identified and initiated as mutually agreed. UGNX will use its Commercially Reasonable Efforts to complete the assignment process prior to the Profit Share Territory Transition Date.

(d) **Patient Support Service Programs.**

(i) Both Parties agree that the patient support services program transition from UGNX patient HUB services, UltraCare ("UltraCare"), to Kyowa Kirin's patient HUB services, Kyowa Kirin Cares ("Kyowa Kirin Cares") as set forth in the Transition Plan shall be completed by the Profit Share Transition Date or as close to the Profit Share Transition Date as possible, but in no event later than [***], provided, however, that the Parties agree that the foregoing deadlines shall not apply to [***] ("Excluded Data and Services"). The Parties agree to discuss in good faith the timeline and activities related to the transfer of Excluded Data and Services and to include such agreed upon activities (and timelines) in the Transition Plan. For clarity sake, the Transition Plan shall also include a mutually agreed schedule of patient data transition activities to enable the appropriate transition of patients from UltraCare to Kyowa Kirin Cares, within the aforementioned time period (or such longer time period as it relates to the Excluded Data and Services). As of the Profit Share Transition Date, all new patients prescribed the Licensed Products will be enrolled in Kyowa Kirin Cares and all patient services offered to such new patients and established patients transferred into Kyowa Kirin Cares from UltraCares, will be governed by business rules established [***] in accordance with Applicable Laws. At UGNX's request, [***]. KKUS and UGNX will create a mutually agreeable reasonable schedule that will allow KKUS personnel to observe in real time (but virtually if public health conditions require) existing patient support service programs and other interactions with service providers and Customers, and to accompany UGNX personnel to these observations, as set forth in the Transition Plan, in each case to the extent such participation or observations by KKUS do not significantly disrupt the work of UGNX personnel and are not prohibited by Applicable Laws or the terms of the agreements between UGNX and such service providers or Customers, including without limitation and as applicable, required consent forms from patients or caregiver. Where such participation or observation is prohibited by the terms of the agreements between UGNX and such service providers or Customers or requires consent, approval, or permission forms from patients or caregivers, UGNX shall use its Commercially Reasonable Efforts to obtain the necessary agreements, consents, approvals, and permissions to permit KKUS personnel to engage in such participation or observation.

(e) **DMP Operational Plan**.

(i) The Transition Committee shall develop a separate operational plan for the Disease Monitoring Program ("**DMP**") in the Profit Share Territory that consists of the Phase 4 Clinical Trials for XLH and TIO (the "**In-Clinic DMPs**") and the Phase 5 Clinical Trial known as BEYONDXLH (the "**On-Line DMP**") (such plan, the "**DMP Operational Plan**"), and includes the allocation of rights and responsibilities provided for in this Section 6.7.2(e). The DMP Operational Plan will provide for, and KKUS shall have the right to, actively participate in the DMP steering committees (specifically, the internal KKUS and UGNX DMP Steering Committee and external DMP Steering Committee) in the Profit Share Territory prior to the Profit Share Territory Transition Date, and UGNX will provide KKUS with relevant information reasonably requested by KKUS related to the Licensed Product, XLH or TIO regarding any such scheduled meetings, including making relevant introductions for KKUS to external DMP Steering Committee participants, to permit KKUS to prepare for and attend all such meetings. For the avoidance of doubt, the Parties agree that the activities and obligations set forth in this Section 6.7.2(e) shall apply only to the DMP in the Profit Share Territory and shall have no effect on the DMP outside of the Profit Share Territory.

(ii) UGNX will jointly prepare with KKUS the annual report to FDA due in 2023 for the In-Clinic DMPs, and will provide KKUS with relevant information and assistance to permit KKUS to timely submit such report as set forth in the DMP Operational Plan. After 2023, KKUS will be solely responsible for preparation and submission of annual reports to the FDA for the In-Clinic DMPs. Both Parties agree that as of and after the Profit Share Territory Transition Date, KKUS shall have the right to fully access the DMP data in the Profit Share Territory.

(iii) Without limiting UGNX's obligations under this Agreement, UGNX will provide KKUS with relevant data related to the Licensed Product, XLH or TIO arising under any activities under the DMP to permit KKUS to respond to any requests from a Regulatory Authority or other third parties such as medical journals, in each case as set forth in the DMP Operational Plan.

(f) **UGNX Personnel.** During the Ramp-Up Period, UGNX and KKUS shall coordinate on the transition of the Licensed Product to Targets in the U.S. as follows:

(i) UGNX shall have the right to continue to use Sales Representatives employed by UGNX to make Sales Calls to the Targets identified in the Transition Plan. UGNX shall also have the right to continue to use RDLs employed by UGNX to continue to provide disease state education on the Licensed Product for its approved indications in XLH and TIO in the U.S. and UCGs and PALs employed by UGNX to continue to provide patient service support on the Licensed Product in the U.S. and to transition patients to KKUS (collectively, such UGNX Sales Representatives, RDLs, UCGs and PALs referred to collectively, as the "**UGNX Personnel**"). The number of UGNX Personnel that UGNX shall have the right to use will be in UGNX's sole discretion provided that the costs of such UGNX Personnel are in accordance with the Marketing Budget in effect and approved by the JSC. For the avoidance of doubt, KKUS shall [***] pursuant to Section 7.1 of the Agreement.

(ii) Subject to clause (iii) of this Section 6.7.2(f), KKUS shall have the right to use up to [***] rare disease specialists employed by it to engage with Targets in the U.S. identified in the Transition Plan to educate on the applicable disease states of XHL and TIO and to conduct account profiling for such Targets. KKUS shall be [***] of such rare disease specialists. In the event any such Target desires to learn about the Licensed Product, KKUS rare disease specialists will direct such Target to UGNX in accordance with an agreed-upon process to be mutually determined by UGNX and KKUS.

(iii) In the event of any departures, other attrition, or reassignment of UGNX Personnel, UGNX shall have the right to fill the vacancy at its sole discretion with a UGNX consultant, temporary employee, contractor or UGNX employee. In the event UGNX notifies KKUS that it has determined that it will not fill a vacancy of a UGNX Sales Representative, KKUS shall have the right to fill such position with an additional KKUS rare disease specialist beyond its existing [***] rare disease specialists [***].

(iv) For clarity, UGNX shall remain solely responsible for preparing all Marketing Materials for use in the U.S. until the Profit Share Territory Transition Date in accordance with Section 6.5 of the Agreement; provided however that: (A) KKUS reserves the right to limit its Sales Representatives' use of any such Marketing Materials to only those Marketing Materials expressly approved by KKUS; and (B) KKUS may prepare corporate materials for use by KKUS during the Ramp-Up-Period as mutually agreed upon with UGNX.

6.7.3. **Education**. Prior to the Profit Share Territory Transition Date, upon KKUS's reasonable request and [***], UGNX will provide educational overviews to KKUS related to the Licensed Product in the Profit Share Territory that UGNX determines is relevant for the transition and as set forth in the Transition Plan."

8. Effective as of the 12th Amendment Effective Date, Section 6.10.2(c) and 6.10.2(d) shall be deleted in its entirety and replaced with the following:

"(c) Any contract amendments required to transfer or assign agreements between UCI and third parties to KKCA to permit KKCA to operate under or receive the benefit of such agreements will be identified and initiated as mutually agreed. UCI will use its Commercially Reasonable Efforts to complete the assignment process prior to the Profit Share Territory Transition Date.

(d) To the extent mutually determined by the Parties to be necessary, KKCA and UCI will create a mutually agreeable reasonable schedule that will allow KKCA personnel to observe in real time (but virtually if public health conditions require) existing patient support service programs and other interactions with service providers and Customers, and to accompany UGI personnel to these observations, as set forth in the Transition Plan, in each case to the extent such participation or observations by KKCA do not significantly disrupt the work of UCI personnel and are not prohibited by Applicable Laws or the terms of the agreements between UCI and such service providers or Customers, including without limitation and as applicable, required consent forms from patients or caregiver. Where such participation or observation is prohibited by the terms of the agreements between UCI and such service providers or Customers or requires consent, approval, or permission forms from patients or caregivers, UCI shall use its Commercially Reasonable Efforts to obtain the necessary agreements, consents, approvals, and permissions to permit KKCA personnel to engage in such participation or observation."

9. Effective as of the 12th Amendment Effective Date, Section 6.10.3 shall be deleted in its entirety and replaced with the following:

"6.10.3 **Education**. Prior to the Profit Share Territory Transition Date, upon KKCA's reasonable request and [***], UGNX will provide educational overviews to KKCA related to the Licensed Product in the Profit Share Territory that UGNX determines is relevant for the transition and as set forth in the Transition Plan."

10. Effective as of the 12th Amendment Effective Date, new Section 6.11 and 6.12 shall be added that provides as follows:

"6.11. **Post-Profit Share Territory Transition Date.**

(a) **Ramp-Down Period**. Solely during the Ramp-Down Period, UGNX and KKUS shall transition the making of Sales Calls to Targets in the U.S. as set forth below. The Parties agree that this Section 6.11(a) shall have no effect on or be construed to limit in any way UGNX's rights or activities related to promoting the Licensed Product in the Profit Share Territory to Medical Geneticists.

