Ultragenyx Pharmaceutical Inc.
Form 10-Q
May 08, 2018

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 March 31, 2018

OR

TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934.
For the transition period from to .

Commission File No. 001-36276

ULTRAGENYX PHARMACEUTICAL INC.

(Exact name of registrant as specified in its charter)

Delaware	27-2546083
(State or other jurisdiction of incorporation or organization)	(I.R.S. Employer Identification No.)

60 Leveroni Court	
Novato, California	94949
(Address of principal executive offices)	(Zip Code)

(415) 483-8800

(Registrant's telephone number, including area code)

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 and posted on its corporate Website, if any, every Interactive Data File required to be submitted and posted 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 and post such files). YES NO

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, 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. (Check one):

Large accelerated filer		Accelerated filer
Non-accelerated filer	(Do not check if a smaller reporting company)	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 May 3, 2018, the registrant had 49,772,297 shares of common stock issued and outstanding.

ULTRAGENYX PHARMACEUTICAL INC.

FORM 10-Q FOR THE QUARTER ENDED MARCH 31, 2018

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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," "intend," "may," "plan," "potential," "predict," "project," "seek," "should," "target," "will," "would," or the negative of these w 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, future revenue, capital requirements, and our needs for additional financing;
- our ability to develop, acquire, and advance product candidates into, and successfully complete, clinical studies;
- the implementation of our business model and strategic plans for our business, products and product candidates and the integration and performance of any businesses we have acquired or may acquire;
    - the initiation, timing, progress, and results of ongoing and future preclinical and clinical studies, and our research and development programs;
- the scope of protection we are able to establish and maintain for intellectual property rights covering our products and product candidates;
- our ability to maintain and establish collaborations or strategic relationships or obtain additional funding;
- our ability to maintain and establish relationships with third parties, such as contract research organizations, contract manufacturing organizations, suppliers, and distributors;
- our financial performance and the expansion of our organization;
- our ability to obtain supply of our products and product candidates;
- the scalability and commercial viability of our manufacturing methods and processes;
- developments and projections relating to our competitors and our industry; and
    - other risks and uncertainties, including those listed under Part II, Item 1A. Risk Factors.

Any forward-looking statements in this Quarterly Report reflect our current views with respect to future events or to our future financial performance and involve known and unknown risks, uncertainties, and other factors that may cause our actual results, performance, or achievements to be materially different from any future results, performance, or achievements expressed or implied by these forward-looking statements. Factors that may cause actual results to differ materially from current expectations include, among other things, those discussed under Part II, Item 1A. Risk Factors and discussed 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.

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PART I. FINANCIAL INFORMATION

Item 1. Financial Statements

ULTRAGENYX PHARMACEUTICAL INC.

CONDENSED CONSOLIDATED BALANCE SHEETS

(Unaudited)

(In thousands, except share amounts)

	March 31, 2018	December 31, 2017
Assets		
Current assets:		
Cash and cash equivalents	$226,730	$ 100,488
Short-term investments	314,616	134,005
Accounts receivable	3,671	5,172
Inventory	2,068	757
Restricted cash	542	461
Prepaid expenses and other current assets	33,953	28,700
Total current assets	581,580	269,583
Property and equipment, net	20,830	21,837
Restricted cash	1,931	2,092
Long-term investments	29,907	9,975
Intangible assets, net	137,122	141,545
Goodwill	44,406	44,406
Other assets	1,574	1,315
Total assets	$817,350	$ 490,753
Liabilities and Stockholders' Equity		
Current liabilities:		
Accounts payable	$7,569	$ 8,886
Accrued liabilities	49,291	61,427
Deferred rent—current portion	723	701
Total current liabilities	57,583	71,014
Deferred tax liabilities	31,166	31,166
Other liabilities	4,944	5,119
Total liabilities	93,693	107,299
Stockholders' equity:		
Preferred stock — 25,000,000 shares authorized; nil outstanding as of March 31, 2018 and December 31, 2017	—	—
Common stock — 250,000,000 shares authorized; 49,665,203 and 44,167,071 shares issued and outstanding as of March 31, 2018 and December 31, 2017, respectively	50	44
Additional paid-in capital	1,526,972	1,221,762

Accumulated other comprehensive loss	(946)	(5,680)
Accumulated deficit	(802,419)	(832,672)
Total stockholders' equity	723,657	383,454
Total liabilities and stockholders' equity	$817,350	$490,753

See accompanying notes.

ULTRAGENYX PHARMACEUTICAL INC.

CONDENSED CONSOLIDATED STATEMENTS OF OPERATIONS

(Unaudited)

(In thousands, except share and per share amounts)

	Three Months Ended March 31,	
	2018	2017
Revenues:		
Collaboration and license	$9,362	$—
Product sales	1,315	—
Total revenues	10,677	—
Operating expenses:		
Cost of sales	225	—
Research and development	75,504	51,269
Selling, general and administrative	31,435	18,685
Total operating expenses	107,164	69,954
Loss from operations	(96,487)	(69,954)
Other income (expense), net:		
Interest income	1,737	1,082
Gain from sale of priority review voucher	130,000	—
Other income (expense)	(4,958)	582
Income (loss) before income taxes	30,292	(68,290)
Provision for income taxes	(39)	—
Net income (loss)	$30,253	$(68,290)
Net income (loss) per share:		
Basic	$0.63	$(1.63)
Diluted	$0.62	$(1.63)
Shares used in computing net income (loss) per share:		
Basic	48,190,511	41,841,612
Diluted	49,077,742	41,841,612

See accompanying notes.

ULTRAGENYX PHARMACEUTICAL INC.

CONDENSED CONSOLIDATED STATEMENTS OF COMPREHENSIVE LOSS

(Unaudited)

(In thousands)

	Three Months Ended March 31,	
	2018	2017
Net income (loss)	$30,253	$(68,290)
Other comprehensive income (loss):		
Foreign currency translation adjustments	(289)	(648)
Transfer of cumulative translation adjustment for the substantial liquidation of a foreign subsidiary	5,272	—
Unrealized loss on available-for-sale securities	(249)	(26)
Other comprehensive income (loss):	4,734	(674)
Total comprehensive income (loss)	$34,987	$(68,964)

See accompanying notes.

ULTRAGENYX PHARMACEUTICAL INC.

CONDENSED CONSOLIDATED STATEMENTS OF CASH FLOWS

(Unaudited)

(In thousands)

	Three Months Ended March 31,	
	2018	2017
Operating activities:		
Net income (loss)	$30,253	$(68,290)
Adjustments to reconcile net income (loss) to net cash used in operating activities:		
Gain from sale of priority review voucher	(130,000)	—
Stock-based compensation	18,797	14,499
Amortization of premium (discount) on investment securities, net	(239)	549
Depreciation and amortization	6,160	1,161
Foreign currency remeasurement (gain) loss	4,773	(648)
Changes in operating assets and liabilities:		
Prepaid expenses and other current assets	(5,063)	930
Other assets	(259)	75
Accounts payable	(1,317)	2,989
Accrued liabilities and other liabilities	(12,583)	(12,470)
Net cash used in operating activities	(89,478)	(61,205)
Investing activities:		
Purchase of property and equipment	(475)	(485)
Proceeds from sale of priority review voucher	130,000	—
Purchase of investments	(260,830)	(87,527)
Proceeds from the sale of investments	—	12,415
Proceeds from maturities of investments	60,277	64,977
Net cash used in investing activities	(71,028)	(10,620)
Financing activities:		
Proceeds from issuance of common stock in connection with a public offering, net	270,969	—
Proceeds from issuance of common stock in connection with at-the-market offering, net	11,808	67,591
Proceeds from issuance of common stock from equity awards, net	3,642	1,378
Net cash provided by financing activities	286,419	68,969
Effect of exchange rate changes on cash	249	17
Net increase (decrease) in cash, cash equivalents and restricted cash	126,162	(2,839)
Cash, cash equivalents and restricted cash at beginning of period	103,041	164,607
Cash, cash equivalents and restricted cash at end of period	$229,203	$161,768

See accompanying notes.

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ULTRAGENYX PHARMACEUTICAL INC.

Notes to Condensed Consolidated Financial Statements

1. Organization

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

The Company is focused on the identification, acquisition, development, and commercialization of novel products for the treatment of rare and ultra-rare diseases, with a focus on serious, debilitating genetic diseases. The Company has two approved therapies. Crysvita® (burosumab) is approved by the U.S. Food and Drug Administration (FDA) for the treatment of X-linked hypophosphatemia (XLH) in adult and pediatric patients one year of age and older, and has received European conditional marketing authorization for the treatment of XLH with radiographic evidence of bone disease in children 1 year of age and older and adolescents with growing skeletons. The Company has also received FDA approval for Mepsevii™ (vestronidase alfa), the first medicine approved for the treatment of children and adults with MPS VII, also known as Sly syndrome.

The Company is conducting Phase 2 and Phase 3 studies of Crysvita, an antibody targeting fibroblast growth factor 23 (FGF23), in pediatric and adult patients with XLH and a Phase 2 study in tumor induced osteomalacia (TIO), both rare diseases that impair bone mineralization; a Phase 3 study for UX007 in patients with glucose transporter type-1 deficiency syndrome (Glut1 DS), a brain energy deficiency, who are experiencing movement disorders; a Phase 2 clinical study of UX007 in patients severely affected by long-chain fatty acid oxidation disorders (LC-FAOD), a genetic disorder in which the body is unable to convert long chain fatty acids into energy; a Phase 1/2 open label clinical study of DTX 301, an adeno-associated virus 8 (AAV8) gene therapy product candidate designed for the treatment of patients with ornithine transcarbamylase (OTC) deficiency, the most common urea cycle disorder; and has an active IND for DTX 401, an AAV8 gene therapy clinical candidate for the treatment of patients with glycogen storage disease type Ia, or GSDIa. The Company operates as one reportable segment.

The Company has sustained operating losses and expects such annual losses to continue over the next several years. The Company’s ultimate success depends on the outcome of its research and development activities. Management expects to incur additional losses in the future to conduct product research and development and recognizes the need to raise additional capital to fully implement its business plan. Through March 31, 2018, the Company has relied primarily on the proceeds from equity offerings to finance its operations.

The Company intends 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 will need to reevaluate its operating plans.

2. Summary of Significant Accounting Policies

Basis of Presentation

The accompanying unaudited condensed consolidated financial statements include the amounts of the Company and our wholly-owned subsidiaries and have been prepared in accordance with U.S. generally accepted accounting principles (GAAP) for interim financial information and in accordance with the instructions to Form 10-Q and Rule 10-01 of Regulation S-X. Accordingly, they do not include all of the information and footnotes required by GAAP for complete financial statements. The unaudited interim consolidated financial statements have been prepared on the same basis as the annual financial statements. In the opinion of management, the accompanying unaudited condensed

consolidated financial statements reflect all adjustments (consisting only of normal recurring adjustments) considered necessary for a fair presentation. These financial statements should be read in conjunction with the audited financial statements and notes thereto for the preceding fiscal year contained in the Company's Annual Report on Form 10-K filed on February 21, 2018 with the United States Securities and Exchange Commission (SEC).

The results of operations for the three months ended March 31, 2018 are not necessarily indicative of the results to be expected for the year ending December 31, 2018. The condensed consolidated balance sheet as of March 31, 2018 has been derived from audited financial statements at that date, but does not include all of the information required by GAAP for complete financial statements.

Use of Estimates

The accompanying consolidated financial statements have been prepared in accordance with GAAP. The preparation of the consolidated financial statements in conformity with GAAP requires management to make estimates and assumptions that affect the reported amounts of assets and liabilities, disclosure of contingent liabilities and the reported amounts of expenses in the consolidated financial statements and the accompanying notes. On an ongoing basis, management evaluates its estimates, including those related to sales return reserves, clinical trial accruals, fair value of assets and liabilities, income taxes, and stock-based compensation. 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 as collateral for its obligations under its facility leases.

In November 2016, the Financial Accounting Standards Board (FASB) issued Accounting Standards Update (ASU) 2016-18, Statement of Cash Flows (Topic 230): Restricted Cash, which requires restricted cash to be presented with cash and cash equivalents on the statement of cash flows and disclosure of how the statement of cash flows reconciles to the balance sheet if restricted cash is shown separately from cash and cash equivalents on the balance sheet. The Company adopted the standard as of January 1, 2018 on a retrospective basis, wherein the statement of cash flow of each period presented was adjusted to reflect the effects of applying the new guidance. The following table provides a reconciliation of cash, cash equivalents, and restricted cash reported within the consolidated balance sheets that sum to the total of the same such amounts shown in the consolidated statement of cash flows (in thousands):

	March 31, 2018	March 31, 2017
Cash and cash equivalents	$226,730	$159,501
Restricted cash, current	542	271
Restricted cash, non-current	1,931	1,996
Total cash, cash equivalents, and restricted cash shown in the statements of cash flows	$229,203	$161,768

Goodwill

In January 2017, the FASB issued ASU No. 2017-04, Goodwill and Other - Simplifying the Test for Goodwill Impairment, which eliminated the requirement to determine the fair value of individual assets and liabilities of a reporting unit to measure goodwill impairment. Under this guidance, goodwill impairment testing shall be performed by comparing the fair value of the reporting unit with its carrying amount and recognizing an impairment charge for the amount by which the carrying amount exceeds the reporting unit’s fair value. The Company had early adopted the new goodwill guidance as of January 1, 2018 on a prospective basis. The adoption did not have an effect on the Consolidated Financial Statements on the adoption date.

Revenue Recognition

Product sales

The Company sells Mepsevii through a limited number of distributors. Under Accounting Standards Codification (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 Mepsevii and UX007 on a “named patient” basis, which are allowed in certain countries prior to the commercial approval of the product in the territory. 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 when the uncertainty associated with the variable consideration is subsequently resolved. Product sales are recorded net of estimated government-mandated rebates and chargebacks, distribution fees, estimated product returns and other deductions.

Provisions for returns and other adjustments are provided for in the period the related revenue is recorded. Historical data are not yet readily available and reliable for use in estimating the amount of the reduction in gross revenue. The estimates applied are periodically reviewed and will be adjusted as necessary.