(i) Subject to clause (iv) of this Section 6.11(a), KKUS plans to use [***] Sales Representatives employed by it to make Sales Calls to all Targets in the U.S. (subject to vacancies and attrition in the ordinary course of business). For clarity, while KKUS anticipates using the Business Employees to partially fill such Sales Representative positions, in the event that any Business Employee elects not to accept a KKUS Sales Representative position pursuant to Section 13.7 of this Agreement, KKUS shall have the right to recruit to fill such position with Sales Representatives from outside the UGNX organization. For clarity, nothing in this Section 6.11(a) shall prevent KKUS from engaging, and KKUS shall have the right and authority to engage, any and all such additional personnel that KKUS believes may be useful for promoting and marketing the Licensed Product in the Profit Share Territory. KKUS shall be solely responsible for all costs related to its Sales Representatives.

(ii) Subject to clause (iv) of this Section 6.11(a), UGNX has the right to use up to [***] of the Sales Representatives employed by UGNX to make Sales Calls in the U.S. based on Targets identified by KKUS, to support KKUS Sales Representatives in making Sales Calls and providing continued introductions to Targets as set forth in the Transition Plan; provided however that from and after [***], such number shall be decreased to [***] Sales Representatives. In addition, UGNX shall also have the right to continue to use up to [***] UCGs and/or PALs employed by UGNX to provide patient support services related to the Licensed Product in the U.S. (any of the up to [***] UGNX Sales Representatives and the up to [***] UCGs or PALs involved in this Ramp-Down Period shall each be known as a "**UGNX Ramp-Down Representative**"). For the avoidance of doubt, UGNX shall have the right and authority to maintain and engage personnel related to UGNX training, marketing, commercial analytics and other activities as set forth in the Transition Plan to support the commercialization of the Licensed Product in the Profit Share Territory ("**UGNX Support Personnel**"), in its sole discretion within the scope agreed in advance by the JSC. Notwithstanding the termination of the Profit Share Period, KKUS [***] for each such UGNX Ramp-Down Representative actively providing services during the period of time permitted by this Section 6.11(a)(ii) and UGNX Support Personnel in support of the Licensed Product [***]. Notwithstanding Section 6.1.7(b) of the Agreement contemplating a Marketing Budget including Commercialization Costs only through the Profit Share Territory Transition Date, the Parties agree that the Marketing Budget prepared by UGNX during the Ramp-Down Period shall also [***] through the Ramp-Down Period. The review and approval of such Marketing Budget shall continue to be governed by

Section 6.1.7(b) of the Agreement. Commencing upon the end of the [***] of the Ramp-Down Period, within [***] following the end of each [***], UGNX shall send KKUS [***], including providing all relevant supporting documentation. KKUS will pay each such invoice within [***] within receipt of such invoice. UGNX shall also have the right, [***], to continue to use up to [***] RDLs employed by UGNX to provide services related to the Licensed Product in the U.S.

(iii) In no event will KKUS be involved in the day-to-day direction or supervision of any UGNX Ramp-Down Representative, UGNX Support Personnel or RDL. For the avoidance of doubt, except as expressly provided otherwise in this Section 6.11(a)(iii), UGNX policies and procedures shall continue to apply to the UGNX Ramp-Down Representatives, UGNX Support Personnel and RDLs. During the Ramp-Down Period, UGNX Ramp-Down Representatives shall comply with the [***] business rules, which shall be designed in accordance with Applicable Laws, for all patient services offered to patients enrolled in Kyowa Kirin Cares. At UGNX's request [***]. The Parties further agree in good faith to establish compliance policies and procedures in accordance with Applicable Laws and industry codes to govern interactions between the Parties' respective employees engaged in the Commercialization of the Licensed Product.

(iv) In the event of any departures, other attrition, or reassignment of such UGNX Ramp-Down Representatives and/or RDLs, UGNX shall have the right to fill the vacancy at its sole discretion with a UGNX consultant, temporary employee, contractor or UGNX employee. In the event UGNX notifies KKUS that it has determined that it will not fill a vacancy of a UGNX Sales Representative, KKUS shall have the right to fill such position with an additional KKUS Sales Representative beyond its existing [***] Sales Representatives [***].

(v) For clarity, during the Ramp-Down Period, KKUS shall be responsible for preparing all Marketing Materials for use by both UGNX and KKUS Sales Representatives in the U.S. from and after the Profit Share Territory Transition Date, provided however, that UGNX reserves the right to modify such Marketing Materials for use by the UGNX Ramp-Down Representatives if the subcommittees of both Parties responsible for reviewing Marketing Materials reasonably determines that such modifications are needed to comply with Applicable Laws and as mutually agreed by both Parties.

(vi) KKUS will, upon UGNX's reasonable request, provide assistance to UGNX in educating UGNX personnel on the KKUS Marketing Materials and related programs and procedures (if applicable) to be used by both UGNX and KKUS Sales Representatives after the Profit Share Territory Transition Date.

(b) **Responsibility for UGNX Ramp-Down Representatives**. The following provisions shall apply with respect to the UGNX Ramp-Down Representatives.

(i) Each UGNX Ramp-Down Representative shall continue as an employee of UGNX. Without limiting the foregoing, with respect to each UGNX Ramp-Down Representative, UGNX shall be responsible for (and KKUS shall have no responsibility for) all employment-related obligations to such UGNX Ramp-Down Representative other than as expressly stated in this Agreement.

(ii) For clarity, except with respect to those provisions relating to the hiring of UGNX Transferred Employees, no provision in this Agreement is intended to create, nor shall it be deemed or construed to create, any employment relationship between KKUS and any employee of UGNX. In addition, this Agreement shall not create, and shall not be construed as creating, any joint-or co-employer relationship with respect to any UGNX personnel, including any UGNX Ramp-Down Representative.

11. Effective as of the 12th Amendment Effective Date, a new Section 9.3.3 shall be added that provides as follows:

"9.3.3 From and after the Profit Share Territory Transition Date, KKUS shall make good faith efforts to ensure that all Customer contracts with respect to the Licensed Product provide UGNX and KKUS with access to and the right to audit the data supporting Net Sales calculations, as described in Section 9.1 of this Agreement. KKUS shall make good faith efforts to include the foregoing audit rights in its Customer contracts with respect to the Licensed Product."

12. Effective as of the 12th Amendment Effective Date, a new Section 9.4.3 shall be added that provides as follows:

"9.4.3 From and after the Profit Share Territory Transition Date, KKCA shall make good faith efforts to ensure that all Customer contracts with respect to the Licensed Product provide UCI and KKCA with access to and the right to audit the data supporting Net Sales calculations, as described in Section 9.1 of this Agreement. KKCA shall make good faith efforts to include the foregoing audit rights in its Customer contracts with respect to the Licensed Product."

13. Effective as of July 26, 2022, a new Section 12.2.1 shall be added that provides as follows:

"12.2.1 **Business Employees**. UGNX hereby represents and warrants to KKC that, as of each of [***], and the applicable Employment Commencement Date for each UGNX Transferred Employee,: (a) UGNX is not and never has been bound by any collective bargaining agreement or other agreement with any labor organization, union, or other employee-representative organization with respect to the Business Employees; (b) there is no labor strike, picketing, work stoppage, concerted refusal to work overtime, labor arbitration, walkout, or other proceeding in respect to the grievance of any Business Employees pending or threatened; (c) to the knowledge of UGNX, no union organizing campaign is in progress with respect to any Business Employees and there have never been any organizing efforts relating to the Business Employees; (d) with respect to the Business Employees, UGNX is in compliance, and has been in compliance since April 1, 2020, in all material respects with all Applicable Laws respecting labor, employment, fair employment practices, terms and conditions of employment, immigration, workers' compensation, occupational safety and health requirements, plant closings, wages and hours, worker classification (including as to classification as an employee, contractor, volunteer, exempt or non-exempt), withholding of taxes, employment discrimination, disability rights or benefits, equal opportunity, labor relations, employee leave issues and related matters; and (e) since April 1, 2020, there has been no proceeding against UGNX related to the Business Employees relating to the alleged violation of any Applicable Laws pertaining to labor relations or employment matters, including any charge or complaint filed before the Equal Employment Opportunity Commission or similar governmental entity alleging unlawful discrimination, harassment, retaliation, or noncompliance with any Applicable Laws relating to employment practices, or any charge or complaint filed before the National Labor Relations Board or similar governmental entity alleging any unfair labor practice, or any other proceeding before any other governmental entity alleging non-compliance with any Applicable Laws pertaining to labor relations or employment matters, by UGNX, nor has, to the knowledge of UGNX, any such proceeding been threatened."

14. Effective as of [***], a new Section 13.7 shall be added that provides as follows:

"13.7 **Business Employees**.

13.7.1 On [***], KKUS made offers of at-will employment to those individuals specified in Schedule 13.7, as the same may be amended from time to time (collectively, the "**Business Employees**") pursuant to the Consent Letter entered into by the UGNX and KKC dated [***], with all such offers of at-will employment on terms and conditions as determined by KKUS in its sole discretion. KKUS shall inform UGNX of each Business Employee who is offered and/or accepts employment. Each Business Employee who timely accepts employment, who is employed in good standing by UGNX on the day immediately prior to the Profit Share Territory Transition Date, and who otherwise satisfies all contingencies set forth in such Business Employee's offer letter, shall commence employment with KKUS on the Profit Share Territory Transition Date. Additionally, a Business Employee who accepts an offer of employment, but is on a leave of absence for any reason on the date immediately prior to the Profit Share Territory Transition Date (each, an "**Inactive Employee**"), shall not commence employment with KKUS sooner than the date such Inactive Employee's leave of absence has ended (and such Inactive Employee shall not commence employment if such leave of absence has not ended within [***] of the Profit Share Territory Transition Date).

13.7.2 From and after [***], until the later of the Profit Share Territory Transition Date or the last date on which a UGNX Transferred Employee commences employment with KKUS (the "**Business Employee Transition Period**"), UGNX shall: (a) provide reasonable access by KKUS to the Business Employees for purposes of communicating with them regarding offers of employment and transitional matters solely as it relates to such Business Employee's potential employment with KKUS; (b) cooperate in good faith regarding any written communications to be distributed to any Business Employees related to their offers of employment with KKUS, and shall consult with KKUS before distributing any such communications to any Business Employees; and (c) promptly inform KKUS if any Business Employee that KKUS has offered employment has (i) been terminated or resigned; (ii) taken or been placed on a leave of absence (and providing reasonable detail for such leave of absence to the extent not prohibited by Applicable Laws); or (iii) been disciplined, demoted, or otherwise is not in good standing with UGNX.

13.7.3 To facilitate the continued employment of Business Employees, and avoid the loss of the goodwill, investment, training, and other intangibles associated with the Business Employees, during the Business Employee Transition Period, except as consented to in writing by KKUS (which consent shall not be unreasonably withheld), UGNX shall not: (a) make changes to Business Employee compensation or benefits other than normal merit, cost-of-living and promotion-related base salary or wage increases consistent with past practice; (b) enter into, negotiate, or discuss any collective bargaining agreement or other agreement with any labor organization, union, or other employee-representative organization; or (c) promote or change the job title of any Business Employee other than as part of a normal merit- based promotion or change consistent with past practice, or to fill a vacancy arising from the departure of another Business Employee.

13.7.4 On the day each UGNX Transferred Employee commences employment with KKUS (each, the "**Employment Commencement Date**"), UGNX shall terminate the employment of such UGNX Transferred Employee, and waive and release any restrictive covenants that may restrict their employment at KKUS. UGNX shall be solely responsible for paying such UGNX Transferred Employees all hourly pay, commission, bonus, salary, accrued vacation, fringe, pension or profit sharing benefits or severance pay for any period relating to their employment with UGNX or prior to the Employment Commencement Date, and UGNX shall pay all such amounts to all UGNX Transferred Employees within the time required by Applicable Laws. Without limiting the foregoing, UGNX shall be responsible for all liabilities and obligations associated with or arising with respect to employee benefits accrued for, incurred, or provided by UGNX or its Affiliates to the UGNX Transferred Employees (including Inactive Employees) upon or prior to each such individual's Employment Commencement Date, regardless of whether such liabilities or obligations must be satisfied before or after the Employment Commencement Date, including without limitation the provision of health and disability insurance coverage. In no event shall KKUS or any of its Affiliates be responsible for the payment of any compensation or benefits, in whatever form, as a result of: (a) the termination of employment of Business Employees or any other person by UGNX or any of its Affiliates; (b) the failure of a Business Employee to become a UGNX Transferred Employee; or (c) a delay in the Employment Commencement Date for an Inactive Employee.

15. Effective as of [***], Section 14.1 shall be amended by replacing the definition of KKC Indemnitees in the first sentence with the following:

"14.1 **Indemnity by UGNX**. UGNX hereby agrees to defend, hold harmless, and indemnify KKC, its agents, directors, officers, contractors, and employees, and KKC Affiliates (including their respective agents, directors, officers, contractors, and employees) (the "**KKC Indemnitees**")"

16. Effective as of [***], Section 14.2 of the Agreement shall be amended by replacing the definition of UGNX Indemnitees in the first sentence with the following:

"14.2 **Indemnity by KKC**. KKC hereby agrees to defend, hold harmless, and indemnify UGNX, its agents, directors, officers, contractors, and employees, and UGNX Affiliates (including their respective agents, directors, officers, contractors, and employees) (the "**UGNX Indemnitees**")"

17. Effective as of the 12th Amendment Effective Date, Section 14.5 shall be amended with the addition of the following sentences at the end of the current provision:

"In addition, during the Ramp-Down Period and for [***] thereafter, UGNX shall procure and maintain, at its sole cost and expense, the following types of insurance, with limits of liability, retentions or deductibles and other terms and conditions that are consistent with industry standards and no less than any statutorily-required limits, affording coverage for claims by or against, acts, errors or omissions of, or injuries or loss sustained by, any UGNX Sales Personnel in connection with performance under this Agreement: (a) automobile liability insurance for bodily injury and property damage covering UGNX owned, hired, and non-owned automobiles; (b) workers compensation insurance and employers liability insurance; and (c) employment practices liability insurance that includes, without limitation, insurance coverage for third party discrimination claims. For clarity, the foregoing shall not serve to restrict or otherwise reduce any of UGNX's obligations under this Agreement, including its indemnification obligations hereunder."

18. Effective as of [***], a new Section 14.8 shall be added that provides as follows:

"14.8 **UGNX Employees.** UGNX hereby agrees to defend, hold harmless and indemnify the KKC Indemnitees from and against any and all Third Party Losses, including Losses relating to formal or informal investigations or inquiries, incurred by a KKC Indemnitee concerning conduct, activities, employment, or termination of any UGNX employee, including a UGNX Transferred Employee, that occurred prior to employment with KKC or any KKC Affiliate, provided that, nothing herein shall preclude UGNX from pursuing any claims or losses that arise from acts or omissions of KKC or any KKC Affiliate."

19. Effective as of the 12th Amendment Effective Date, Section 15.6.2 shall be amended by adding the following Sections to the existing provision:

"Section 14.5 (for the time period provided therein), 6.11(b), 13.7.4 and Section 14.8."

20. Effective as of [***], Section 17.1 shall be deleted in its entirety and replaced with the following:

"17.1. **Solicitation of Employees**.

17.1.1 From and after [***], a Party may solicit or hire any former employee of the other Party as long as solicitation, hiring, or other employment discussions with such former employee are not initiated (directly or indirectly) until after said individual's employment with the other Party has terminated. Contract employees shall be treated as equivalent to full-time employees for purposes of this section.

17.1.2 During the remainder of the Term, neither Party nor its Affiliates shall, directly nor through its representatives or agents, solicit for employment or hire any officer, director, employee, contract employee, or consultant of the other Party or its Affiliates who is known by such Party or its Affiliates to be currently participating in the subject matter of this Agreement or who participated in the development of the Drug Substance or a Licensed Product. For the avoidance of doubt, any officer, director, employee, contract employee, or consultant of any Party or its Affiliates who falls outside the scope of the first sentence of this paragraph shall not be subject to this non-solicitation provision. Notwithstanding the foregoing, during the remainder of the Term the first sentence of this paragraph does not prohibit a Party from soliciting and hiring employees of the other Party through general public advertisement, not targeted at such other Party's employees, including but not limited to the Party's career website, LinkedIn, Indeed, other online career sites or in connection with job fairs. Additionally, notwithstanding the foregoing, it shall not be a violation of this section or any other provision of the Agreement for KKUS to solicit or hire any Business Employee.

17.1.3. The Parties acknowledge that a breach or threatened breach of this section would give rise to irreparable harm to the non-breaching Party, for which monetary damages would not be an adequate remedy, and hereby agrees that in the event of a breach or a threatened breach by the breaching Party of any such obligations, the non-breaching Party shall, in addition to any and all other rights and remedies that may be available to it in respect of such breach, be entitled to equitable relief, including a temporary restraining order, an injunction, specific performance and any other relief that may be available from a court of competent jurisdiction (without any requirement to post bond). In the event this paragraph should ever be adjudicated to exceed the time, geographic, product or service or other limitations permitted by Applicable Laws in any jurisdiction, then any court is expressly empowered to reform such covenant, and such covenant shall be deemed reformed, in such jurisdiction to the maximum time, geographic, product or service or other limitations permitted by Applicable Laws."

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

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

[Signature page follows]

IN WITNESS WHEREOF, the Parties have executed this Amendment as of the 12th Amendment Effective Date.

	KYOWA KIRIN CO., LTD.		**ULTRAGENYX PHARMACEUTICAL INC**
By:	/s/ Tomohiro Sudo	By:	/s/ Thomas Kassberg
Name:	Tomohiro Sudo	Name:	Thomas Kassberg
Title:	Executive Officer Director, Global Product Strategy Department, Strategy Division	Title:	Chief Business Officer

AMENDMENT NO. 2 TO EXECUTIVE EMPLOYMENT AGREEMENT

This Amendment No. 2 to Executive Employment Agreement (the "**Amendment**"), dated September 13, 2022 (the "**Effective Date**"), is between ULTRAGENYX PHARMACEUTICAL INC. (the "**Company**") and EMIL D. KAKKIS, M.D., PH.D. (the "**Executive**"). Capitalized terms used but not defined herein have the meanings given to them in the Agreement (as defined below).