Collaboration and license revenue

The Company has certain license and collaboration agreements that are within the scope of ASC 808, Collaborative Agreements, which provides guidance on the presentation and disclosure of collaborative arrangements. Funding received related to research and development services and pre-commercialization costs are classified as a reduction of research and development expenses and selling, general and administrative expenses, respectively in the consolidated statement of operations because the provision of such services for collaborative partners are not considered to be part of the Company’s ongoing major or central operations.

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

The Company also recognizes collaboration and license revenue under certain of the Company’s license or collaboration agreements that are within the scope of ASC 606. The terms of these agreements may contain multiple performance obligations, which may include licenses and research and development activities. The Company evaluates these agreements under ASC 606 to determine the distinct performance obligations.

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. Variable 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. Revenue is recognized by measuring the progress toward complete satisfaction of the performance obligations using an input measure.

Recently Issued Accounting Pronouncements

In February 2016, the FASB issued ASU No. 2016-02, Leases, which requires an entity that is a lessee to record a right of use asset and a corresponding lease liability on the balance sheet for all leases with terms longer than 12 months. This guidance also requires disclosures about the amount, timing, and uncertainty of cash flows arising from leases. This guidance is effective for annual reporting periods beginning after December 15, 2018, and interim periods within those annual periods, using a modified retrospective approach, and early adoption is permitted. The Company is evaluating the effect that this guidance will have on its Consolidated Financial Statements and related disclosures.

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 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 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):

	March 31, 2018			
Fair Value Hierarchy	Amortized	Gross Unrealized Gains	Losses	Estimated

		Cost			Fair Value
Money market funds	Level 1	$ 158,296	$ —	$ —	$ 158,296
Time deposits	Level 2	10,000	—	—	10,000
Corporate bonds	Level 2	90,462	—	(289)	90,173
Commercial paper	Level 2	79,388	—	—	79,388
Asset-backed securities	Level 2	30,928	—	(59)	30,869
U.S. Government Treasury and agency securities	Level 2	160,388	—	(283)	160,105
Total		$ 529,462	$ —	$ (631)	$ 528,831

	December 31, 2017				
	Fair Value Hierarchy	Amortized Cost	Gross Unrealized Gains	Losses	Estimated Fair Value
Money market funds	Level 1	$ 79,670	$ —	$ —	$ 79,670
Corporate bonds	Level 2	39,330	—	(90)	39,240
U.S. Government Treasury and agency securities	Level 2	105,029	—	(290)	104,739
Total		$ 224,029	$ —	$ (380)	$ 223,649

At March 31, 2018, the remaining contractual maturities of available-for-sale securities were less than two years. There have been no significant realized gains or losses on available-for-sale securities for the periods presented. All marketable securities with unrealized losses at March 31, 2018 have a loss that was considered to be temporary in nature. The Company does not intend to sell the investments that are in an unrealized loss position before recovery of their amortized cost basis.

4. Balance Sheet Components

Inventory

Inventory consists of the following (in thousands):

	March 31, 2018	December 31, 2017
Work-in-progress	$1,808	$ 737
Finished goods	260	20
Total inventory	$2,068	$ 757

Accrued Liabilities

Accrued liabilities consist of the following (in thousands):

	March 31, 2018	December 31, 2017
Research and clinical study expenses	$21,680	$ 17,141
Payroll and related expenses	16,774	26,527
Repayment liability under collaboration agreement	3,460	3,681
Contract liability	—	5,986
Other	7,377	8,092
Total accrued liabilities	$49,291	$ 61,427

5. License and Research Agreements

Kyowa Hakko Kirin Collaboration and License Agreement

In August 2013, the Company entered into a collaboration and license agreement with Kyowa Hakko Kirin Co., Ltd. (KHK). Under the terms of this collaboration and license agreement, as amended, the Company and KHK will collaborate on the development and commercialization of Crysvita in the field of orphan diseases in the United States and Canada, or the profit share territory, and in the European Union and Switzerland, or the European territory, and the Company will have the right to develop and commercialize such products in the field of orphan diseases in Mexico and Central and South America, or Latin America. In the field of orphan diseases, and except for ongoing studies being conducted by KHK, the Company will be the lead party for development activities in the profit share territory and in the European territory until the applicable transition date; the Company will also be the lead party for core development activities conducted in Japan and Korea, for which the core development plan is limited to clinical trials mutually agreed to by the Company and KHK. The Company will share 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 KHK, and KHK shall be responsible for 100% of the costs for development activities in Japan and Korea. On the applicable transition date in the profit share territory and the European territory, KHK will become the lead party and be responsible for the costs of the development activities. However, the Company will

continue to share the costs of the studies commenced prior to the applicable transition date equally with KHK. The Company has the primary responsibility for conducting certain research and development services. Crysvita was approved in the European Union in November 2017 and was approved by the FDA in April 2018. The Company and KHK will share commercial responsibilities and profits in the profit share territory until the applicable transition date and KHK will commercialize Crysvita in the European territory. The Company will develop and commercialize Crysvita in Latin America.

KHK will manufacture and supply Crysvita for clinical use globally and will manufacture and supply Crysvita for commercial use in the profit share territory and Latin America. The remaining profit or loss from commercializing products in the profit-share territory, until the applicable transition date, will be shared between the Company and KHK on a 50/50 basis. Thereafter, the Company will be entitled to receive a tiered double-digit revenue share in the mid-to-high 20% range in the profit share territory. Net proceeds from any sale of the priority review voucher issued in connection with the approval of Crysvita will be shared equally with KHK. The Company will also be entitled to receive a royalty of up to 10% on net sales in the European territory. In Latin America, the Company will pay to KHK a low single-digit royalty on net sales.

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

The Company is accounting for the agreement as a collaboration agreement as defined in ASC 808, Collaborative Agreements. The Company's expenses were reduced by $8.2 million and $7.4 million for the three months ended March 31, 2018 and 2017, respectively, for KHK's share of the research and development expenses and were reduced by $3.8 million and $0.5 million for the three months ended March 31, 2018 and 2017, respectively, for KHK's share of the selling, general and administrative expenses. As of March 31, 2018 and December 31, 2017, the Company had receivables in the amount of $12.3 million and $10.3 million, respectively, for this collaboration arrangement.

Takeda License and Collaboration and Purchase Agreements

In June 2016, the Company executed a collaboration and license agreement with Takeda Pharmaceutical Company Limited (Takeda). Pursuant to the agreement, which became effective in July 2016, the Company obtained an exclusive license for a pre-clinical compound from Takeda in a pre-determined field of use. The Company is responsible for the development costs for the pre-clinical compound and the identified option product pursuant to an initial development plan. Because the license to the pre-clinical compound has no alternative future use, the estimated fair value of $0.7 million was recorded as a research and development expense upon acquisition. Any products resulting from the pre-clinical compound or the identified option product is referred to in this report as the "licensed product." The Company discontinued the development efforts on the pre-clinical compound in the pre-determined field of use and the identified option product.

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

In July 2016, the Company consummated a common stock purchase agreement, executed in conjunction with the collaboration and license agreement, whereby Takeda purchased 374,590 shares of the Company's common stock for $40.0 million in cash. The fair market value of the common stock issued to Takeda was $27.3 million, based on the closing stock price of $72.95 on the date of issuance, resulting in a $12.7 million premium paid to the Company. The Company also received a put option to require Takeda to purchase an additional $25.0 million in shares of the Company's common stock which was exercised in October 2016, whereby Takeda purchased 352,530 shares of the Company's common stock for $25.0 million in cash. Takeda is subject to a five-year standstill (subject to customary exceptions or release). The Company estimated the fair value of the put options to be $0.9 million and recorded the put options in additional paid-in capital.

The research and license agreement and the stock purchase agreement are being accounted for as one arrangement because they were entered into at the same time with interrelated financial terms. The Company analogized to Topic 606 for the accounting for the arrangements. The Company concluded that there are multiple promised goods and services under the collaboration agreement, including obligations related to research and development services with respect to licensed products as well as committee participation, which were determined to represent distinct performance obligations. The total consideration received from Takeda was $14.3 million and was comprised of the $12.7 million premium on the sale of the common stock, the $0.9 million estimated fair value of the put options, and the $0.7 million estimated fair value of the pre-clinical compound.

The Company is responsible for the costs under the initial development plan. A significant portion of this work is performed by Takeda which is substantively complete as of March 31, 2018. The Company concluded that the payment to Takeda is not in return for a distinct service that Takeda transfers to the Company, therefore, the payment made to Takeda is accounted for as a reduction in the transaction price. As of March 31, 2018, the Company concluded that $3.3 million of the estimated transaction price should not be constrained because it is probable that a significant reversal in the amount to be recognized will not occur. The unconstrained transaction price was allocated to the distinct performance obligations on a relative standalone selling price basis. The Company recorded $0.8

million for the three months ended March 31, 2018 and none for the three months ended March 31, 2017 as a reduction of research and development expenses by measuring the progress toward complete satisfaction of the individual performance obligation using an input measure. The Company will continue to re-evaluate the application of the constraint to the transaction price at each reporting period end date.

Costs incurred by the Company associated with co-development activities performed under this collaboration are included in research and development expense in the accompanying consolidated statements of operations. As of March 31, 2018 and December 31, 2017, the Company had a repayment liability in the amount of $3.5 million and $3.7 million, respectively, and no contract liability as of March 31, 2018 and a $0.6 million contract liability as of December 31, 2017.

Bayer HealthCare LLC

The Company has an agreement with Bayer Healthcare LLC (Bayer) to research, develop and commercialize adeno-associated virus gene therapy products for treatment of hemophilia A (DTX 201). Under this agreement, Bayer has been granted an exclusive license to develop and commercialize one or more novel gene therapies for hemophilia A. The Company is responsible for the development of DTX201 under the agreement through a proof-of-concept (POC) clinical trial, in accordance with the mutually agreed upon research budget. Upon the successful demonstration of clinical POC, the agreement requires that Bayer use commercially reasonable efforts to manage and fund any subsequent clinical trials and commercialization of gene therapy products for treatment of hemophilia A. Bayer will have worldwide rights to commercialize the potential future product.

Bayer is responsible to fund certain research and development services performed by the Company in the performance of its obligations under the annual research plan and budget. Under the terms of the agreement with Bayer, the Company is eligible to receive development and commercialization milestone payments of up to $232.0 million, as well as, royalty payments ranging in the high single-digit to low double-digit percentages, not exceeding the mid-teens, of net sales of licensed products. In December 2017, the first milestone was achieved and the Company subsequently received the $5.0 million milestone from Bayer.

As of the acquisition date of November 7, 2017, the Company valued the contract under ASC 805, Business Combinations, and recorded an intangible asset of $13.5 million. The intangible asset will be amortized to research and development expense over the remainder of the research term which is expected to be complete in 2019. The Company recorded a research and development expense of $4.4 million for the three months ended March 31, 2018 for the amortization of the intangible asset.

The Company evaluated the agreement under ASC 606 Revenue from Contracts with Customers, and recorded a contract liability as of November 7, 2017 of $2.5 million. It was determined that the performance obligations under the agreement includes (i) research and development services to be provided over the research term, (ii) a development and commercialization license and (iii) the Company’s participation in certain committees. It was determined that these performance obligations are not distinct in the context of the contract and therefore are a single performance obligation. The Company calculated the transaction price by including the unconstrained milestones along with the estimated payments for research and development services and recorded $9.3 million as collaboration and license revenue for the three months ended March 31, 2018, by measuring the progress toward complete satisfaction of the performance obligation using an input measure. The performance obligation under the contract is expected to be substantially complete by end of 2019. As of March 31, 2018 and December 31, 2017, the Company had a $0.8 million of contract asset and a $5.4 million of contract liability, respectively.

6. 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 March 31, 2018, there were 1,828,073 shares reserved under the 2014 Plan for the future issuance of equity awards and 2,292,906 shares reserved for the 2014 Employee Stock Purchase Plan.

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

	Three Months Ended March 31,	
	2018	2017
Research and development	$11,247	$8,543
Selling, general and administrative	7,550	5,956
Total stock-based compensation	$18,797	$14,499

7. Net Income (Loss) Per Share

Basic net income (loss) per share has been computed by dividing the net income (loss) by the weighted-average number of shares of common stock outstanding during the period. Diluted net income (loss) per share is calculated by dividing net income (loss) by the weighted-average number of shares of common stock and potential dilutive securities outstanding during the period. For the three months ended March 31, 2017, there was no difference between basic and diluted net loss per share since the effect of the dilutive securities would be antidilutive and therefore were

excluded from the diluted net loss per share calculation. The following table sets forth the computation of the basic and diluted net income (loss) per share (in thousands, except share and per share data):

	Three Months Ended March 31,	
	2018	2017
Net income (loss), basic and diluted	$30,253	$(68,290)
Weighted-average shares used in computing net income (loss) per share, basic	48,190,511	41,841,612
Weighted-average effect of dilutive securities:		
Options to purchase common stock and RSUs	742,796	—
Employee stock purchase plan	3,683	—
Common stock warrants	140,752	—
Weighted-average shares used in computing net income (loss) per share, diluted	49,077,742	41,841,612
Net income (loss) per share:		
Basic	$0.63	$(1.63)
Diluted	$0.62	$(1.63)

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 March 31,	
	2018	2017
Options to purchase common stock and RSUs	5,150,737	5,303,718
Employee stock purchase plan	—	24,590
Common stock warrants	—	149,700
	5,150,737	5,478,008

8. Equity Transactions

In July 2017, the Company entered into an At-The-Market, or ATM, sales agreement with Cowen and Company, LLC (Cowen), whereby the Company can sell up to $150.0 million in aggregate proceeds of common stock from time to time, through Cowen as its sales agent. In March 2018, the Company and Cowen entered into an amendment to the ATM sales agreement to sell, from time to time, the remaining $72.6 million in common stock under the sales agreement under the Company's new registration statement that was filed with the SEC on February 21, 2018. During the three months ended March 31, 2018, 240,417 shares were sold pursuant to the sales agreement, resulting in net proceeds of approximately $11.8 million, after commissions and other offering costs.