WHEREAS, the Company and the Executive are parties to that certain Executive Employment Agreement, dated as of June 15, 2011, as amended by Amendment No. 1 to Executive Employment Agreement dated as of August 8, 2014 (the "**Agreement**"); and

WHEREAS, the Company and the Executive now desire to amend certain terms of the Agreement in accordance with the terms set forth herein.

NOW, THEREFORE, in consideration of the mutual covenants, terms and conditions set forth herein, the parties agree as follows:

1. Section III.B. of the Agreement is hereby deleted in its entirety and replaced with the following:

"**B. Severance**. Except in situations where the employment of Executive is terminated For Cause, By Death or By Disability (as defined in Section IV below), in the event that the Company terminates Executive's employment at any time, Executive will be eligible to receive the following (collectively, the "**Severance Benefits**"):

(i) An amount equivalent to (x) 24 months of Executive's then-current Base Salary, *plus* (y) Executive's target bonus for the year in which such termination occurs (collectively, the "**Severance Amount**"), payable in equal installments over the 24-month period following such termination in accordance with the Company's standard payroll practices commencing on the Company's first regular payroll date that follows the 60th day after the Executive's date of termination (with the first payment including the accrued installments of the Severance Amount between the Executive's date of termination and the date of the first payment); provided, however that if such termination occurs on or within the 12-month period following a Covered Transaction (as defined below), the Severance Amount shall instead equal (A) 24 months of Executive's then-current Base Salary, *plus* (y) two times Executive's target bonus for the year in which such termination occurs.

(ii) Subject to Executive's timely and proper election of health continuation coverage under the Consolidated Omnibus Budget Reconciliation Act of 1985, as amended ("**COBRA**"), reimbursement on a monthly basis for the monthly COBRA premium paid by Executive for Executive and his dependents (the "**COBRA Reimbursement**"), payable on the first regularly scheduled pay date in the calendar month immediately following the calendar month in which Executive submits to the Company documentation of the applicable premium payment having been paid by Executive (which shall be submitted within 30 days of payment). Executive shall be eligible to receive the COBRA Reimbursement until the earliest of (x) the second anniversary of the date of such termination; (y) the date on which Executive becomes eligible to receive coverage from another employer or other source; or (z) the date Executive is no longer eligible to receive COBRA continuation coverage; provided, however, that if Executive ceases to be eligible for COBRA (other than as a result of becoming eligible for Medicare or coverage under other group health plans), the Company shall pay to Executive within 30 days following the date Executive ceases to be so eligible a lump sum amount equal to (A) 24, *less* the number of months of COBRA that have been previously been reimbursed as of such date, *multiplied by* (B) the amount of the COBRA premiums paid in the final month of COBRA eligibility. Notwithstanding the foregoing, if the Company's payments under this paragraph would violate applicable law or result in the imposition of penalties under applicable law, the parties agree to reform this paragraph in a manner as is necessary to comply with applicable law.

Executive's eligibility for the Severance Benefits is conditioned on Executive having first signed a release agreement in the form attached as Exhibit A and such release becoming effective within 60 days following the Executive's date of termination. For the avoidance of doubt, Executive shall not be entitled to any Severance Benefits if Executive's employment is terminated For Cause, By Death or By Disability or if Executive's employment is terminated by Executive (except as otherwise provided in Section V.B, below).

2. Sections V.B. and V.C. of the Agreement is hereby deleted in its entirety and replaced with the following:

"**B. Termination for Good Reason**. In the event Executive terminates his employment for Good Reason (as defined below), Executive will be eligible to receive the Severance Benefits on the terms set forth in Section III.B. above, including the enhanced Severance Benefits in the event such termination occurs on or within 12 months following a Covered Transaction. Thereafter all obligations of the Company or its successor under this Agreement shall cease.

For purposes of this Agreement, "**Good Reason**" shall mean any of the following events if the event is effected by the Company without the consent of Executive: (A) a change in Executive's position with the Company which materially reduces Executive's level of responsibility; (B) a material reduction in Executive's Base Salary, except for reductions that are comparable to reductions generally applicable to similarly situated executives of the Company; or (C) a relocation of Executive's principal place of employment by more than 50 miles. Notwithstanding the foregoing, Executive's termination shall only be for Good Reason if (x) Executive provides written notice to the Company of the Good Reason within 90 days of the event constituting Good Reason, (y) the Company fails to cure the Good Reason within a 30-day period following such notice, and (z) Executive's termination is effective within 30 days following the expiration of such cure period.

3. Except as otherwise expressly amended herein, all terms and provisions of the Agreement shall remain in full force and effect.

4. In the event of a conflict between the provisions of this Amendment and the provisions of the Agreement, the provisions of this Amendment shall control.

5. This Amendment shall be governed by and construed in accordance with the laws of the State of California.

6. This Amendment may be executed simultaneously in two or more counterparts, and by PDF or other electronic transmission, each of which counterparts shall be deemed an original, but all of which together shall constitute one and the same instrument, provided that all such counterparts, in the aggregate, shall contain the signatures of all parties hereto.

[*Signature page(s) follow*]

IN WITNESS WHEREOF, the parties have duly executed this Amendment as of the Effective Date.

ULTRAGENYX PHARMACEUTICAL INC.	EMIL D. KAKKIS, M.D., PH.D.
By: /s/ Ernie Meyer	/s/ Emil D. Kakkis, M.D., Ph.D.
Name: Ernie Meyer	Signature
Title: EVP, Chief Human Resources Officer	

Exhibit 10.3

September 13, 2022

Camille Bedrosian M.D.

Re: Amendment No. 1 to Offer Letter

Dear Camille:

On behalf of Ultragenyx Pharmaceutical Inc. (the "Company"), I am pleased to present to you this Amendment No. 1 (this "Amendment"), which amends the Offer of Employment Letter Agreement with you dated January 15, 2018 (the "Offer Letter") as follows:

1. The section with the heading "**Change of Control**" is hereby deleted in its entirety.

2. The first paragraph under the heading "**Severance**" in the Offer Letter is hereby deleted in its entirety and replaced with the following:

"If, at any time, your employment with the Company or its successor is terminated without Cause (as defined below) (but not as a result of your death or disability) or you resign your employment due to a Constructive Termination (as defined below), in each case not during the Protection Period (as defined below), so long such termination constitutes a "separation from service" (as defined under Treasury Regulation Section 1.409A-1(h), without regard to any alternative definition thereunder, a "Separation from Service"), the Company shall:

(i) accelerate the vesting of any equity-based compensation awards granted to you in connection with your employment as if you remained employed for an additional 12 months following the date of your Separation from Service;

(ii) extend the exercise period applicable to any options to purchase the Company's common stock you hold at the time of such termination such that you will have until the date that is 12 months after the date of your Separation from Service to exercise any of the vested shares (determined as of the date of your Separation from Service) subject to the stock options, but in no event will the exercise period be extended until later than the date of expiration of the term of such stock option as set forth in the agreement evidencing such stock option;

(iii) pay you, as severance, an amount equivalent to (x) 12 months of your then-current Base Salary, *plus* (y) your target bonus for the year in which the your Separation from Service occurs, subject to standard payroll deductions and withholdings (the "Severance Amount"), payable in equal installments over the 12-month period following such Separation from Service in accordance with the Company's standard payroll practices commencing on the Company's first regular payroll date that follows the 60th day after such Separation from Service (with the first payment including the accrued installments of the Severance Amount between the date of your Separation from Service and the date of the first payment); and

(iv) subject to your timely and proper election of health continuation coverage under the Consolidated Omnibus Budget Reconciliation Act of 1985, as amended ("COBRA"), reimburse you on a monthly basis for the monthly COBRA premium paid by you for you and your dependents, payable on the first regularly scheduled pay date in the calendar month immediately following the calendar month in which you submit to the Company documentation of the applicable premium having been paid by you (which shall be submitted within 30 days of payment) (the "COBRA Reimbursement"). You will be eligible to receive the COBRA Reimbursement until the earliest of (A) the 12-month anniversary of the date of your Separation from Service; (B) the date you are no longer eligible to receive COBRA continuation coverage; or (C) the date on which you become eligible to receive coverage from another employer or other source. Notwithstanding the foregoing, if the Company's payments under this paragraph would violate applicable law or result in the imposition of penalties under applicable law, the parties agree to reform this paragraph in a manner as is necessary to comply with applicable law.

Notwithstanding the foregoing, in the event that your employment with the Company or its successor is terminated without Cause (but not as a result of your death or disability) or you resign your employment due to a Constructive Termination, in each case, on or within 24 months following the consummation of a Covered Transaction (as defined in the Plan) (such 24-month period, the "Protection Period), so long as such termination constitutes a Separation from Service, then the Company shall:

(a) accelerate the vesting of any equity-based compensation awards granted to you in connection with your employment with respect to 100% of the then-unvested shares then subject to such awards;

(b) extend the exercise period applicable to any options to purchase the Company's common stock you hold at the time of such termination such that you will have until the date that is 12 months after the date of your Separation from Service to exercise any of the vested shares (determined as of the date of your Separation from Service) subject to the stock options, but in no event will the exercise period be extended until later than the date of expiration of the term of such stock option as set forth in the agreement evidencing such stock option;

(c) pay you, as severance, an amount equivalent to (x) 18 months of your then-current Base Salary, *plus* (y) 1.5 times your target bonus for the year in which the your Separation from Service occurs, subject to standard payroll deductions and withholdings (the "CIC Severance Amount"), payable in equal installments over the 24-month period following such Separation from Service in accordance with the Company's standard payroll practices commencing on the Company's first regular payroll date that follows the 60th day after such Separation from Service (with the first payment including the accrued installments of the CIC Severance Amount between the date of your Separation from Service and the date of the first payment); and

(d) subject to your timely and proper election of health continuation coverage under COBRA, reimburse you on a monthly basis for the monthly COBRA premium paid by you for you and your dependents, payable on the first regularly scheduled pay date in the calendar month immediately following the calendar month in which you submit to the Company documentation of the applicable premium having been paid by you (which shall be submitted within 30 days of payment) (the "CIC COBRA Reimbursement"). You will be eligible to receive the CIC COBRA Reimbursement until the earliest of (A) the 18-month anniversary of the date of your Separation from Service; (B) the date you are no longer eligible to receive COBRA continuation coverage; or (C) the date on which you become eligible to receive coverage from another employer or other source. Notwithstanding the foregoing, if the Company's payments under this paragraph would violate applicable law or result in the imposition of penalties under applicable law, the parties agree to reform this paragraph in a manner as is necessary to comply with applicable law."

3. Except as expressly amended herein, all terms and provisions of the Offer Letter shall remain in full force and effect.

4. In the event of a conflict between the provisions of this Amendment and the provisions of the Offer Letter, the provisions of this Amendment shall control.

5. This Amendment shall be governed by and construed in accordance with the laws of the State of California, without giving effect to principles of conflict of laws.

6. This Amendment may be executed in one or more counterparts, each of which will be deemed to be an original as against any party that has signed it, but all of which together will constitute one and the same instrument.

Sincerely,

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

I voluntarily accept and agree to terms and conditions of this Amendment.

/s/ Camille Bedrosian, M.D.	October 21, 2022
Camille Bedrosian, M.D.	Date

Exhibit 10.4

September 13, 2022

Mardi C. Dier

Re: Amendment No. 2 to Offer Letter

Dear Mardi:

On behalf of Ultragenyx Pharmaceutical Inc. (the "Company"), I am pleased to present to you this Amendment No. 2 (this "Amendment"), which amends the Offer of Employment Letter Agreement with you dated August 28, 2020 and as amended by Amendment No. 1 dated October 9, 2020 (collectively, the "Offer Letter") as follows:

1. The section with the heading "**Change of Control**" is hereby deleted in its entirety.

2. The first paragraph under the heading "**Severance**" in the Offer Letter is hereby deleted in its entirety and replaced with the following:

"If, at any time, your employment with the Company or its successor is terminated without Cause (as defined below) (but not as a result of your death or disability) or you resign your employment due to a Constructive Termination (as defined below), in each case not during the Protection Period (as defined below), so long such termination constitutes a "separation from service" (as defined under Treasury Regulation Section 1.409A-1(h), without regard to any alternative definition thereunder, a "Separation from Service"), the Company shall:

(i) extend the exercise period applicable to any options to purchase the Company's common stock you hold at the time of such termination such that you will have until the date that is 12 months after the date of your Separation from Service to exercise any of the vested shares (determined as of the date of your Separation from Service) subject to the stock options, but in no event will the exercise period be extended until later than the date of expiration of the term of such stock option as set forth in the agreement evidencing such stock option;

(ii) pay you, as severance, an amount equivalent to (x) 12 months of your then-current Base Salary, *plus* (y) your target bonus for the year in which the your Separation from Service occurs, subject to standard payroll deductions and withholdings (the "Severance Amount"), payable in equal installments over the 12-month period following such Separation from Service in accordance with the Company's standard payroll practices commencing on the Company's first regular payroll date that follows the 60th day after such Separation from Service (with the first payment including the accrued installments of the Severance Amount between the date of your Separation from Service and the date of the first payment); and

(iii) subject to your timely and proper election of health continuation coverage under the Consolidated Omnibus Budget Reconciliation Act of 1985, as amended ("COBRA"), reimburse you on a monthly basis for the monthly COBRA premium paid by you for you and your dependents, payable on the first regularly scheduled pay date in the calendar month immediately following the calendar month in which you submit to the Company documentation of the applicable premium having been paid by you (which shall be submitted within 30 days of payment) (the "COBRA Reimbursement"). You will be eligible to receive the COBRA Reimbursement until the earliest of (A) the 12-month anniversary of the date of your Separation from Service; (B) the date you are no

longer eligible to receive COBRA continuation coverage; or (C) the date on which you become eligible to receive coverage from another employer or other source. Notwithstanding the foregoing, if the Company's payments under this paragraph would violate applicable law or result in the imposition of penalties under applicable law, the parties agree to reform this paragraph in a manner as is necessary to comply with applicable law.

Notwithstanding the foregoing, in the event that your employment with the Company or its successor is terminated without Cause (but not as a result of your death or disability) or you resign your employment due to a Constructive Termination, in each case, on or within 18 months following the consummation of a Covered Transaction (as defined in the Plan) (such 18-month period, the "Protection Period), so long as such termination constitutes a Separation from Service, then the Company shall:

(a) accelerate the vesting of any equity-based compensation awards granted to you in connection with your employment with respect to 100% of the then-unvested shares then subject to such awards;

(b) extend the exercise period applicable to any options to purchase the Company's common stock you hold at the time of such termination such that you will have until the date that is 12 months after the date of your Separation from Service to exercise any of the vested shares (determined as of the date of your Separation from Service) subject to the stock options, but in no event will the exercise period be extended until later than the date of expiration of the term of such stock option as set forth in the agreement evidencing such stock option;

(c) pay you, as severance, an amount equivalent to (x) 18 months of your then-current Base Salary, *plus* (y) 1.5 times your target bonus for the year in which the your Separation from Service occurs, subject to standard payroll deductions and withholdings (the "CIC Severance Amount"), payable in equal installments over the 18-month period following such Separation from Service in accordance with the Company's standard payroll practices commencing on the Company's first regular payroll date that follows the 60th day after such Separation from Service (with the first payment including the accrued installments of the CIC Severance Amount between the date of your Separation from Service and the date of the first payment); and

(d) subject to your timely and proper election of health continuation coverage under COBRA, reimburse you on a monthly basis for the monthly COBRA premium paid by you for you and your dependents, payable on the first regularly scheduled pay date in the calendar month immediately following the calendar month in which you submit to the Company documentation of the applicable premium having been paid by you (which shall be submitted within 30 days of payment) (the "CIC COBRA Reimbursement"). You will be eligible to receive the CIC COBRA Reimbursement until the earliest of (A) the 18-month anniversary of the date of your Separation from Service; (B) the date you are no longer eligible to receive COBRA continuation coverage; or (C) the date on which you become eligible to receive coverage from another employer or other source. Notwithstanding the foregoing, if the Company's payments under this paragraph would violate applicable law or result in the imposition of penalties under applicable law, the parties agree to reform this paragraph in a manner as is necessary to comply with applicable law."

3. Except as expressly amended herein, all terms and provisions of the Offer Letter shall remain in full force and effect.

4. In the event of a conflict between the provisions of this Amendment and the provisions of the Offer Letter, the provisions of this Amendment shall control.

5. This Amendment shall be governed by and construed in accordance with the laws of the State of California, without giving effect to principles of conflict of laws.

6. This Amendment may be executed in one or more counterparts, each of which will be deemed to be an original as against any party that has signed it, but all of which together will constitute one and the same instrument.

Sincerely,

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

I voluntarily accept and agree to terms and conditions of this Amendment.

/s/ Mardi C. Dier September 13, 2022
Mardi C. Dier Date

Exhibit 10.5

September 13, 2022

Thomas R. Kassberg

Re: Amendment No. 2 to Offer Letter

Dear Tom:

On behalf of Ultragenyx Pharmaceutical Inc. (the "Company"), I am pleased to present to you this Amendment No. 2 (this "Amendment"), which amends the Offer of Employment Letter Agreement with you dated October 31, 2011 and as amended by Amendment No. 1 dated August 8, 2014 (collectively, the "Offer Letter") as follows:

1. The third paragraph under the heading "**Stock Options**" is hereby deleted in its entirety.

2. The first paragraph under the heading "**Severance**" in the Offer Letter is hereby deleted in its entirety and replaced with the following:

"If, at any time, your employment with the Company or its successor is terminated without Cause (as defined below) (but not as a result of your death or disability) or you resign your employment due to a Constructive Termination (as defined below), in each case not during the Protection Period (as defined below), so long such termination constitutes a "separation from service" (as defined under Treasury Regulation Section 1.409A-1(h), without regard to any alternative definition thereunder, a "Separation from Service"), the Company shall:

(i) extend the exercise period applicable to any options to purchase the Company's common stock you hold at the time of such termination such that you will have until the date that is 12 months after the date of your Separation from Service to exercise any of the vested shares (determined as of the date of your Separation from Service) subject to the stock options, but in no event will the exercise period be extended until later than the date of expiration of the term of such stock option as set forth in the agreement evidencing such stock option;