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

9. Accumulated Other Comprehensive Income (Loss)

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

	March 31, 2018	December 31, 2017
Foreign currency translation adjustments	$ (315)	$ (5,298)
Unrealized loss on securities available-for-sale	(631)	(382)
Total accumulated other comprehensive loss	$ (946)	$ (5,680)

10. Gain from Sale of Priority Review Voucher

On January 10, 2018, the Company completed the sale of a Rare Pediatric Disease Priority Review Voucher (PRV) to Novartis Pharma AG for $130.0 million. The Company received the PRV from the FDA in connection with the approval of Mepsevii. The full amount was received and recorded as a gain from sale of PRV as the PRV did not have a carrying value at the time of the sale.

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

The following discussion and analysis of our financial condition and results of operations should be read in conjunction with the accompanying unaudited consolidated financial statements and related notes in Item 1 and with the audited consolidated financial statements and the related notes included in our Annual Report on Form 10-K for the year ended December 31, 2017 (the "Annual Report").

Overview

We are a biopharmaceutical company focused on the identification, acquisition, development, and commercialization of novel products for the treatment of serious rare and ultra-rare diseases, with a focus on serious, debilitating genetic diseases. We target diseases for which the unmet medical need is high, the biology for treatment is clear, and for which there are no currently approved therapies. Since our inception in 2010, we have in-licensed potential treatments for multiple rare genetic disorders. 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 three product categories: biologics, small-molecule substrate replacement therapies, and gene therapy product candidates. Enzymes are proteins that the body uses to process materials needed for normal cellular function, and substrates are the materials upon which enzymes act. When enzymes or substrates are missing, the body is unable to perform its normal cellular functions, often leading to significant clinical disease. Several of our therapies are intended to replace deficient enzymes or substrates. Gene therapy is a therapeutic approach in which an isolated gene sequence or segment of DNA is administered to a patient, most commonly for the purpose of treating a genetic disease that is caused by mutations. Gene therapy aims to address the disease-causing effects of absent or dysfunctional genes by delivering functional copies of the gene to the patient's cells, offering the potential for durable therapeutic benefit.

Our biologic products include approved therapies Crysvita® (burosumab) and Mepsevii™ (vestronidase alfa):

- Crysvita is an antibody targeting fibroblast growth factor 23, or FGF23, that is approved for the treatment of X-linked hypophosphatemia, or XLH, a rare, hereditary, progressive and lifelong musculoskeletal disorder characterized by renal phosphate wasting caused by excess FGF23 production. The U.S. Food and Drug Administration, or FDA, approved Crysvita on April 17, 2018 for the treatment of XLH in adult and pediatric patients one year of age and older. In Europe, Crysvita received European conditional marketing authorization on February 23, 2018 for the treatment of XLH with radiographic evidence of bone disease in children one year of age and older and adolescents with growing skeletons. A filing for adults with XLH is also planned in Europe. We have an ongoing global Phase 3 study in pediatric patients with XLH data expected in the second half of 2018.

Crysvita is also being developed for the treatment of tumor-induced osteomalacia, or TIO. TIO results from typically benign tumors that produce excess levels of FGF23, which can lead to severe hypophosphatemia, osteomalacia, fractures, fatigue, bone and muscle pain, and muscle weakness. We expect 48-week data from our Phase 2 TIO study in mid-2018.

We are collaborating with Kyowa Hakko Kirin, or KHK, and Kyowa Kirin International, or Kyowa Kirin, a wholly owned subsidiary of KHK, on the development and commercialization of Crysvita globally, based on the collaboration and license agreement between us and KHK.

- Mepsevii is approved by the FDA for the treatment of children and adults with Mucopolysaccharidosis VII, also known as MPS VII or Sly syndrome. Mepsevii is an intravenous, or IV, enzyme replacement therapy for the treatment of MPS VII, a rare lysosomal storage disease that often leads to multi-organ dysfunction, pervasive skeletal

disease, and death. In Europe, the European Medicines Agency, or EMA, is currently reviewing the Marketing Authorization Application, or MAA. An opinion from the Committee for Medicinal Products for Human Use, or CHMP, is expected in mid-2018.

Our substrate replacement therapy pipeline includes UX007 in clinical development for the treatment of two diseases:

- UX007 is a synthetic triglyceride with a specifically designed chemical composition being studied in an open-label Phase 2 study for the treatment of long-chain fatty acid oxidation disorders, or LC-FAOD. LC-FAOD 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. We reported positive 78-week data from the Phase 2 study in LC-FAOD patients. Following an end-of-phase 2 meeting with the FDA, we are submitting additional information and will work with FDA to determine whether an early submission based on the Phase 2 data can be pursued. We expect to come to a decision regarding a potential early submission in mid-2018. We are simultaneously finalizing a full protocol for a Phase 3, randomized, controlled study examining major clinical events as the primary endpoint as discussed with the FDA, and plan to initiate this Phase 3 study in the second half of 2018.
- UX007 is also being studied for the treatment of glucose transporter type-1 deficiency syndrome, or Glut1 DS, a rare metabolic disease of brain energy deficiency that is characterized by seizures, developmental delay, and movement disorder. We have completed enrollment of, and randomized, 43 patients in the Phase 3 study in movement disorders, and expect to

announce data from this study in the second half of 2018. If positive, the movement disorder study could serve as the basis for regulatory submissions.

Our gene therapy pipeline includes DTX301 and DTX401 in clinical development for the treatment of two diseases:

- DTX301 is an adeno-associated virus 8, or AAV8, gene therapy product candidate designed for the treatment of patients with Ornithine transcarbamylase, or OTC, deficiency. OTC is part of the urea cycle, an enzymatic pathway in the liver that converts excess nitrogen, in the form of ammonia, to urea for excretion. OTC deficiency is the most common urea cycle disorder and leads to increased levels of ammonia. Patients with OTC deficiency suffer from acute hyperammonemic episodes that can lead to hospitalization, adverse cognitive and neurological effects, and death. In March 2018, we announced positive safety and efficacy results from the first dose cohort of the Phase 1/2 open-label clinical trial of DTX301. The Data Monitoring Committee, or DMC, completed its review of the Cohort 1 data, and we have proceeded to the second, higher-dose cohort of the study. Data from the second cohort should be available in the second half of 2018.
- DTX401 is an 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 glycogen storage disease. Our IND was accepted by the FDA in April 2018 and we expect data from the first cohort of the Phase 1/2 study in the second half of 2018.

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

Recent program updates

CRYSVITA for the treatment of XLH

In April 2018 we and Kyowa Kirin announced the FDA approval and commercial launch of Crysvita for the treatment of XLH in adult and pediatric patients one year of age and older. With the approval of Crysvita, the FDA issued a Rare Pediatric Disease Priority Review Voucher, or PRV, which confers priority review to a subsequent drug application that would not otherwise qualify for priority review. If we sell the PRV, the proceeds from the sale would be split evenly with KHK.

In February 2018 we and Kyowa Kirin announced that Crysvita received a positive European Commission decision granting a conditional marketing authorization to Kyowa Kirin for the treatment of X-linked hypophosphatemia (XLH) with radiographic evidence of bone disease in children 1 year of age and older and adolescents with growing skeletons.

In February 2018, we reported 64 week data from our Phase 2 study in children less than five years old (mean age 2.9 years), showing continued improvement in rickets and bowing. These longer term data from this study demonstrated that outcomes with Crysvita treatment were consistent with and further improved from what was seen at 40 weeks. These included sustained improvements in serum phosphorus levels, and a progressive reduction into the normal range of alkaline phosphatase. There were continued improvements in bowing and rickets scores at 64 weeks. The safety profile observed in this study was consistent with other Crysvita studies.

In February 2018, we reported that bone biopsy data from adult patients in our bone quality study demonstrated continued improvement in osteomalacia. At 48 weeks, all ten patients with evaluable paired bone biopsies demonstrated meaningful improvements from baseline in mean osteoid volume/bone volume. The mean decrease from 26.1% to 11.2% among these patients represents a 57% improvement from baseline in mean osteoid volume/bone volume which is the gold standard for the evaluation of osteomalacia. The patients also demonstrated mean improvements of 32% and 26% in osteoid thickness and osteoid surface/bone surface parameters respectively, and a meaningful improvement in mineralization lag time. These results, including safety, are consistent with the data provided to the FDA in the first 6 of these 10 patients showing a substantial reduction in osteomalacia.

Mepsevii for the treatment of MPSVII

With the approval of Mepsevii in November 2017, the FDA issued a PRV, and we completed the sale of the PRV in January 2018 for $130.0 million.

UX007 for the treatment of LC-FAOD

In January 2018, we announced an update to our development plan for UX007 in LC-FAOD. Following an end-of-phase 2 meeting, we are working to provide additional information to submit to FDA for consideration of an early filing based on the positive results from the Phase 2 study.

The clinical effect observed in the Phase 2 study was considered important, but it was not clear if there were dietary or other changes in the regimen as each patient crossed over onto UX007 that might have accounted for the improvement. We are working to provide additional information to FDA to support that the improvement demonstrated was likely due to UX007 and not any other changes. After this information is submitted and evaluated by FDA, we plan to determine with the FDA whether an early submission could be pursued. We are simultaneously finalizing a full protocol for a Phase 3, randomized, controlled study examining major clinical events as the primary endpoint as discussed with the FDA. This study would provide additional information that would be important in utilization and reimbursement long-term for UX007. If the FDA agrees to an early submission based on the Phase 2 study, the Phase 3 study would serve as a post-approval commitment for label expansion. Alternatively, the Phase 3

study could serve as a registrational study if an early filing is not possible.

UX007 for the treatment of Glut1 DS

In February 2018, we completed enrollment of, and randomized, 43 patients in the Phase 3 study of UX007 for the treatment of Glut1 DS patients with the movement disorder phenotype. The study is a randomized, double-blind, placebo-controlled, cross-over study designed to assess the efficacy and safety of UX007 in patients who are experiencing disabling paroxysmal movement disorders associated with Glut1 DS. Movement disorder events are defined as disabling if they affect or limit a patient's ability to perform activities of daily living. Eligible patients were randomized in a 1:1 ratio to one of two treatment sequences. Patients in the first group will begin a two-week titration period followed by an 8-week treatment period on UX007. Patients then begin a 2-week washout period, followed by a 2-week titration period and 8-week period on placebo. Patients in the second group follow the same schedule except that they begin with placebo and then cross over to UX007. The primary endpoint compares the frequency of disabling paroxysmal movement disorder events during the 8-week treatment period with UX007, to the frequency of disabling movement disorder events during the 8-week placebo treatment period as recorded by a daily electronic diary. Secondary endpoints include the duration of disabling paroxysmal movement disorder events; walking capacity and endurance measured by the 12-minute walk test; patient-reported health-related quality of life assessments of physical function, mobility, upper extremity function, fatigue and pain; cognitive function and safety. Following the 22-week blinded crossover study period, patients may roll into the open-label extension period to continue on UX007 treatment. We expect data from this study in the second half of 2018.

DTX301 for the treatment of OTC deficiency

In March 2018, we announced positive safety and efficacy data from the first dose cohort of the Phase 1/2 study of DTX301 in OTC deficiency. All three patients in the first, lowest-dose cohort received a single DTX301 dose of 2.0 × 10^12 GC/kg, and the pre-defined endpoint for efficacy evaluation occurred 12 weeks after dosing. The first patient's rate of ureagenesis was normalized, maintained and then substantially increased over 24 weeks. The rate of ureagenesis at baseline was 67% of normal (200 umol/kg/hr), with the normal rate of ureagenesis defined as 300 umol/kg/hr. The patient had an initial peak effect at 6 weeks at 112% of normal (67% increase from baseline to 335 umol/kg/hr), and then declined at week 12 to 87% of normal (30% increase from baseline to 261 umol/kg/hr,) during the steroid regimen that was used to treat the patient's mild alanine aminotransferase, or ALT, elevations. After steroids were weaned, ureagenesis began to rebound to 91% of normal at week 20 (36% increase from baseline to 273 umol/kg/hr) and then substantially increased to 134% of normal at week 24 (100.8% increase from baseline to 402 umol/kg/hr). The protocol allows for the tapering or discontinuation of alternate urea-cycle pathway medications. At week 24, all alternate urea-cycle pathway medications were discontinued based on Patient 1 choice and with investigator concurrence. In the 3 weeks since stopping these medications, the patient has been doing well clinically as reported by the investigator. The second and third patients did not show a clinically meaningful change in rate of ureagenesis over 20 weeks and 12 weeks, respectively. As of the February 15, 2018 cutoff date, there have been no infusion-related adverse events and no serious adverse events reported. All adverse events have been Grade 1 or 2 and have resolved. The only treatment-related adverse events were the previously-reported mild, clinically asymptomatic and manageable elevations in ALT in two patients, peaking at 45 (Patient 1) and 118 IU/L (Patient 2). These ALT elevations were mild and similar to what has been observed in other programs using adeno-associated virus, or AAV, gene therapy. Both patients completed a standard tapering course of corticosteroids as outpatients to treat the ALT elevations. Their ALT levels have remained in the normal range (below 40 U/L) since completing the tapering course. The third patient's ALT levels remained in the normal range through twelve weeks. All three patients have remained clinically and metabolically stable.

The DMC completed its review of the Cohort 1 data, and we are proceeding to the second, higher-dose cohort of the study. Three patients will be enrolled in Cohort 2 and will each receive a single DTX301 dose of 6.0 × 10^12 GC/kg. Data from the second cohort are expected in the second half of 2018.

DTX401 for the treatment of GSDIa

In April 2018 we announced the FDA's acceptance of our IND for DTX401for the treatment of patients with GSDIa. We expect data from the first cohort of the Phase 1/2 study in the second half of 2018.

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 equity securities.

We have incurred net losses in each year since inception. Our net income (loss) was $30.3 million and $(68.3) million for the three months ended March 31, 2018 and 2017, respectively. 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.

Critical Accounting Policies and Significant Judgments and Estimates

Our management's discussion and analysis of our financial condition and results of operations is based on our consolidated financial statements, which have been prepared in accordance with GAAP. The preparation of these

consolidated financial statements requires us to make estimates and assumptions that affect the reported amounts of assets and liabilities and the disclosure of contingent assets and liabilities at the date of the financial statements, as well as the reported expenses incurred during the reporting periods. Our estimates are based on our historical experience and on various other factors that we believe are reasonable under the circumstances, the results of which form the basis for making judgments about the carrying value of assets and liabilities that are not readily apparent from other sources. Actual results may differ from these estimates under different assumptions or conditions. There have been no significant and material changes in our critical accounting policies during the three months ended March 31, 2018, 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 months ended March 31, 2018 to the three months ended March 31, 2017:

Revenue (dollars in thousands)

	Three Months Ended March 31, 2018	2017	Dollar Change	% Change
Revenues:				
Collaboration and license	$9,362	$ —	$9,362	*
Product sales	1,315	—	1,315	*
Total revenues	$10,677	$ —	$10,677	*

*not meaningful

We recognized $9.4 million in collaboration and license revenue primarily from our research arrangement with Bayer and $1.3 million in product sales for sales of Mepsevii and UX007 for the three months ended March 31, 2018. The increase in collaboration and license revenue is due to our acquisition of Dimension Therapeutics Inc., or Dimension, and the assumption of the agreement with Bayer through the acquisition. The increase in product sales is primarily due to the approval of Mepsevii in November 2017.

Cost of Sales (dollars in thousands)

	Three Months Ended March 31, 2018	2017	Dollar Change	% Change
Cost of sales	$225	$ —	$ 225	*

We recognized $0.2 million in cost of sales related to Mepsevii, which was approved by the FDA in November 2017, which includes a reserve of $0.2 million recorded for excess inventory. Prior to the approval, manufacturing and related costs were expensed; accordingly, these costs were not capitalized and as a result are not fully reflected in the costs of sales during the current period. If manufacturing and related costs were capitalized prior to the approval period, we expect that cost of sales for the three months ended March 31, 2018 would have been approximately $0.4 million for our commercial product sales, which includes $0.2 million of excess inventory reserves recorded for the three months ended March 31, 2018. We expect cost of sales to increase in relation to product revenues as we deplete these previously expensed inventories and in turn, the inventory cost of Mepsevii will increase as we produce and then sell Mepsevii product that has an inventory cost that reflects the full cost of manufacturing similar biologic products.

Research and Development Expenses (dollars in thousands)

	Three Months Ended March 31, 2018	2017	Dollar Change	% Change	
Crysvita	$11,223	$9,694	$1,529	16	%
Mepsevii	6,333	8,426	(2,093)	-25	%

UX007	11,943	10,743	1,200	11	%
DTX201	9,960	—	9,960	*	
DTX301	3,426	—	3,426	*	
DTX401	5,958	—	5,958	*	
Ace-ER	2,881	6,237	(3,356)	-54	%
Other research costs and preclinical costs	23,780	16,169	7,611	47	%
Total research and development expenses	$75,504	$51,269	$24,235	47	%

Research and development expenses increased $24.2 million for the three months ended March 31, 2018 compared to the same period in 2017. The increase in research and development expenses is primarily due to:

- for Crysvita, an increase of $1.5 million for the three months ended March 31, 2018 related to patient diagnosis efforts, medical and scientific education expense, and regulatory filing preparation costs, net of KHK reimbursement;
- for Mepsevii, a decrease of $2.1 million for the three months ended March 31, 2018 related to the post-approval capitalization of manufacturing expenses and reduced clinical trial activity with the progressive completion of our extension studies;
- for UX007, an increase of $1.2 million for the three months ended March 31, 2018 primarily related to the conduct of our Phase 3 movement disorder study and regulatory filing preparation activities;
- for DTX201, $10.0 million for the three months ended March 31, 2018 primarily related to clinical manufacturing expense, IND filing preparation expense, and amortization of fair value related to our Bayer collaboration agreement; as the program

costs are reflected only after the acquisition of Dimension in November 2017, there is no previous year basis of comparison;

- for DTX301, $3.4 million for the three months ended March 31, 2018 related to the conduct of the Phase 1/2 study; as the program costs are reflected only after the acquisition of Dimension in November 2017, there is no previous year basis of comparison;
- for DTX401, $6.0 million for the three months ended March 31, 2018 related to clinical manufacturing expense, IND filing preparation expense, and preparations for our Phase 1/2 clinical study; as the program costs are reflected only after the acquisition of Dimension in November 2017, there is no previous year basis of comparison;
- for Ace-ER, a decrease of 3.4 million for the three months ended March 31, 2018 due to a reduction in our spend on the Ace-ER program as a consequence of our decision to terminate the program in 2017; and
- an increase of $7.6 million for the three months ended March 31, 2018 in other research and development costs including operating expenses related to our research stage programs and research collaborations (including programs acquired with Dimension acquisition), general expenses in support of our clinical and research program pipelines, and certain cost allocations.

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

Selling, General and Administrative Expenses (dollars in thousands)

	Three Months Ended March 31,		Dollar	%
	2018	2017	Change	Change
Selling, general and administrative	$31,435	$18,685	$12,750	68 %

Selling, general and administrative expenses increased $12.8 million for the three months ended March 31, 2018 compared to the same period in 2017. The increase in selling, general and administrative expenses was primarily due to increases in commercial planning costs, professional services costs, stock-based compensation, and personnel costs resulting from an increase in the number of employees in support of our activities.

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

Interest Income (dollars in thousands)

	Three Months Ended March 31,		Dollar	%
	2018	2017	Change	Change
Interest income	$1,737	$1,082	$ 655	61 %

Interest income increased $0.7 million for the three months ended March 31, 2018 compared to the same period in 2017, primarily due to an increase in our balance of invested funds and due to an increase in yields on our investment

portfolio.

Gain from Sale of Priority Review Voucher (dollars in thousands)

	Three Months Ended March 31, 2018	2017	Dollar Change	% Change
Gain from sale of priority review voucher	$130,000	$ —	$130,000	*

The gain from sale of the PRV of $130.0 million for the three months ended March 31, 2018 was due to the completion of the sale of the PRV we received from the FDA in connection with the approval of Mepsevii.

Other Income (Expense) (dollars in thousands)

	Three Months Ended March 31, 2018	2017	Dollar Change	% Change
Other income (expense)	$(4,958)	$582	$(5,540)	-952 %

Other income (expense) decreased $5.5 million for the three months ended March 31, 2018 compared to the same period in 2017. The expense recognized during the three months ended March 31, 2018 was primarily due to the recognition of cumulative foreign currency translation losses related to the substantial liquidation of subsidiaries with a functional currency other than the U.S. Dollar. These recognized foreign currency losses are substantially offset by the reclassification adjustment reported as a component of other comprehensive income (loss).

Liquidity and Capital Resources

We have funded our operations primarily from the sale of equity securities. In July 2017, we entered into an at-the-market sales agreement with Cowen and Company, LLC, or Cowen, under which we may offer and sell from time to time common stock having aggregate gross proceeds of up to $150.0 million. In March 2018, we amended our sales agreement with Cowen to allow us to sell, from time to time, the remaining $72.6 million in common stock remaining under the sales agreement. During the three months ended March 31, 2018, the proceeds from the offering were approximately $11.8 million, after commissions and other offering costs. In January 2018, we completed an underwritten public offering in which we sold 5,043,860 shares of common stock and received net proceeds of approximately $271.0 million.

As of March 31, 2018, we had $571.3 million in available cash, cash equivalents, and investments. 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 investments are held in a variety of deposit accounts, interest-bearing accounts, corporate bond securities, U.S government securities and money market funds. Cash in excess of immediate requirements is invested with a view toward liquidity and capital preservation, and we seek to minimize the potential effects of concentration and credit risk.

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

	Three Months Ended March 31,	
	2018	2017
Cash used in operating activities	$(89,478)	$(61,205)
Cash used in investing activities	(71,028)	(10,620)
Cash provided by financing activities	286,419	68,969
Effect of exchange rate changes on cash	249	17
Net increase (decrease) in cash, cash equivalents and restricted cash	$126,162	$(2,839)

Cash Used in Operating Activities

Our primary use of cash is to fund operating expenses, which consist primarily of research and development 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 three months ended March 31, 2018 was $89.5 million and reflected net income of $30.3 million, non-cash charges of $18.8 million for stock-based compensation and $6.2 million for depreciation and amortization of intangible asset acquired, offset by $130.0 million for the gain from sale of the PRV, and $0.2 million for the amortization of discount paid on purchased investments. There was also $4.8 million of non-cash foreign currency remeasurement losses in connection with the substantial liquidation of subsidiaries due to a change in the Company’s tax structure and fluctuations of exchange rates related to intercompany transactions with foreign subsidiaries that are denominated in our reporting currency. Cash used in operating activities also reflected a $5.1 million increase in prepaid expenses and other current assets, a $0.3 million increase in other assets, a $1.3

million decrease in accounts payable primarily due to the timing of payments and receipt of invoices, and a $12.6 million decrease in accrued expenses and other liabilities primarily as a result of a decrease in accrued bonus due to the payout of the 2017 annual bonus and accrued expenses due to the timing of the receipt of invoices.

Cash used in operating activities for the three months ended March 31, 2017 was $61.2 million and reflected a net loss of $68.3 million, offset by non-cash charges of $14.5 million for stock-based compensation, $0.5 million for the amortization of premium paid on purchased investments, and $1.2 million for depreciation and amortization. There was also $0.6 million for a foreign currency remeasurement gain due to an intercompany transaction exposure increase and the strengthening of the respective foreign exchange rates. Cash used in operating activities also reflected a $0.9 million decrease in prepaid expenses and other current assets primarily due to decreases in receivables, prepaid manufacturing and a prepayment related to collaboration activities offset by increases in prepaid insurance and subscriptions, a $3.0 million increase in accounts payable primarily due to the timing of payments and receipt of invoices, offset by a $12.5 million decrease in accrued expenses and other liabilities primarily as a result of a decrease in accrued bonus due to the payout of the 2016 annual bonus and accrued expenses due to the receipt of invoices.

Cash Used in Investing Activities

Cash used in investing activities for the three months ended March 31, 2018 was $71.0 million and related to purchases of investments of $260.8 million and purchases of property and equipment of $0.5 million, offset by proceeds from the sale of PRV of $130.0 million, and proceeds from maturities of investments of $60.3 million.

Cash used in investing activities for the three months ended March 31, 2017 was $10.6 million and related to purchases of investments of $87.5 million and purchases of property and equipment of $0.5 million, offset by proceeds from maturities of investments of $65.0 million, and the sale of investments of $12.4 million.

Cash Provided by Financing Activities

Cash provided by financing activities for the three months ended March 31, 2018 was $286.4 million and was comprised of $271.0 million from the sale of common stock in our underwritten public offering $11.8 million from the sale of common stock in our ATM offering, and $3.6 million in net proceeds from the issuance of common stock pursuant to equity awards.

Cash provided by financing activities for the three months ended March 31, 2017 was $69.0 million and was comprised of $67.6 million from the sale of common stock in our ATM offering, and $1.4 million in net proceeds from the issuance of common stock upon the exercise of stock options.

Funding Requirements

We anticipate, excluding non-recurring items, that we will continue to generate annual losses for the foreseeable future, and we expect the losses to increase as we continue the development of, and seek regulatory approvals for, our product candidates, and begin to commercialize our approved products. Due to certain non-recurring or infrequent items like the sale of priority review vouchers, we may have income or lower levels of losses in the near term in quarterly periods that may not be indicative of future periods or trends. We will likely require additional capital to fund our operations, complete our ongoing and planned clinical studies and commercialize our products, and 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 and any products that we may develop;
- 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; and
- the terms and timing of any collaborative, licensing, and other arrangements that we may establish, including any required upfront milestone and royalty payments thereunder.

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

Contractual Obligations and Commitments

During the three months ended March 31, 2018, there were no material changes to our contractual obligations and commitments described under Management's Discussion and Analysis of Financial Condition and Results of Operations in our Annual Report on Form 10-K for the year ended December 31, 2017.

Off-Balance Sheet Arrangements

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

Item 3. Quantitative and Qualitative Disclosures About Market Risk

Interest Rate Risk

Our exposure to market risk for changes in interest rates relates primarily to interest earned on our cash equivalents and investments. 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 March 31, 2018, we had cash, cash equivalents, and investments totaling $571.3 million which includes bank deposits, money market funds, U.S. government treasury and agency securities, and investment-grade corporate bond securities which are subject to default, changes in credit rating, and changes in market value. The securities in our investment portfolio are classified as available for sale and are subject to interest rate risk and will decrease in value if market interest rates increase. A hypothetical 100 basis point change in interest rates during any of the periods presented would not have had a material impact on our consolidated financial statements. To date, we have not experienced a loss of principal on any of 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. An adverse movement in foreign exchange rates could have a material effect on payments made to foreign suppliers and for license agreements. We have exposure to currency risk related to intercompany balances with our foreign subsidiaries, resulting in the foreign currency gains and losses generated on the remeasurement of our intercompany balances with our foreign subsidiaries, which are reported in other income (expense). The intercompany amounts are largely offset by the translation gains (losses) reported in other comprehensive income (loss), resulting in immaterial impact on stockholders' equity. A hypothetical 10% change in foreign exchange rates during any of the periods presented would not have had a material impact on our consolidated financial statements.

Item 4. Controls and Procedures

Evaluation of Disclosure Controls and Procedures

We carried out an evaluation, under the supervision and with the participation of our management, including our Chief Executive Officer and our Chief Financial Officer, of the effectiveness of our "disclosure controls and procedures" as of the end of the period covered by this 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 March 31, 2018. For the purpose of this review, disclosure controls and procedures means controls and procedures designed to ensure that information required to be disclosed by us in the reports that we file or submit is recorded, processed, summarized and reported within the time periods specified in the SEC's rules and forms. These disclosure controls and procedures include, without limitation, controls and procedures designed to ensure that information required to be disclosed by us in the reports that we file or submit is accumulated and communicated to management, including our principal executive officer and principal financial officer, as appropriate to allow timely decisions regarding required disclosure. In designing and evaluating the disclosure controls and procedures, our management recognized that any controls and procedures, no matter how well designed and operated, can provide only reasonable assurance of achieving the desired control objectives, and our management necessarily was required to apply its judgment in evaluating the cost-benefit relationship of possible

controls and procedures.