(ii) pay you, as severance, an amount equivalent to (x) 12 months of your then-current Base Salary, *plus* (y) your target bonus for the year in which the your Separation from Service occurs, subject to standard payroll deductions and withholdings (the "Severance Amount"), payable in equal installments over the 12-month period following such Separation from Service in accordance with the Company's standard payroll practices commencing on the Company's first regular payroll date that follows the 60th day after such Separation from Service (with the first payment including the accrued installments of the Severance Amount between the date of your Separation from Service and the date of the first payment); and

(iii) subject to your timely and proper election of health continuation coverage under the Consolidated Omnibus Budget Reconciliation Act of 1985, as amended ("COBRA"), reimburse you on a monthly basis for the monthly COBRA premium paid by you for you and your dependents, payable on the first regularly scheduled pay date in the calendar month immediately following the calendar month in which you submit to the Company documentation of the applicable premium having been paid by you (which shall be submitted within 30 days of payment) (the "COBRA Reimbursement"). You will be eligible to receive the COBRA Reimbursement until the earliest of (A) the 12-month anniversary of the date of your Separation from Service; (B) the date you are no

longer eligible to receive COBRA continuation coverage; or (C) the date on which you become eligible to receive coverage from another employer or other source. Notwithstanding the foregoing, if the Company's payments under this paragraph would violate applicable law or result in the imposition of penalties under applicable law, the parties agree to reform this paragraph in a manner as is necessary to comply with applicable law.

Notwithstanding the foregoing, in the event that your employment with the Company or its successor is terminated without Cause (but not as a result of your death or disability) or you resign your employment due to a Constructive Termination, in each case, on or within 18 months following the consummation of a Covered Transaction (as defined in the Plan) (such 18-month period, the "Protection Period), so long as such termination constitutes a Separation from Service, then the Company shall:

(a) accelerate the vesting of any equity-based compensation awards granted to you in connection with your employment with respect to 100% of the then-unvested shares then subject to such awards;

(b) extend the exercise period applicable to any options to purchase the Company's common stock you hold at the time of such termination such that you will have until the date that is 12 months after the date of your Separation from Service to exercise any of the vested shares (determined as of the date of your Separation from Service) subject to the stock options, but in no event will the exercise period be extended until later than the date of expiration of the term of such stock option as set forth in the agreement evidencing such stock option;

(c) pay you, as severance, an amount equivalent to (x) 18 months of your then-current Base Salary, *plus* (y) 1.5 times your target bonus for the year in which the your Separation from Service occurs, subject to standard payroll deductions and withholdings (the "CIC Severance Amount"), payable in equal installments over the 18-month period following such Separation from Service in accordance with the Company's standard payroll practices commencing on the Company's first regular payroll date that follows the 60th day after such Separation from Service (with the first payment including the accrued installments of the CIC Severance Amount between the date of your Separation from Service and the date of the first payment); and

(d) subject to your timely and proper election of health continuation coverage under COBRA, reimburse you on a monthly basis for the monthly COBRA premium paid by you for you and your dependents, payable on the first regularly scheduled pay date in the calendar month immediately following the calendar month in which you submit to the Company documentation of the applicable premium having been paid by you (which shall be submitted within 30 days of payment) (the "CIC COBRA Reimbursement"). You will be eligible to receive the CIC COBRA Reimbursement until the earliest of (A) the 18-month anniversary of the date of your Separation from Service; (B) the date you are no longer eligible to receive COBRA continuation coverage; or (C) the date on which you become eligible to receive coverage from another employer or other source. Notwithstanding the foregoing, if the Company's payments under this paragraph would violate applicable law or result in the imposition of penalties under applicable law, the parties agree to reform this paragraph in a manner as is necessary to comply with applicable law."

3. Except as expressly amended herein, all terms and provisions of the Offer Letter shall remain in full force and effect.

4. In the event of a conflict between the provisions of this Amendment and the provisions of the Offer Letter, the provisions of this Amendment shall control.

5. This Amendment shall be governed by and construed in accordance with the laws of the State of California, without giving effect to principles of conflict of laws.

6. This Amendment may be executed in one or more counterparts, each of which will be deemed to be an original as against any party that has signed it, but all of which together will constitute one and the same instrument.

Sincerely,

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

I voluntarily accept and agree to terms and conditions of this Amendment.

/s/ Thomas R. Kassberg	September 13, 2022
Thomas R. Kassberg	Date

Exhibit 10.6

September 13, 2022

Karah Parschauer

Re: Amendment No. 1 to Offer Letter

Dear Karah:

On behalf of Ultragenyx Pharmaceutical Inc. (the "Company"), I am pleased to present to you this Amendment No. 1 (this "Amendment"), which amends the Offer of Employment Letter Agreement with you dated April 26, 2016 (the "Offer Letter") as follows:

1. The fourth paragraph under the heading "**Equity Grants**" is hereby deleted in its entirety.

2. The first paragraph under the heading "**Severance**" in the Offer Letter is hereby deleted in its entirety and replaced with the following:

   "If, at any time, your employment with the Company or its successor is terminated without Cause (as defined below) (but not as a result of your death or disability) or you resign your employment due to a Constructive Termination (as defined below), in each case not during the Protection Period (as defined below), so long such termination constitutes a "separation from service" (as defined under Treasury Regulation Section 1.409A-1(h), without regard to any alternative definition thereunder, a "Separation from Service"), the Company shall:

   (i) extend the exercise period applicable to any options to purchase the Company's common stock you hold at the time of such termination such that you will have until the date that is 12 months after the date of your Separation from Service to exercise any of the vested shares (determined as of the date of your Separation from Service) subject to the stock options, but in no event will the exercise period be extended until later than the date of expiration of the term of such stock option as set forth in the agreement evidencing such stock option;

   (ii) pay you, as severance, an amount equivalent to (x) 12 months of your then-current Base Salary, *plus* (y) your target bonus for the year in which the your Separation from Service occurs, subject to standard payroll deductions and withholdings (the "Severance Amount"), payable in equal installments over the 12-month period following such Separation from Service in accordance with the Company's standard payroll practices commencing on the Company's first regular payroll date that follows the 60th day after such Separation from Service (with the first payment including the accrued installments of the Severance Amount between the date of your Separation from Service and the date of the first payment); and

   (iii) subject to your timely and proper election of health continuation coverage under the Consolidated Omnibus Budget Reconciliation Act of 1985, as amended ("COBRA"), reimburse you on a monthly basis for the monthly COBRA premium paid by you for you and your dependents, payable on the first regularly scheduled pay date in the calendar month immediately following the calendar month in which you submit to the Company documentation of the applicable premium having been paid by you (which shall be submitted within 30 days of payment) (the "COBRA Reimbursement"). You will be eligible to receive the COBRA Reimbursement until the earliest of (A) the 12-month anniversary of the date of your Separation from Service; (B) the date you are no

longer eligible to receive COBRA continuation coverage; or (C) the date on which you become eligible to receive coverage from another employer or other source. Notwithstanding the foregoing, if the Company's payments under this paragraph would violate applicable law or result in the imposition of penalties under applicable law, the parties agree to reform this paragraph in a manner as is necessary to comply with applicable law.

Notwithstanding the foregoing, in the event that your employment with the Company or its successor is terminated without Cause (but not as a result of your death or disability) or you resign your employment due to a Constructive Termination, in each case, on or within 18 months following the consummation of a Covered Transaction (as defined in the Plan) (such 18-month period, the "Protection Period), so long as such termination constitutes a Separation from Service, then the Company shall:

(a) accelerate the vesting of any equity-based compensation awards granted to you in connection with your employment with respect to 100% of the then-unvested shares then subject to such awards;

(b) extend the exercise period applicable to any options to purchase the Company's common stock you hold at the time of such termination such that you will have until the date that is 12 months after the date of your Separation from Service to exercise any of the vested shares (determined as of the date of your Separation from Service) subject to the stock options, but in no event will the exercise period be extended until later than the date of expiration of the term of such stock option as set forth in the agreement evidencing such stock option;

(c) pay you, as severance, an amount equivalent to (x) 18 months of your then-current Base Salary, *plus* (y) 1.5 times your target bonus for the year in which the your Separation from Service occurs, subject to standard payroll deductions and withholdings (the "CIC Severance Amount"), payable in equal installments over the 18-month period following such Separation from Service in accordance with the Company's standard payroll practices commencing on the Company's first regular payroll date that follows the 60th day after such Separation from Service (with the first payment including the accrued installments of the CIC Severance Amount between the date of your Separation from Service and the date of the first payment); and

(d) subject to your timely and proper election of health continuation coverage under COBRA, reimburse you on a monthly basis for the monthly COBRA premium paid by you for you and your dependents, payable on the first regularly scheduled pay date in the calendar month immediately following the calendar month in which you submit to the Company documentation of the applicable premium having been paid by you (which shall be submitted within 30 days of payment) (the "CIC COBRA Reimbursement"). You will be eligible to receive the CIC COBRA Reimbursement until the earliest of (A) the 18-month anniversary of the date of your Separation from Service; (B) the date you are no longer eligible to receive COBRA continuation coverage; or (C) the date on which you become eligible to receive coverage from another employer or other source. Notwithstanding the foregoing, if the Company's payments under this paragraph would violate applicable law or result in the imposition of penalties under applicable law, the parties agree to reform this paragraph in a manner as is necessary to comply with applicable law."

3. Except as expressly amended herein, all terms and provisions of the Offer Letter shall remain in full force and effect.

4. In the event of a conflict between the provisions of this Amendment and the provisions of the Offer Letter, the provisions of this Amendment shall control.

5. This Amendment shall be governed by and construed in accordance with the laws of the State of California, without giving effect to principles of conflict of laws.

6. This Amendment may be executed in one or more counterparts, each of which will be deemed to be an original as against any party that has signed it, but all of which together will constitute one and the same instrument.

Sincerely,

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

I voluntarily accept and agree to terms and conditions of this Amendment.

/s/ Karah Parschauer	September 14, 2022
Karah Parschauer	Date

Exhibit 10.7

September 13, 2022

Dennis Huang

Re: Amendment No. 1 to Offer Letter

Dear Dennis:

On behalf of Ultragenyx Pharmaceutical Inc. (the "Company"), I am pleased to present to you this Amendment No. 1 (this "Amendment"), which amends the Offer of Employment Letter Agreement with you dated February 20, 2015 (the "Offer Letter") as follows:

1. The fourth paragraph under the heading "**Equity Grants**" is hereby deleted in its entirety.

2. The first paragraph under the heading "**Severance**" in the Offer Letter is hereby deleted in its entirety and replaced with the following:

"If, at any time, your employment with the Company or its successor is terminated without Cause (as defined below) (but not as a result of your death or disability) or you resign your employment due to a Constructive Termination (as defined below), in each case not during the Protection Period (as defined below), so long such termination constitutes a "separation from service" (as defined under Treasury Regulation Section 1.409A-1(h), without regard to any alternative definition thereunder, a "Separation from Service"), the Company shall:

(i) extend the exercise period applicable to any options to purchase the Company's common stock you hold at the time of such termination such that you will have until the date that is 12 months after the date of your Separation from Service to exercise any of the vested shares (determined as of the date of your Separation from Service) subject to the stock options, but in no event will the exercise period be extended until later than the date of expiration of the term of such stock option as set forth in the agreement evidencing such stock option;

(ii) pay you, as severance, an amount equivalent to (x) 12 months of your then-current Base Salary, *plus* (y) your target bonus for the year in which the your Separation from Service occurs, subject to standard payroll deductions and withholdings (the "Severance Amount"), payable in equal installments over the 12-month period following such Separation from Service in accordance with the Company's standard payroll practices commencing on the Company's first regular payroll date that follows the 60th day after such Separation from Service (with the first payment including the accrued installments of the Severance Amount between the date of your Separation from Service and the date of the first payment); and

(iii) subject to your timely and proper election of health continuation coverage under the Consolidated Omnibus Budget Reconciliation Act of 1985, as amended ("COBRA"), reimburse you on a monthly basis for the monthly COBRA premium paid by you for you and your dependents, payable on the first regularly scheduled pay date in the calendar month immediately following the calendar month in which you submit to the Company documentation of the applicable premium having been paid by you (which shall be submitted within 30 days of payment) (the "COBRA Reimbursement"). You will be eligible to receive the COBRA Reimbursement until the earliest of (A) the 12-month anniversary of the date of your Separation from Service; (B) the date you are no

longer eligible to receive COBRA continuation coverage; or (C) the date on which you become eligible to receive coverage from another employer or other source. Notwithstanding the foregoing, if the Company's payments under this paragraph would violate applicable law or result in the imposition of penalties under applicable law, the parties agree to reform this paragraph in a manner as is necessary to comply with applicable law.

Notwithstanding the foregoing, in the event that your employment with the Company or its successor is terminated without Cause (but not as a result of your death or disability) or you resign your employment due to a Constructive Termination, in each case, on or within 18 months following the consummation of a Covered Transaction (as defined in the Plan) (such 18-month period, the "Protection Period), so long as such termination constitutes a Separation from Service, then the Company shall:

(a) accelerate the vesting of any equity-based compensation awards granted to you in connection with your employment with respect to 100% of the then-unvested shares then subject to such awards;

(b) extend the exercise period applicable to any options to purchase the Company's common stock you hold at the time of such termination such that you will have until the date that is 12 months after the date of your Separation from Service to exercise any of the vested shares (determined as of the date of your Separation from Service) subject to the stock options, but in no event will the exercise period be extended until later than the date of expiration of the term of such stock option as set forth in the agreement evidencing such stock option;

(c) pay you, as severance, an amount equivalent to (x) 18 months of your then-current Base Salary, *plus* (y) 1.5 times your target bonus for the year in which the your Separation from Service occurs, subject to standard payroll deductions and withholdings (the "CIC Severance Amount"), payable in equal installments over the 18-month period following such Separation from Service in accordance with the Company's standard payroll practices commencing on the Company's first regular payroll date that follows the 60th day after such Separation from Service (with the first payment including the accrued installments of the CIC Severance Amount between the date of your Separation from Service and the date of the first payment); and

(d) subject to your timely and proper election of health continuation coverage under COBRA, reimburse you on a monthly basis for the monthly COBRA premium paid by you for you and your dependents, payable on the first regularly scheduled pay date in the calendar month immediately following the calendar month in which you submit to the Company documentation of the applicable premium having been paid by you (which shall be submitted within 30 days of payment) (the "CIC COBRA Reimbursement"). You will be eligible to receive the CIC COBRA Reimbursement until the earliest of (A) the 18-month anniversary of the date of your Separation from Service; (B) the date you are no longer eligible to receive COBRA continuation coverage; or (C) the date on which you become eligible to receive coverage from another employer or other source. Notwithstanding the foregoing, if the Company's payments under this paragraph would violate applicable law or result in the imposition of penalties under applicable law, the parties agree to reform this paragraph in a manner as is necessary to comply with applicable law."

3. Except as expressly amended herein, all terms and provisions of the Offer Letter shall remain in full force and effect.

4. In the event of a conflict between the provisions of this Amendment and the provisions of the Offer Letter, the provisions of this Amendment shall control.

5. This Amendment shall be governed by and construed in accordance with the laws of the State of California, without giving effect to principles of conflict of laws.

6. This Amendment may be executed in one or more counterparts, each of which will be deemed to be an original as against any party that has signed it, but all of which together will constitute one and the same instrument.

Sincerely,

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

I voluntarily accept and agree to terms and conditions of this Amendment.

/s/ Dennis Huang September 14, 2022
Dennis Huang Date

Exhibit 10.8

September 13, 2022

Erik Harris

Re: Amendment No. 3 to Offer Letter

Dear Erik:

On behalf of Ultragenyx Pharmaceutical Inc. (the "Company"), I am pleased to present to you this Amendment No. 3 (this "Amendment"), which amends your original offer of employment dated May 16, 2017 as amended by Addendum No. 1 dated August 3, 2015 and Addendum No. 2 dated June 19, 2019 (collectively, the "Offer Letter") as follows:

1. The section with the heading "**Change of Control**" is hereby deleted in its entirety.

2. The first paragraph under the heading "**Severance**" in the Offer Letter is hereby deleted in its entirety and replaced with the following:

"If, at any time, your employment with the Company or its successor is terminated without Cause (as defined below) (but not as a result of your death or disability) or you resign your employment due to a Constructive Termination (as defined below), in each case not during the Protection Period (as defined below), so long such termination constitutes a "separation from service" (as defined under Treasury Regulation Section 1.409A-1(h), without regard to any alternative definition thereunder, a "Separation from Service"), the Company shall:

(i) extend the exercise period applicable to any options to purchase the Company's common stock you hold at the time of such termination such that you will have until the date that is 12 months after the date of your Separation from Service to exercise any of the vested shares (determined as of the date of your Separation from Service) subject to the stock options, but in no event will the exercise period be extended until later than the date of expiration of the term of such stock option as set forth in the agreement evidencing such stock option;

(ii) pay you, as severance, an amount equivalent to (x) 12 months of your then-current Base Salary, *plus* (y) your target bonus for the year in which the your Separation from Service occurs, subject to standard payroll deductions and withholdings (the "Severance Amount"), payable in equal installments over the 12-month period following such Separation from Service in accordance with the Company's standard payroll practices commencing on the Company's first regular payroll date that follows the 60th day after such Separation from Service (with the first payment including the accrued installments of the Severance Amount between the date of your Separation from Service and the date of the first payment); and

(iii) subject to your timely and proper election of health continuation coverage under the Consolidated Omnibus Budget Reconciliation Act of 1985, as amended ("COBRA"), reimburse you on a monthly basis for the monthly COBRA premium paid by you for you and your dependents, payable on the first regularly scheduled pay date in the calendar month immediately following the calendar month in which you submit to the Company documentation of the applicable premium having been paid by you (which shall be submitted within 30 days of payment) (the "COBRA Reimbursement"). You will be eligible to receive the COBRA Reimbursement until the earliest of (A) the 12-month anniversary of the date of your Separation from Service; (B) the date you are no

longer eligible to receive COBRA continuation coverage; or (C) the date on which you become eligible to receive coverage from another employer or other source. Notwithstanding the foregoing, if the Company's payments under this paragraph would violate applicable law or result in the imposition of penalties under applicable law, the parties agree to reform this paragraph in a manner as is necessary to comply with applicable law.