Changes in Internal Control over Financial Reporting

There have been no changes in our internal control over financial reporting (as defined in Rules 13a-15(f) and 15d-15(f) under the Exchange Act) during our first quarter ended March 31, 2018, 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 and we may, from time to time, make claims or take legal actions to assert our rights, including intellectual property rights as well as claims relating to 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 risks, together with all the other information in this report, including our financial statements and notes thereto, before deciding to invest in our common stock. If any of the following risks actually materialize, our operating results, financial condition, and liquidity could be materially adversely affected. As a result, the trading price of our common stock could decline and you could lose part or all of your investment.

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 our Annual Report.

Risks Related to Our Financial Condition and Capital Requirements

We have a limited operating history on which to assess our business, have incurred significant losses since our inception, and anticipate that, excluding non-recurring events, we will continue to incur significant losses for the foreseeable future.

We are a biopharmaceutical company with a limited operating history. We have incurred net losses in each year since our inception in April 2010.

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. To date, we have financed our operations primarily through the sale of equity securities. The amount of our future net losses will depend, in part, on non-recurring events, the rate of our future expenditures and our ability to obtain funding through equity or debt financings, strategic collaborations, or grants. Our future revenue will depend upon the size of any markets in which our products are approved and any of our product candidates may receive approval, and our ability to achieve sufficient market acceptance, pricing, reimbursement, and adequate market share for our products and product candidates in those markets. However, even if we obtain adequate market share for our products and product candidates, because the potential markets in which our products and product candidates may ultimately receive regulatory approval are very small, and our expenses may be greater than expected, we may never become

profitable (excluding non-recurring events) despite obtaining such market share and acceptance of our products and product candidates that may receive approval.

We expect to continue to incur significant expenses and increasing operating losses for the foreseeable future, excluding non-recurring events. 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 product candidates;
- change or add additional manufacturers or suppliers;
- seek regulatory and marketing approvals for our product candidates that successfully complete clinical studies;
- establish Medical Affairs field teams to initiate relevant disease education;
- 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 establish our international subsidiaries;
- 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 planned future 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.

Further, 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 not generated any significant revenue from product sales and we may never be profitable, excluding non-recurring events.

We have two products approved for commercialization but have not generated any significant revenue from product sales. Our ability to generate significant revenue and achieve profitability depends on our ability, alone or with strategic collaboration partners, to successfully commercialize our products and to complete the development of, and obtain the regulatory and marketing approvals necessary to commercialize, one or more of our product candidates. We do not anticipate generating significant revenue from product sales in the near future. Our ability to generate substantial future revenue from product sales, including named patient sales, and to potentially be profitable depends heavily on our success in many areas, including but not limited to:

- completing research and nonclinical and clinical development of our product candidates;
- obtaining regulatory and marketing approvals 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 clinical development and the 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 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;
- addressing any competing technological and market developments;
- identifying, assessing, licensing, acquiring, and/or developing new product candidates, technologies, and/or businesses;
- negotiating favorable terms 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.

We anticipate incurring significant costs associated with commercializing our products and any approved product candidate. Our expenses could increase beyond expectations if we are required by the FDA, the EMA, or other regulatory agencies, domestic or foreign, to change our manufacturing processes or assays, or to perform clinical, nonclinical, or other types of studies in addition to those that we currently anticipate. In cases where we are successful in obtaining regulatory approvals to market one or more of our product candidates, our revenue will be dependent, in part, upon the size of the markets in the territories for which we gain regulatory approval, the accepted price for the product, the approved indication(s), the ability to obtain reimbursement at any price, and whether we own the commercial rights for that territory. If the number of our addressable rare disease patients is not as significant as we estimate, the indication approved by regulatory authorities is narrower than we expect, or the reasonably accepted

population for treatment is narrowed by competition, physician choice, or treatment guidelines, we may not generate significant revenue from sales of our products, even if approved.

We expect we will need to raise additional capital to fund our activities. This additional financing may not be available on acceptable terms, or 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 we continue to advance our product candidates through preclinical and clinical development and increase our commercialization efforts, we expect our expenses to increase substantially in connection with our ongoing activities.

As of March 31, 2018, our available cash, cash equivalents, and investments were $571.3 million. We will likely require additional capital to commercialize our products and to 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 supplies, and establishing commercial supplies, of our product candidates and any products that we may develop;
- 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 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 may adversely affect our ability to develop and commercialize our product candidates. In addition, we cannot guarantee that future financing will be available in sufficient amounts or on terms acceptable to us, if at all. Moreover, the terms of any financing may adversely affect the holdings or the rights of our stockholders and the issuance of additional securities, whether equity or debt, by us, or the possibility of such issuance, may cause the market price of our shares to decline. The sale of additional equity or convertible securities would dilute all of our stockholders. If we incur debt, it could result in increased fixed payment obligations and we may be required to agree to certain restrictive covenants, such as limitations on our ability to incur additional debt, limitations on our ability to acquire, sell, or license intellectual property rights, and other operating restrictions that could adversely impact our ability to conduct our business. If we are granted priority review vouchers in connection with regulatory approvals for our product candidates, we may be unable to sell the vouchers or, if we do sell the vouchers, we may have to sell them on unfavorable terms and at prices that are lower than expected. Regulatory authorities may also cease granting such vouchers in the future. We could also be required to seek funds through collaborative partnerships, strategic alliances, and licensing or other arrangements and we may be required to relinquish rights to some of our technologies or product candidates, future revenue streams, research programs, and other product candidates or otherwise agree to terms unfavorable to us, any of which may have a material adverse effect on our business, operating results, and prospects. Even if we believe we have sufficient funds for our current or future operating plans, we may seek additional capital if market conditions are favorable or if we have specific strategic considerations.

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

Risks Related to the Discovery and Development of Our Product Candidates

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

Before obtaining marketing approval from regulatory authorities for the sale of our product candidates, we must conduct extensive clinical studies to demonstrate the safety and efficacy of the product candidates in humans. Clinical testing is expensive, time consuming, and uncertain as to outcome. We cannot guarantee that any clinical studies will be conducted as planned or completed on schedule, if at all. A failure of one or more clinical studies can occur at any stage of testing, and our future clinical studies may not be successful. Product candidates that have shown promising results in early-stage clinical studies may still suffer significant setbacks in subsequent clinical studies. The safety or efficacy results generated to date in clinical studies for Crysvita and UX007 do not ensure that later clinical studies will demonstrate similar results. For example, our Phase 3 study that evaluated Ace-ER in patients with GNE myopathy did not achieve its primary or secondary endpoints and efficacy results from our Phase 2 study of UX007 in Glut1 DS patients with seizures did not meet the primary endpoint. Results from investigator-sponsored studies or compassionate-use studies may not be confirmed in company-sponsored studies or may negatively impact the prospects for our programs. Additionally, given the nature of the rare diseases we are seeking to treat, we often have to devise newly-defined endpoints

to be tested in our studies, which can lead to some subjectivity in interpreting study results and could result in regulatory agencies not agreeing with the validity of our endpoints, or our interpretation of the clinical data, and therefore denying approval. For example, for our Glut1 DS Phase 3 clinical trial, we have proposed utilizing a patient diary to track movement disorder events. Based on FDA feedback expressing concern about the clinical meaningfulness of all such events tracked, we modified the clinical endpoint. Even so, there is no guarantee that these modifications to the endpoint will be acceptable to the FDA or other regulatory agencies. 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. Additionally, we have in the past, and may in the future elect to review interim clinical data at multiple time points during the studies, which could introduce bias into the study results and potentially result in denial of approval.

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

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

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

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

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

For planning purposes, we estimate the timing of the accomplishment of various scientific, clinical, regulatory, and other product development goals, which we sometimes refer to as milestones. These milestones may include the commencement or completion of scientific studies and clinical trials, the submission 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 are heavily dependent on the success of our product candidates, some of which are in the early stages of clinical development, which is a lengthy and expensive process with uncertain outcomes and the potential for substantial delays. We cannot give any assurance that any of our product candidates will receive regulatory approval, which is necessary before they can be commercialized.

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. To date, we have focused substantially all of our efforts and financial resources on identifying, acquiring, and developing our product candidates, including conducting clinical studies and providing selling, general and administrative support for these operations. We cannot be certain that any clinical studies will be conducted as planned or completed on schedule, if at all. Our inability to successfully complete nonclinical and clinical development could result in additional costs to us and negatively impact our ability to generate revenue. Our future success is dependent on our ability to successfully develop, obtain regulatory approval for, and then successfully commercialize our product candidates. We currently generate no significant revenue from sales of drugs, and we may never be able to develop or successfully commercialize an additional marketable drug.

Each of our product candidates is in development and will require additional clinical development; management of nonclinical, clinical, and manufacturing activities; regulatory approval; obtaining adequate manufacturing supply; building a commercial organization; significant marketing efforts; and reimbursement before we generate any significant revenue from commercial product sales, if ever. There can be no assurance that we will be able to secure regulatory approval for our product candidates, for the specified indications, or within projected time periods. For example, in November 2016, we withdrew our first filing application for regulatory approval that sought conditional marketing authorization in the EU for Ace-ER, and in August 2017 we discontinued further clinical development of Ace-ER. Even if we obtain regulatory approval, it may be withdrawn under certain circumstances. In addition, confirmatory clinical studies could be required for a conditional marketing authorization and could fail to demonstrate sufficient safety and efficacy to obtain full approval.

Some of our product candidates are in the early-stage translational research phases of development. Such early-stage programs will require substantial investment to reach clinical studies and regulatory approval, and their risk of failure is high. For example, our collaboration with Arcturus focuses on an advanced but less established technology platform that will require significant effort and investment. A failure in that collaboration or our other early-stage programs may negatively affect our operational results.

We generally plan to seek regulatory approval to commercialize our product candidates in the United States, the EU, and in additional foreign countries where we have commercial rights. To obtain regulatory approval in other countries, we must comply with numerous and varying regulatory requirements of such other countries regarding safety, efficacy, chemistry, manufacturing, and controls, clinical studies, commercial sales, pricing, and distribution of our product candidates. Even if we are successful in obtaining approval in one jurisdiction, we cannot ensure that we will

obtain approval in any other jurisdiction. If we are unable to obtain approval for our product candidates in multiple jurisdictions, our revenue and results of operations could be negatively affected.

We cannot be certain that any of our product candidates will be successful in clinical studies or receive regulatory approval. Further, our product candidates may not receive regulatory approval even if they are successful in clinical studies. If we do not receive regulatory approvals for our product candidates, we may not be able to continue our operations.

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

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

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

- we estimate that several hundred patients in the United States suffer from TIO, for which Crysvita is being studied;

- we estimate that several thousand patients in the United States suffer from LC-FAOD, for which UX007 is being studied;
- we estimate that several thousand patients in the United States suffer from Glut1 DS, for which UX007 is being studied;
- we estimate that approximately 8,000 patients in the developed world suffer from late-onset OTC deficiency, for which DTX301 is being studied, and these all may not be treatable if they are immune to the virus; and
- we estimate that approximately 6,000 patients worldwide suffer from GSD1a, for which DTX 401 is being studied, and these all may not be treatable if they are immune to the virus.

In addition to the rarity of these diseases, the eligibility criteria of our clinical studies will further limit the pool of available study participants as we will require patients to have specific characteristics that we can measure or to assure their disease is either severe enough or not too advanced to include them in a study. For example, enrolling patients in the UX007 Glut1 DS Phase 3 movement disorder study could face delays if a higher than expected number of patients that we identify for the study are on the ketogenic diet. Additionally, the process of finding and diagnosing patients may prove costly, especially since the rare diseases we are studying are commonly under diagnosed. We also may not be able to identify, recruit, and enroll a sufficient number of patients to complete our clinical studies because of the perceived risks and benefits of the product candidate under study, the proximity and availability of clinical study sites for prospective patients, and the patient referral practices of physicians. The availability and efficacy of competing therapies and clinical studies can also adversely impact enrollment. If patients are unwilling to participate in our studies for any reason, the timeline for recruiting patients, conducting studies, and obtaining regulatory approval of potential products may be delayed, the commercial prospects of our product candidates will be harmed, and our ability to generate product revenue from any of these product candidates could be delayed or prevented. In addition, any delays in completing our clinical studies will increase our costs, slow down our product candidate development and approval process, and jeopardize our ability to commence product sales and generate revenue. Any of these occurrences may harm our business, financial condition, and prospects significantly. In addition, many of the factors that cause, or lead to, a delay in the commencement or completion of clinical studies may also ultimately lead to the denial of regulatory approval of our product candidates.

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 one product, and it is possible that none of our existing product candidates or any product candidates we may seek to develop in the future will ever obtain regulatory approval.

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

regulatory approval, for many reasons, including but not limited to the following:

- the FDA or comparable foreign regulatory authorities may disagree with the design, implementation, or conduct of our clinical studies;
- the FDA or other comparable foreign 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;
- the FDA or comparable foreign 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 in the United States or elsewhere;
- we may be unable to demonstrate to the FDA or comparable foreign regulatory authorities that a product candidate's risk-benefit ratio for its proposed indication is acceptable;

- the FDA or comparable foreign regulatory authorities may fail to approve the manufacturing processes, test procedures and specifications, or facilities of third-party manufacturers with which we contract for clinical and commercial supplies;
- 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 the FDA or comparable foreign regulatory authorities may significantly change in a manner rendering our clinical data insufficient for approval.

Furthermore, the disease states we are evaluating often will not have clear regulatory paths for approval and/or do not have validated outcome measures. In these circumstances, we work closely with the regulatory authorities to define the approval path and may have to qualify outcome measures as part of our development programs. For example, for patients with XLH there is no available regulatory precedent describing requirements for obtaining approval to treat this disease, and there are no validated patient-reported outcome measures that are specific to this disease. Additionally, many of the disease states we are targeting are highly heterogeneous in nature, which may impact our ability to determine the treatment benefit of our potential therapies. For example, patients with FAOD and Glut1 DS have a highly heterogeneous disease course, which may impact our ability to determine the true treatment benefit of our product candidates in these patients.

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

FDA, the U.S. National Institutes of Health, or NIH, Health Canada, and the EMA have demonstrated caution in their regulation of gene therapy treatments, and ethical and legal concerns about gene therapy and genetic testing may result in additional regulations or restrictions on the development and commercialization of our gene therapy product candidates, which may be difficult to predict.

The clinical trial requirements of FDA, the NIH, Health Canada, the EMA and other regulatory authorities and the criteria these regulators use to determine the safety and efficacy of a product candidate vary substantially according to the type, complexity, novelty and intended use and market of the product candidate. The regulatory approval process for novel product candidates such as our gene therapy product candidates can be more expensive and take longer than for other, better known or more extensively studied product candidates. Only one AAV gene therapy product, Glybera from uniQure N.V., or uniQure, has received marketing authorization from the European Commission and one AAV gene therapy product, LUXTURNA™ (voretigene neparvovec) from Spark Therapeutics, has been approved in the United States. Different or additional preclinical studies or clinical trials may be required to support regulatory approval in each respective jurisdiction.

Additionally, FDA, the NIH, Health Canada, and the EMA have each expressed interest in further regulating biotechnology, including gene therapy and genetic testing. For example, the EMA advocates a risk-based approach to the development of a gene therapy product. Agencies at both the federal and state level in the United States, as well as U.S. congressional committees and foreign governments, have also expressed interest in further regulating the biotechnology industry. Such action may delay or prevent commercialization of some or all of our product candidates. For example, in 1999, a patient suffering from OTC deficiency died during a gene therapy clinical trial that utilized an adenovirus vector. It was discovered that adenoviruses could generate an extreme immune system reaction that can be life-threatening. Thereafter, in January 2000, FDA halted that trial and began investigating 69 other gene therapy trials underway in the United States. Eventually, 28 trials were reviewed, with 13 requiring remedial action. Subsequently, in 2003, FDA suspended 27 additional gene therapy trials involving several hundred patients after learning that a child treated in France had developed leukemia.

Regulatory requirements in the United States and abroad governing gene therapy products have changed frequently and may continue to change in the future. FDA has established the Office of Cellular, Tissue and Gene Therapies

within its Center for Biologics Evaluation and Research to consolidate the review of gene therapy and related products, and has established the Cellular, Tissue and Gene Therapies Advisory Committee to advise this review. Prior to submitting an IND, our human gene therapy clinical trials are subject to review by the NIH Office of Biotechnology Activities', or OBA's, Recombinant DNA Advisory Committee, or the RAC. As of April 2016, the updated NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules, including gene therapy, provide the opportunity for one or more oversight bodies (institutional review board, or IRB, or the institutional biosafety committee, or IBC) to request a public RAC review based on their own review of the protocol and NIH requirements. Regardless of the request for public review, NIH RAC members make their own assessment as to whether the protocol would significantly benefit from a public RAC review. The RAC's recommendations are shared with FDA and the oversight bodies. The RAC can delay the initiation of a clinical trial, even if FDA has reviewed the trial design and details and has not objected to its initiation or has notified the sponsor that the study may begin. Conversely, FDA can put an IND on a clinical hold even if the RAC has provided a favorable review or has recommended against an in-depth, public review. Moreover, under guidelines published by the NIH, patient enrollment in our gene therapy clinical trials cannot begin until, among other things, the investigator for that clinical trial has received a letter from the OBA indicating that the protocol registration process has been completed. Upon receipt of the letter from OBA confirming completion of protocol registration the investigator may obtain final approval from the oversight bodies and patient enrollment may begin if all other applicable regulatory authorizations have been obtained.

If there is a public RAC review, the receipt of the final recommendation letter concludes the protocol registration process and then oversight body, or bodies, approval can be issued. While the RAC completed its initial public review for DTX301 and DTX201, approving the protocols and issuing written recommendations, the RAC will continue to review DTX301 and DTX201, and may recommend additional public reviews in the future with respect to DTX301, DTX201, or any of our other product candidates. In addition, adverse developments in clinical trials of gene therapy products conducted by others may cause FDA or other oversight bodies to change the requirements for approval of any of our product candidates. Similarly, the EMA governs the development of gene therapies in the EU and may issue new guidelines concerning the development and marketing authorization for gene therapy products and require that we comply with these new guidelines.

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

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

Undesirable side effects caused by our product candidates could cause us or regulatory authorities to interrupt, delay, or halt clinical studies or further development, and could result in a more restrictive label, the delay or denial of regulatory approval by the FDA or other comparable foreign authorities, or a Risk Evaluation and Mitigation Strategy, or REMS, plan, which could include a medication guide outlining the risks of such side effects for distribution to patients, restricted distribution, a communication plan for healthcare providers, and/or other elements to assure safe use. Some of our product candidates are in the early stages of development and the safety profile has not been established. For example, in completed Phase 2 study, LC-FAOD patients treated with UX007 experienced treatment-related adverse events, the most common of which were diarrhea, abdominal/gastrointestinal pain and vomiting. There were no deaths, but there was one treatment-related serious adverse event of moderate gastroenteritis with vomiting. In a completed Phase 2 seizure study, Glut1 DS patients with seizures treated with UX007 experienced treatment-related adverse events, the most common of which were vomiting, diarrhea, and abdominal pain. There were no deaths, and no treatment-related serious adverse events. Gene therapy product candidates using AAV vectors, like DTX301, have been associated with immunologic reaction to the capsid protein or gene at early time points after administration. For example, in our recently discontinued Phase 1/2 clinical trial of DTX101 in hemophilia B, we observed elevated laboratory alanine transaminase levels, or ALTs. In previous clinical trials involving AAV viral vectors for gene therapy, some subjects experienced adverse events, including the development of a T-cell mediated immune response against the vector capsid proteins. In addition, theoretical side effects of AAV vectors include replication and spread of the virus to other parts of the body and insertional oncogenesis, which is the process whereby the insertion of a gene near a gene that is important in cell growth or division results in uncontrolled cell division, which could potentially enhance the risk of malignant transformation or cancer. Potential procedure-related events are similar to those associated with standard coronary diagnostic procedures, and may include vascular injury (e.g., damage to the femoral, radial or brachial arteries at the site of vascular access, or damage to the coronary arteries) or myocardial injury. Future product candidates may also cause these or similar side effects as development proceeds. Results of our studies or investigator-sponsored trials could reveal a high and unacceptable severity and prevalence of these or other side effects. In such an event, our studies could be suspended or terminated, and the FDA or comparable foreign regulatory authorities could order us to cease further development of or deny or withdraw

approval of our product candidates for any or all targeted indications.

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

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

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

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

If preclinical studies for DTX201 for hemophilia A, DTX701 for Wilson disease, DTX501 for PKU, and DTX601 for citrullinemia type I, or all of our future product candidates do not result in the determination of a minimally effective dose range, we may not obtain the regulatory approvals required to initiate clinical testing.

As with any systemically delivered adeno-associated virus, or AAV, gene therapy, it is important that we accurately determine a minimally effective dose in order to successfully execute our clinical trial. Exposure to the AAV virus has been shown to induce the production of neutralizing antibodies, which can reduce or eliminate the therapeutic effect of subsequently administered intravenous AAV therapies such as our product candidates. Because of the potential for immune response producing neutralizing antibodies making patients ineligible for a second dose of that vector, clinical trials are required to determine the minimum effective dose and the maximum safe dose. If our preclinical studies fail to demonstrate a starting dose in the clinic that might be reasonably expected to result in a clinical benefit, regulatory agencies may not approve the start of our clinical trials. In addition, even if we start our clinical program, we may not be able to recruit patients who will seek assurance of a clinical benefit following administration of our therapy.

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

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

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

Any regulatory approvals that we receive for our product candidates may be subject to limitations on the approved indicated uses for which the product may be marketed or other conditions of approval, or contain requirements for potentially costly post-marketing testing, including Phase IV clinical studies, and surveillance to monitor the safety and efficacy of the product candidate. We could also be asked to conduct post-marketing clinical studies to verify the safety and efficacy of our products in general or in specific patient subsets. If original marketing approval was obtained via the accelerated approval or conditional marketing authorization pathways, we would be required to conduct a successful post-marketing clinical study to confirm clinical benefit for our products. An unsuccessful

post-marketing study or failure to complete such a study could result in the withdrawal of marketing approval. We will be required to report certain adverse events and manufacturing problems, if any, to the FDA and comparable foreign regulatory authorities. Any new legislation addressing drug safety issues could result in delays in product development or commercialization, or increased costs to assure compliance. We will have to comply with requirements concerning advertising and promotion for our products. Promotional communications with respect to prescription drugs are subject to a variety of legal and regulatory restrictions and must be consistent with the information in the product's approved label. As such, we may promote our products only for indications or uses for which they have approval. The holder of an approved NDA, BLA, MAA, or other comparable application must submit new or supplemental applications and obtain approval for certain changes to the approved product, product labeling, or manufacturing process.

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

- issue warning or notice of violation letters;
- impose civil or criminal penalties;
- suspend or withdraw regulatory approval;

- suspend any of our ongoing clinical studies;
- refuse to approve pending applications or supplements to approved applications submitted by us;
- impose restrictions on our operations, including closing our contract manufacturers' facilities;
- seize or detain products, or require a product recall; or
- require entry into a consent decree.

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

Our gene therapy approach utilizes vectors derived from viruses, which may be perceived as unsafe or may result in unforeseen adverse events. Negative public opinion and increased regulatory scrutiny of gene therapy may damage public perception of the safety of our product candidates and adversely affect our ability to conduct our business or obtain regulatory approvals for our product candidates.

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

Our transition from HEK293 to a HeLa platform may require additional toxicology and comparability studies for gene therapy product candidates, which may result in delays to the approval process for our current or future programs and increased costs resulting from additional preclinical trials.

We have conducted some of our preclinical evaluations with viral vectors produced on adherent and suspension platforms utilizing human embryonic kidney 293, or HEK293, and HeLa cells, the latter an immortal cell line used in scientific research. HeLa is the oldest and most commonly used human cell line. We are conducting our Phase 1/2 trial of DTX301, and plan to conduct our Phase 1/2 trials of DTX401, and potentially other programs using viral vectors produced on the HEK293 platform. We plan to conduct our Phase 1/2 trial of DTX201 using viral vectors produced on the HeLa platform. For Phase 3 studies and commercial production of each of our gene therapy product candidates, we plan to use HeLa. Even if we successfully complete our planned preclinical studies and clinical trials using vectors produced on our adherent and suspension HEK293 and HeLa platforms, FDA or other regulatory authorities may require additional toxicology and/or a clinical bridge study, or comparability study, the latter showing comparability of vectors produced on the HeLa platform prior to commencing Phase 3 trials of DTX301, DTX401, DTX701, DTX501, and DTX601 delaying the development process. For example, while FDA has agreed to our plan, other regulators may require additional assessments of HeLa material during the manufacturing of our products as well as additional animal studies. In addition, if we make manufacturing or formulation changes to our product candidates in the future, we may need to conduct additional preclinical studies to bridge our modified product candidates to earlier versions.

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

We currently anticipate that we will need companion diagnostics to determine whether or not we can dose a particular patient with each of our products. We expect to use predictive biomarkers to identify the right patients for certain of our product candidates. For example, to evaluate therapeutic response of DTX301, we plan to measure ammonia levels and other biomarkers, including ^{13}C-acetate, which are established measures of OTC deficiency disease status and ureagenesis. We cannot assure you that ^{13}C-acetate or any other future potential biomarker will in fact prove predictive, be reliably sourced, or be accepted by the FDA or other regulatory authorities. In addition, our success may depend, in part, on the development and commercialization of companion diagnostics. We also expect the FDA will require the development and regulatory approval of a companion diagnostic assay as a condition to approval of DTX301. There has been limited success to date industrywide in developing and commercializing these types of companion diagnostics. Development and manufacturing of companion diagnostics is complex and there are limited manufacturers with the

necessary expertise and capability. Even if we are able to find a qualified collaborator, it may not be able to manufacture the companion diagnostics at a cost or in quantities or on timelines necessary for use with our product candidates. To be successful, we need to address a number of scientific, technical and logistical challenges. We have not yet initiated development and commercialization of companion diagnostics. We have little experience in the development and commercialization of diagnostics and may not be successful in developing and commercializing appropriate diagnostics to pair with any of our product candidates that receive marketing approval. University of Pennsylvania School of Medicine currently conducts some of our clinical assays pursuant to a sponsored research agreement, one of which is required for our ongoing Phase 1/2 clinical trial. We intend to enter into agreements with third parties for the automation, characterization and validation, of our companion diagnostic and the manufacture of its critical reagents. However, we may be unable to enter into any such agreement on favorable terms, or at all.

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

Risks Related to our Reliance on Third Parties

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

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

candidates and/or we may be required to repeat clinical or nonclinical studies, which would delay the regulatory approval process.

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

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

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

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

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

- KHK has no obligation under our agreement to use diligent efforts to commercialize Crysvita in Europe. The timing and amount of any royalty payments we may receive under our agreement will depend on, among other things, the efforts, allocation of resources, and successful commercialization of Crysvita by KHK in Europe. Additionally, if KHK were to decide not to commercialize Crysvita in Europe, and we nevertheless wished to commercialize Crysvita in Europe, we would need to renegotiate with KHK certain terms of our agreement, which we may be unable to do on reasonable terms in a timely manner, or at all;
- the timing and amount of any royalty payments we may receive under our agreement with KHK will depend on, among other things, the efforts, allocation of resources, and successful commercialization of Crysvita by KHK in the United States and Canada under our agreement;
- KHK may change the focus of its commercialization efforts or pursue higher-priority programs;
- KHK may make decisions regarding the indications for our product candidates in countries where it has the sole right to commercialize the product candidates that limit commercialization efforts in those countries or in countries where we have the right to commercialize our product candidates;
- KHK may make decisions regarding market access and pricing in countries where it has the sole right to commercialize our product candidates which can negatively impact our commercialization efforts in countries where we have the right to commercialize our product candidates;
- KHK may fail to manufacture or supply sufficient drug product of Crysvita in compliance with applicable laws and regulations or otherwise for our development and clinical use, which could result in program delays;
- KHK may fail to manufacture or supply sufficient drug product of Crysvita in compliance with applicable laws and regulations or otherwise for our commercial use, if approved, which could result in lost revenue;
- KHK may elect to develop and commercialize Crysvita indications with a larger market than XLH and at a lower price, thereby reducing the profit margin on sales of Crysvita for any orphan indications, including XLH;
- if KHK were to breach or terminate the agreement with us, we would no longer have any rights to develop or commercialize Crysvita or such rights would be limited to non-terminated countries;
- KHK may terminate its agreement with us, adversely affecting our potential revenue from licensed products; and
- the timing and amounts of expense reimbursement that we may receive are uncertain, and the total expenses for which we are obligated to reimburse KHK may be greater than anticipated.