Notwithstanding the foregoing, in the event that your employment with the Company or its successor is terminated without Cause (but not as a result of your death or disability) or you resign your employment due to a Constructive Termination, in each case, on or within 18 months following the consummation of a Covered Transaction (as defined in the Plan) (such 18-month period, the "Protection Period), so long as such termination constitutes a Separation from Service, then the Company shall:

(a) accelerate the vesting of any equity-based compensation awards granted to you in connection with your employment with respect to 100% of the then-unvested shares then subject to such awards;

(b) extend the exercise period applicable to any options to purchase the Company's common stock you hold at the time of such termination such that you will have until the date that is 12 months after the date of your Separation from Service to exercise any of the vested shares (determined as of the date of your Separation from Service) subject to the stock options, but in no event will the exercise period be extended until later than the date of expiration of the term of such stock option as set forth in the agreement evidencing such stock option;

(c) pay you, as severance, an amount equivalent to (x) 18 months of your then-current Base Salary, *plus* (y) 1.5 times your target bonus for the year in which the your Separation from Service occurs, subject to standard payroll deductions and withholdings (the "CIC Severance Amount"), payable in equal installments over the 18-month period following such Separation from Service in accordance with the Company's standard payroll practices commencing on the Company's first regular payroll date that follows the 60th day after such Separation from Service (with the first payment including the accrued installments of the CIC Severance Amount between the date of your Separation from Service and the date of the first payment); and

(d) subject to your timely and proper election of health continuation coverage under COBRA, reimburse you on a monthly basis for the monthly COBRA premium paid by you for you and your dependents, payable on the first regularly scheduled pay date in the calendar month immediately following the calendar month in which you submit to the Company documentation of the applicable premium having been paid by you (which shall be submitted within 30 days of payment) (the "CIC COBRA Reimbursement"). You will be eligible to receive the CIC COBRA Reimbursement until the earliest of (A) the 18-month anniversary of the date of your Separation from Service; (B) the date you are no longer eligible to receive COBRA continuation coverage; or (C) the date on which you become eligible to receive coverage from another employer or other source. Notwithstanding the foregoing, if the Company's payments under this paragraph would violate applicable law or result in the imposition of penalties under applicable law, the parties agree to reform this paragraph in a manner as is necessary to comply with applicable law."

3. Except as expressly amended herein, all terms and provisions of the Offer Letter shall remain in full force and effect.

4. In the event of a conflict between the provisions of this Amendment and the provisions of the Offer Letter, the provisions of this Amendment shall control.

5. This Amendment shall be governed by and construed in accordance with the laws of the State of California, without giving effect to principles of conflict of laws.

6. This Amendment may be executed in one or more counterparts, each of which will be deemed to be an original as against any party that has signed it, but all of which together will constitute one and the same instrument.

Sincerely,

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

I voluntarily accept and agree to terms and conditions of this Amendment.

/s/ Erik Harris October 19, 2022
Erik Harris Date

Exhibit 10.9

September 13, 2022

John Pinion II

Re: Amendment No. 1 to Offer Letter

Dear John:

On behalf of Ultragenyx Pharmaceutical Inc. (the "Company"), I am pleased to present to you this Amendment No. 1 (this "Amendment"), which amends the Offer of Employment Letter Agreement with you dated June 11, 2015 (the "Offer Letter") as follows:

1. The fourth paragraph under the heading "**Equity Grants**" is hereby deleted in its entirety.

2. The first paragraph under the heading "**Severance**" in the Offer Letter is hereby deleted in its entirety and replaced with the following:

"If, at any time, your employment with the Company or its successor is terminated without Cause (as defined below) (but not as a result of your death or disability) or you resign your employment due to a Constructive Termination (as defined below), in each case not during the Protection Period (as defined below), so long such termination constitutes a "separation from service" (as defined under Treasury Regulation Section 1.409A-1(h), without regard to any alternative definition thereunder, a "Separation from Service"), the Company shall:

(i) extend the exercise period applicable to any options to purchase the Company's common stock you hold at the time of such termination such that you will have until the date that is 12 months after the date of your Separation from Service to exercise any of the vested shares (determined as of the date of your Separation from Service) subject to the stock options, but in no event will the exercise period be extended until later than the date of expiration of the term of such stock option as set forth in the agreement evidencing such stock option;

(ii) pay you, as severance, an amount equivalent to (x) 12 months of your then-current Base Salary, *plus* (y) your target bonus for the year in which the your Separation from Service occurs, subject to standard payroll deductions and withholdings (the "Severance Amount"), payable in equal installments over the 12-month period following such Separation from Service in accordance with the Company's standard payroll practices commencing on the Company's first regular payroll date that follows the 60th day after such Separation from Service (with the first payment including the accrued installments of the Severance Amount between the date of your Separation from Service and the date of the first payment); and

(iii) subject to your timely and proper election of health continuation coverage under the Consolidated Omnibus Budget Reconciliation Act of 1985, as amended ("COBRA"), reimburse you on a monthly basis for the monthly COBRA premium paid by you for you and your dependents, payable on the first regularly scheduled pay date in the calendar month immediately following the calendar month in which you submit to the Company documentation of the applicable premium having been paid by you (which shall be submitted within 30 days of payment) (the "COBRA Reimbursement"). You will be eligible to receive the COBRA Reimbursement until the earliest of (A) the 12-month anniversary of the date of your Separation from Service; (B) the date you are no

longer eligible to receive COBRA continuation coverage; or (C) the date on which you become eligible to receive coverage from another employer or other source. Notwithstanding the foregoing, if the Company's payments under this paragraph would violate applicable law or result in the imposition of penalties under applicable law, the parties agree to reform this paragraph in a manner as is necessary to comply with applicable law.

Notwithstanding the foregoing, in the event that your employment with the Company or its successor is terminated without Cause (but not as a result of your death or disability) or you resign your employment due to a Constructive Termination, in each case, on or within 18 months following the consummation of a Covered Transaction (as defined in the Plan) (such 18-month period, the "Protection Period), so long as such termination constitutes a Separation from Service, then the Company shall:

(a) accelerate the vesting of any equity-based compensation awards granted to you in connection with your employment with respect to 100% of the then-unvested shares then subject to such awards;

(b) extend the exercise period applicable to any options to purchase the Company's common stock you hold at the time of such termination such that you will have until the date that is 12 months after the date of your Separation from Service to exercise any of the vested shares (determined as of the date of your Separation from Service) subject to the stock options, but in no event will the exercise period be extended until later than the date of expiration of the term of such stock option as set forth in the agreement evidencing such stock option;

(c) pay you, as severance, an amount equivalent to (x) 18 months of your then-current Base Salary, *plus* (y) 1.5 times your target bonus for the year in which the your Separation from Service occurs, subject to standard payroll deductions and withholdings (the "CIC Severance Amount"), payable in equal installments over the 18-month period following such Separation from Service in accordance with the Company's standard payroll practices commencing on the Company's first regular payroll date that follows the 60th day after such Separation from Service (with the first payment including the accrued installments of the CIC Severance Amount between the date of your Separation from Service and the date of the first payment); and

(d) subject to your timely and proper election of health continuation coverage under COBRA, reimburse you on a monthly basis for the monthly COBRA premium paid by you for you and your dependents, payable on the first regularly scheduled pay date in the calendar month immediately following the calendar month in which you submit to the Company documentation of the applicable premium having been paid by you (which shall be submitted within 30 days of payment) (the "CIC COBRA Reimbursement"). You will be eligible to receive the CIC COBRA Reimbursement until the earliest of (A) the 18-month anniversary of the date of your Separation from Service; (B) the date you are no longer eligible to receive COBRA continuation coverage; or (C) the date on which you become eligible to receive coverage from another employer or other source. Notwithstanding the foregoing, if the Company's payments under this paragraph would violate applicable law or result in the imposition of penalties under applicable law, the parties agree to reform this paragraph in a manner as is necessary to comply with applicable law."

3. Except as expressly amended herein, all terms and provisions of the Offer Letter shall remain in full force and effect.

4. In the event of a conflict between the provisions of this Amendment and the provisions of the Offer Letter, the provisions of this Amendment shall control.

5. This Amendment shall be governed by and construed in accordance with the laws of the State of California, without giving effect to principles of conflict of laws.

6. This Amendment may be executed in one or more counterparts, each of which will be deemed to be an original as against any party that has signed it, but all of which together will constitute one and the same instrument.

Sincerely,

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

I voluntarily accept and agree to terms and conditions of this Amendment.

/s/ John Pinion II September 13, 2022
John Pinion II Date

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: November 2, 2022

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

Exhibit 31.2

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

I, Mardi C. Dier, certify that:

1. I have reviewed this 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: November 2, 2022

/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 September 30, 2022 (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: November 2, 2022	/s/ Emil D. Kakkis Emil D. Kakkis, M.D., Ph.D. President and Chief Executive Officer (Principal Executive Officer)
Dated: November 2, 2022	/s/ Mardi C. Dier Mardi C. Dier Executive Vice President and Chief Financial Officer (Principal Financial Officer)