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

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

We expect our manufacturing strategy will involve the use of one or more CMOs as well as establishing our own capabilities and infrastructure, including at our Woburn, MA facility where we will support continued innovation in vector optimization and development of manufacturing processes required for IND-enabling studies and the reliable production of high quality AAV vectors at commercial scale. We expect that development of our own process development facility will provide us with enhanced control of material supply for both clinical trials and the commercial market, enable the more rapid implementation of process changes, and allow for better long-term margins. However, we have no experience as a company in developing a manufacturing facility and may never be successful in developing our own manufacturing facility or capability. Additionally, given that cGMP gene therapy manufacturing is a nascent industry, there are a small number of CMOs with the experience necessary to manufacture our gene therapy product candidates and we may have difficulty finding or maintaining relationships with such CMOs or hiring experts for internal manufacturing and accordingly, our production capacity may be limited. We may establish multiple manufacturing facilities as we expand our commercial footprint to multiple geographies, which may lead to regulatory delays or prove costly. Even if we are successful, our manufacturing capabilities could be affected by cost-overruns, unexpected delays, equipment failures, lack of capacity, labor shortages, natural disasters, power failures and numerous other factors that could prevent us from realizing the intended benefits of our manufacturing strategy and have a material adverse effect on our business.

Gene therapy products and product candidates are novel, complex, expensive and difficult to manufacture. We could experience manufacturing problems that result in delays in our gene therapy development or commercialization programs or otherwise harm our business.

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

Our gene therapy 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 our gene therapy ones generally cannot be fully characterized. As a result, assays of the finished product candidate may not be sufficient to ensure that the product candidate is consistent from lot to lot or will perform in the intended manner. Accordingly, we employ multiple steps to control the manufacturing process to assure that the process works

reproducibly and the product candidate is made strictly and consistently in compliance with the process. Problems with the manufacturing process, even minor deviations from the normal process, could result in product defects or manufacturing failures that result in lot failures, noncompliance with regulatory requirements, product recalls, product liability claims or insufficient inventory. We may encounter problems achieving adequate quantities and quality of clinical-grade materials that meet FDA, the EMA or other applicable standards or specifications with consistent and acceptable production yields and costs.

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

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

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

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

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

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

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

We acquire most of the drug substances and drug products for our products and product candidates from single sources. The drug substance and drug product for Crysvita are made by KHK pursuant to our license and collaboration agreement with KHK. The drug substance and drug product for Mepsevii are manufactured by Rentschler under a commercial supply and services agreement and accompanying purchase orders. The pharmaceutical-grade drug substance for UX007 is manufactured by IOI Oleo pursuant to our supply agreement with IOI Oleo, and the drug product for UX007 is prepared by Haupt Pharma AG and CPM pursuant to purchase orders. For DTX301, a CMO manufactures clinical materials pursuant to cGMP requirements. We have not currently secured any other suppliers for the drug substance or drug product of our products and product candidates and, although we believe that there are alternate sources of supply that could satisfy our clinical and commercial requirements, we cannot provide assurance that identifying alternate sources and establishing relationships with such sources would not result in significant delay in the commercialization of our products or the development of our product candidates. Additionally, we may not be able to enter into supply arrangements with alternative suppliers on commercially reasonable terms or at all. A delay in the commercialization of our products or the development of our product candidates or having to enter into a new agreement with a different third-party on less favorable terms than we have with our current suppliers could have a material adverse impact upon on our business.

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

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

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

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

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

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

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

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

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

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

Risks Related to Commercialization of Our Product Candidates

If the market opportunities for our 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 product candidates are small, and the addressable patient population potentially even smaller, we must be able to successfully identify patients and acquire a significant market share to achieve profitability and growth.

We focus our research and product development on treatments for rare and ultra-rare genetic diseases. Given the small number of patients who have the diseases that we are targeting, it is critical to our ability to grow and become profitable that we continue to successfully identify patients with these rare and ultra-rare genetic diseases. Some of our current clinical programs may be most appropriate for patients with more severe forms of their disease. For instance, our Phase 2 study of UX007 in LC-FAOD enrolled patients with more severe disease. In addition, while adults make up the majority of the XLH patients, they often have less severe disease that may reduce the penetration of Crysvita in the adult population relative to the pediatric population. Given the overall rarity of the diseases we target, it is difficult to project the prevalence of the more severe forms, or the other subsets of patients that may be most suitable to address with our 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 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 product candidates may be limited or may not be amenable to treatment with our product candidates, and new patients may become increasingly difficult to identify or access, which would adversely affect our results of operations and our business. Further, even if we obtain significant market share for our 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 intend to rely on third-party manufacturers to produce our product candidates. Additionally, these manufacturers do not have experience producing our product candidates at commercial levels and may not achieve the necessary regulatory approvals or produce our 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 our product candidates. Although we intend to rely on third-party manufacturers for commercialization, we have only entered into agreements with such manufacturers to support our clinical studies. We may be unable to negotiate binding agreements with the manufacturers to support our commercialization activities on commercially reasonable terms.

Manufacturers may not have the experience or ability to produce our product candidates at commercial levels. We may run into technical or scientific issues related to manufacturing or development that we may be unable to resolve in a timely manner or with available funds. We also have not completed all of the characterization and validation activities necessary for commercialization and regulatory approvals. If our manufacturing partners are not able to conduct all such necessary activities in accordance with applicable regulations, our commercialization efforts will be harmed.

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

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

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

The biotechnology and pharmaceutical industries are intensely competitive and subject to rapid and significant technological change. We are currently aware of various existing therapies that may compete with our product candidates. For example, XLH is currently treated with oral phosphate and vitamin D therapy, which may compete with Crysvita. Furthermore, B. Braun Medical Inc., or B. Braun, has received orphan drug designation for triheptanoin in Europe for certain LC-FAOD indications and we do not know if B. Braun is planning to initiate clinical development. Triheptanoin is also available in food-grade form, which may compete with our pharmaceutical-grade product. Investigator-sponsored trials evaluating triheptanoin in multiple indications are ongoing. LC-FAOD is currently treated with diet therapy and medium-chain triglyceride oil, which may compete with UX007. Glut1 DS is currently treated primarily with the ketogenic diet and anti-epileptic drugs, which may also compete with UX007. OTC deficiency is currently treated with nitrogen scavenging drugs and severe limitations in dietary protein, which may compete with DTX301. Gene therapy, gene correction, RNA-based therapies, and other approaches may also emerge for the treatment of any of the disease areas in which we focus.

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

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

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

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

The commercial success of any current or future product candidate 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 product candidates will depend in part on the medical community, patients, and payors accepting our product candidates 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 product candidates, if approved for commercial sale, 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 may require significant resources and may never be successful. If our product candidates are approved but 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 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 product candidates will depend substantially, both domestically and abroad, on the extent to which the costs of our product candidates 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 product candidates. Even if coverage is provided, the approved reimbursement amount may not be high enough to allow us to establish or maintain pricing sufficient to sustain our overall enterprise.

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

such as ours, especially our gene therapy product candidates as there is a limited body of established practices and precedents for gene therapy products.

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

Moreover, increasing efforts by governmental and third-party payors in the United States and abroad to cap or reduce healthcare costs may cause such organizations to limit both coverage and the level of reimbursement for new products approved and, as a result, they may not cover or provide adequate payment for our product candidates. We expect to experience pricing pressures in connection with the sale of any of our product candidates due to the trend toward managed healthcare, the increasing influence of health maintenance organizations, and additional legislative changes. For example, recently, 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. 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 United States and in other countries with respect to our proprietary technology, our products, and our product candidates.

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

The patent position of biotechnology and pharmaceutical companies generally is highly uncertain and involves complex legal and factual questions for which legal principles remain unsolved. The patent applications that we own or in-license may fail to result in issued patents with claims that cover our products or product candidates in the United States or in other foreign countries. There is no assurance that all potentially relevant prior art relating to our patents and patent applications has been found, which can invalidate a patent or prevent a patent from issuing from a pending patent application. Even if patents do successfully issue, and even if such patents cover our products or product candidates, third parties may challenge their validity, enforceability, or scope, which may result in such patents being narrowed, found unenforceable, or invalidated. For instance, in June 2017, a third party filed an opposition with the European Patent Office challenging the validity of a European patent owned by the University of Pennsylvania and sub-licensed to us from REGENXBIO relating to the AAV8 capsid used in our DTX301 product candidate. This opposition is in its very early stages and we are unable to estimate the timing or outcome of this matter. Furthermore, even if the patents and patent applications we own or in-license are unchallenged, they may not adequately protect our intellectual property, provide exclusivity for our products or product candidates, or prevent others from designing around our claims. Any of these outcomes could impair our ability to prevent competition from third parties, which may have an adverse impact on our business.

We, independently or together with our licensors, have filed several patent applications covering various aspects of our products or product candidates. We cannot offer any assurances about which, if any, patents will issue, the breadth of any such patent or whether any issued patents will be found invalid and unenforceable or will be threatened by third parties. Any successful opposition to these patents or any other patents owned by or licensed to us after patent issuance could deprive us of rights necessary for the successful commercialization of any product candidates that we may develop. 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.

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

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

Patents have a limited lifespan. In the United States, the natural expiration of a patent is generally 20 years after it is filed. 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 medications.

While patent term extensions under the Hatch-Waxman Act in the United States and under supplementary protection certificates in Europe may be available to extend the patent exclusivity term for Crysvita, Mepsevii, UX007, and DTX301, we cannot provide any assurances that any such patent term extension will be obtained and, if so, for how long. In addition, upon issuance in the United States, any patent term can be adjusted based on certain delays caused by the applicant(s) or the United States Patent and Trademark Office (USPTO). For example, a patent term can be reduced based on certain delays caused by the patent applicant during patent prosecution. If we do not have sufficient patent terms or regulatory exclusivity to protect our products, our business and results of operations will be adversely affected.

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

Changes in either the patent laws or interpretation of the patent laws in the United States and other countries may diminish the value of our patents or narrow the scope of our patent protection. The laws of foreign countries may not protect our rights to the same extent as the laws of the United States. Publications of discoveries in the scientific literature often lag behind the actual discoveries, and patent applications in the United States and other jurisdictions are typically not published until 18 months after filing, or in some cases not at all. We therefore cannot be certain that we or our licensors were the first to make the invention claimed in our owned and licensed patents or pending applications, or that we or our licensor were the first to file for patent protection of such inventions. Assuming the other requirements for patentability are met, in the United States prior to March 15, 2013, the first to make the claimed invention is entitled to the patent, while outside the United States, the first to file a patent application is entitled to the patent. After March 15, 2013, under the Leahy-Smith America Invents Act, or the Leahy-Smith Act, enacted on September 16, 2011, the United States has moved to a first to file system. The Leahy-Smith Act also includes a number of significant changes that affect the way patent applications will be prosecuted and may also affect patent litigation. The effects of these changes are currently unclear as the courts have only begun to address these provisions. In general, 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.

The U.S. Supreme Court has ruled on several patent cases in recent years, either narrowing the scope of protection available in certain circumstances or weakening 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 relate to isolated AAV8 vectors, capsid proteins, or nucleic acids. To the extent that such claims are deemed to be directed to natural products, or to lack an inventive concept above and beyond an isolated natural product, a court may decide the claims are invalid under Myriad. Additionally, there have been recent proposals for additional changes to the patent laws of the United States and other countries that, if adopted, could impact our ability to obtain patent protection for our proprietary technology or our ability to enforce our proprietary technology. Depending on future actions by the U.S. Congress, the U.S. courts, the USPTO and the relevant law-making bodies in other countries, the laws and regulations governing patents could change in unpredictable ways that would weaken our ability to obtain new patents or to enforce our existing patents and patents that we might obtain in the future.

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. We seek to protect our proprietary technology and processes, in part, by entering into

confidentiality agreements with our employees, consultants, scientific advisors, and contractors. We also seek to preserve the integrity and confidentiality of our data and trade secrets by maintaining physical security of our premises and physical and electronic security of our information technology systems. While we have confidence in 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.

Although we expect all of our employees and consultants to assign their inventions to us, and all of our employees, consultants, advisors, and any third parties who have access to our proprietary know-how, information, or technology to enter into confidentiality agreements, we cannot provide any assurances that all such agreements have been duly executed or 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, oppositions, and reexamination proceedings before the USPTO and corresponding foreign patent offices. Numerous U.S. and foreign issued patents and pending patent applications, which are owned by other parties, exist in the fields in which we are developing product candidates. As the biotechnology and pharmaceutical industries expand and more patents are issued, the risk increases that our products or product candidates may be subject to claims of infringement of the patent rights of these other parties.

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

We are aware of three third-party patent families that include issued U.S. patents with claims that, if valid and enforceable, could be construed to cover DTX301, if and when approved, or methods of its manufacture. We are also aware of an additional three third-party patent families that include issued European claims that, if valid and enforceable, could be construed to cover certain methods that may be used in the manufacture of DTX301. In addition, other parties may obtain patents in the future and claim that use of our technologies infringes upon these patents. If any of these patents were held by a court of competent jurisdiction to cover aspects of our formulations, the manufacturing process of our products or any of our product candidates, methods of use, any molecules formed during the manufacturing process or any final product itself, the holders of any such patents may be able to block our ability to commercialize our products or a product candidate unless we obtained a license under the applicable patents, or until such patents expire or are finally determined to be invalid or unenforceable. Such a license may not be available on commercially reasonable terms or at all.

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

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

We currently have rights to the intellectual property, through licenses from third parties and under patents that we own, to develop our product candidates. Because our programs may require the use of proprietary rights held by third parties, the growth of our business will likely depend in part on our ability to acquire, in-license, or use these proprietary rights. For example, our product candidates may require specific formulations to work effectively and efficiently and the rights to these formulations may be held by others. We may be unable to acquire or in-license any compositions, methods of use, processes, or other third-party intellectual property rights from third parties that we

identify as necessary for our product candidates. The licensing and acquisition of third-party intellectual property rights is a competitive area, and a number of more established companies are also pursuing strategies to license or acquire third-party intellectual property rights that we may consider attractive. These established companies may have a competitive advantage over us due to their size, cash resources, and greater clinical development and commercialization capabilities. In addition, companies that perceive us to be a competitor may be unwilling to assign or license rights to us. We also may be unable to license or acquire third-party intellectual property rights on terms that would allow us to make an appropriate return on our investment.

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

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

We may face competition from biosimilars, which may have a material adverse impact on the future commercial prospects of Crysvita, Mepsevii, and DTX301.

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 Crysvita, Mepsevii, and DTX301. In the United States, the Biologics Price Competition and Innovation Act of 2009, or BPCI Act, was included in the Affordable Care Act and created an abbreviated approval pathway for biological products that are demonstrated to be "highly similar," or biosimilar, to or "interchangeable" with an FDA-approved biological product. The BPCI Act prohibits the FDA from approving a biosimilar or interchangeable product that references a brand biological product until 12 years after the licensure of the reference product, but permits submission of an application for a biosimilar or interchangeable product to the FDA four years after the reference product was first licensed. The BPCI Act does not prevent another company from developing a product that is highly similar to the innovative product, generating its own data, and seeking approval. The BPCI Act is complex and is only beginning to be interpreted and implemented by the FDA. Moreover, it is not known whether the BPCI Act will survive in whole or in part if the Affordable Care Act is repealed. As a result, its ultimate impact, implementation, meaning, and long-term existence are subject to uncertainty. Elimination or modification of the BPCI Act, or changes to the FDA's interpretation or implementation of the BPCI Act, could have a material adverse effect on the future commercial prospects for Crysvita, Mepsevii, and DTX301.

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.

Additional competitors could enter the market with generic versions of our small-molecule product candidates, which may result in a material decline in sales of UX007 or future small-molecule product candidates.

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 protect its patents, approval of the ANDA is stayed for 30 months, or as lengthened or shortened by the court.

Accordingly, if UX007 is approved, competitors could file ANDAs for generic versions of UX007, or 505(b)(2) NDAs that reference UX007. If there are patents listed for UX007 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 whether any patents issuing from our pending patent applications will be eligible for listing in the Orange Book, 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 product candidates is dependent on third parties.

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

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

If KHK, the University of Pennsylvania, or any of our future licensing partners fail to appropriately prosecute, maintain, and enforce patent protection for the patents covering any of our product candidates, our ability to develop and commercialize those 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 drug candidates. See “Business—License and Collaboration Agreements” in this Annual Report for a description of our license agreements with KHK, Baylor Research Institute, Saint Louis University, Bayer, REGENXBIO, and the University of Pennsylvania, which include descriptions of the termination provisions of these agreements.

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.

Although we are not currently involved in any intellectual property litigation, we may be involved in lawsuits to protect or enforce our patents or the patents of our licensors, which could be expensive, time consuming, and unsuccessful.

Competitors may infringe our patents or the patents of our licensors. Although we are not currently involved in any intellectual property litigation, if we or one of our licensing partners were to initiate legal proceedings against a third party to enforce a patent covering our products or one of our product candidates, the defendant could counterclaim that the patent covering our product or product candidate is invalid and/or unenforceable. In patent litigation in the United States, defendant counterclaims alleging invalidity and/or unenforceability are commonplace. Grounds for a validity challenge could be an alleged failure to meet any of several statutory requirements, including lack of novelty, obviousness, or non-enablement. Grounds for an unenforceability assertion could be an allegation that someone connected with prosecution of the patent withheld relevant information from the USPTO, or made a misleading statement, during prosecution. The outcome following legal assertions of invalidity and unenforceability is unpredictable.

Interference proceedings or derivation proceedings now available under the Leahy-Smith Act provoked by third parties or brought by us or declared or instituted by the USPTO may be necessary to determine the priority of inventions with respect to our patents or patent applications or those of our licensors. An unfavorable outcome could require us to cease using the related technology or to attempt to license rights to it from the prevailing party. Our business could be harmed if the prevailing party does not offer us a license on commercially reasonable terms. In addition, the validity of our patents could be challenged in the USPTO by one of the new post grant proceedings (i.e., inter partes review or post grant review) now available under the Leahy-Smith Act. Our defense of litigation, interference proceedings, or post grant proceedings under the Leahy-Smith Act may fail and, even if successful, may result in substantial costs and distract our management and other employees. In addition, the uncertainties associated with litigation could have a material adverse effect on our ability to raise sufficient capital to continue our clinical studies, continue our research programs, license necessary technology from third parties, or enter into development partnerships that would help us bring our product candidates to market.

Furthermore, 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 this type of litigation. There could also be public announcements of the results of hearings, motions, or other interim proceedings or developments. 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. Although we try to ensure that our employees, consultants, and independent contractors do not use the proprietary information or know-how of others in their work for us, and we are not currently subject to any claims that our employees, consultants, or independent contractors have wrongfully used or disclosed confidential information of third parties, we may in the future be subject to such claims. Litigation may be necessary to defend against these claims. 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.

We may be subject to claims challenging the inventorship of our patents and other intellectual property.

Although we are not currently experiencing any claims challenging the inventorship of our patents or ownership of our intellectual property, we may in the future be subject to claims that former employees, collaborators, or other third parties have an interest in our patents or other intellectual property as an inventor or co-inventor. For example, we may have inventorship 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. If we fail to successfully defend against such 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. Such an outcome could have a material adverse effect on our business. Even if we are successful in defending against such claims, litigation could result in substantial costs and distract management and other employees.

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

As is the case with other biotechnology and pharmaceutical companies, our success is heavily dependent on intellectual property, particularly patents. Obtaining and enforcing patents in the biotechnology and pharmaceutical

industries involves both technological and legal complexity. Therefore, obtaining and enforcing such patents is costly, time consuming, and inherently uncertain. In addition, the United States has recently enacted and is currently implementing wide-ranging patent reform legislation. Recent U.S. Supreme Court rulings have narrowed the scope of patent protection available in certain circumstances and weakened the rights of patent owners in certain situations. In addition to increasing uncertainty about our ability to obtain patents in the future, this combination of events has created uncertainty with respect to the value of patents, once obtained. Depending on future actions by the U.S. Congress, the federal courts, and the USPTO, the laws and regulations governing patents could change in unpredictable ways that would weaken our ability to obtain new patents or to enforce our existing patents and patents that we might obtain in the future.

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

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

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

Risks Related to Our Business Operations

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. We may not be able to attract and retain personnel on acceptable terms given the competition among numerous pharmaceutical and biotechnology companies for individuals with similar skill sets. In addition, failure to succeed in preclinical or clinical studies may make it more challenging to recruit and retain qualified personnel. The inability to recruit and retain qualified personnel, or the loss of the services of Dr. Kakkis, may impede the progress of our research, development, and commercialization objectives.

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

Our business strategy focuses on the development of drugs that are eligible for FDA and EU orphan drug designation. In the United States, orphan drug designation entitles a party to financial incentives such as opportunities for grant funding towards clinical study costs, tax advantages, and user-fee waivers. In addition, if a product receives the first FDA approval for the indication for which it has orphan designation, the product is entitled to orphan drug exclusivity, which means the FDA may not approve any other application to market the same drug for the same indication for a

period of seven years, except in limited circumstances, such as a showing of clinical superiority over the product with orphan exclusivity or where the manufacturer is unable to assure sufficient product quantity. In the EU, orphan drug designation entitles a party to financial incentives such as reduction of fees or fee waivers and ten years of market exclusivity following drug or biological product approval. This period may be reduced to six years if the orphan drug designation criteria are no longer met, including where it is shown that the product is sufficiently profitable not to justify maintenance of market exclusivity.

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

Even though we have orphan drug designation for UX007 for the treatment of fatty acid oxidation disorders in the United States and for various subtypes of FAOD in Europe, as well as for UX007 for the treatment of Glut1 DS, Crysvita, Mepsevii, and DTX301 in the United States and Europe, we may not be the first to obtain marketing approval for any particular orphan indication due to the uncertainties associated with developing pharmaceutical products. Further, even if we obtain orphan drug exclusivity for a product, that exclusivity may not effectively protect the product from competition because different drugs with different active moieties can be approved for the same condition or the same drug can be approved for a different indication unless there are other exclusivities such as new chemical entity exclusivity preventing such approval. Even after an orphan drug is approved, the FDA or EMA can subsequently approve the same drug with the same active moiety for the same condition if the FDA or EMA concludes that the later drug is safer, more effective, or makes a major contribution to patient care. Orphan drug designation neither shortens the development time or regulatory review time of a drug nor gives the drug any advantage in the regulatory review or approval process.

We will need to expand our organization and we may experience difficulties in managing this growth, which could disrupt our operations.

As our development and commercialization plans and strategies develop, we expect to need additional managerial, operational, field forces, marketing, financial, legal, and other resources. 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.

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

As a result of the accounting for our acquisition of Dimension Therapeutics, Inc. (Dimension) in November 2017, we have recorded on our balance sheet intangible assets for in-process research and development (“IPR&D”) and an acquired contract asset. We test the intangible assets for impairment annually during the fourth quarter and more frequently if events or changes in circumstances indicate that it is more likely than not that the asset is impaired. If the associated research and development effort is abandoned, the related assets will be written-off and we will record a noncash impairment loss on our statement of operations. We have not recorded any impairments since inception.

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

Although a substantial amount of our effort will focus on the continued clinical testing, potential approval, and commercialization of our existing product candidates, the success of our business also depends upon our ability to identify, license, discover, develop, or commercialize additional 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.

If we are unable to maintain and further develop 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. We are also subject to the compliance requirements of Section 404(b) of the Sarbanes-Oxley Act, which results in us incurring substantial expenses and expending significant management efforts. We currently do not have an internal audit group. We may need to hire additional accounting and financial staff with appropriate public company experience and technical accounting knowledge. If we are not able to comply with the requirements of Section 404(b) or if we or our independent registered public accounting firm identify deficiencies in our internal controls over financial reporting that are deemed to be material weaknesses, 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.

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

United States

In the United States, 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. For example, the Affordable Care Act, as amended, substantially changed the way health care is financed by both governmental and private insurers, and significantly impacts the U.S. pharmaceutical industry. The Affordable Care Act, among other things, subjects biologic products to potential competition by lower-cost biosimilars, addresses a new methodology by which rebates owed by manufacturers under the Medicaid Drug Rebate Program are calculated for drugs that are inhaled, infused, instilled, implanted, or injected, increases the minimum Medicaid rebates owed by manufacturers under the Medicaid Drug Rebate Program and extends the rebate program to individuals enrolled in Medicaid managed care organizations, and establishes annual fees and taxes on manufacturers of certain branded prescription drugs. Implementation of the Affordable Care Act remains ongoing, and there remains uncertainty as to how the law’s various provisions will ultimately affect the industry and whether the law will remain in place.

Other legislative changes have been adopted in the United States, including the Cures Act and the Budget Control Act of 2011, or the Budget Act, signed into law on August 2, 2011. The Cures Act introduces a wide range of reforms and the Budget Act, among other things, required reductions in federal spending, which eventually triggered Medicare sequestration—the requirement to reduce Medicare payments to providers up to 2% per fiscal year. In 2013, the 2% Medicare payment reductions were applied to fee-for-service claims with dates of service or dates of discharge on or after April 1, 2013. Sequestration was initially set to expire in fiscal year 2021 but has been extended to 2025.

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.

European Union

In the EU, the European Commission has adopted detailed rules for the safety features appearing on the packaging of medicinal products for human use. The regulations set forth the rules for the features appearing on the packaging of these medicinal products, including, inter alia, the characteristics and technical specifications of the unique identifier that enables the authenticity of medicinal products to be verified and individual packs to be identified, the modalities for the verification of the safety features, and the list of medicinal products and product categories subject and not subject to prescription which shall not bear and bear (respectively) safety features.

The European Commission has also launched a series of public consultations that are aimed at the adoption of notices and guidelines which will serve the interpretation of currently applicable regulations and directives. For example, between August 2015 and December 2016, the European Commission launched public consultations which concerned good manufacturing practices, clinical trials for human medicinal products, and orphan medicinal products. The purpose of the consultation on orphan medicinal products (which will be replaced with a Notice) is to streamline the regulatory framework and to adapt the applicable regulations to technical progress. The consultation focuses on a variety of elements of Regulation (EC) No 141/2000, which include the encouragement of development of orphan medicinal products for communicable diseases and the simplification of the procedure for the reassessment of orphan criteria when two authorization application procedures are pending in parallel for two orphan medicinal products.

We may be subject, directly or indirectly, to federal and state healthcare fraud and abuse laws, false claims laws, and health information privacy and security laws. If we are unable to comply, or have not fully complied, with such laws, we could face substantial penalties.

If we obtain FDA approval for any of our product candidates and begin commercializing those products in the United States, our operations may be directly, or 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. These laws may impact, among other things, our proposed field marketing and education programs. In addition, we may be subject to patient privacy regulation by both the federal government and the states in which we conduct our business. The laws that may affect our ability to operate are described under "Business—Government Regulation" in this 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. 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, and the curtailment or restructuring of our operations, any of which could adversely affect our ability to operate our business and our results of operations.

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

We currently have limited international operations, but our business strategy incorporates significant international expansion, particularly in anticipation of approval of our product candidates. We currently conduct physician and patient association outreach activities, as well as clinical studies, outside of the United States and plan to maintain field forces representatives internationally in the future. Doing business internationally involves a number of risks, including but not limited to:

- multiple, conflicting, and changing laws and regulations such as privacy and data regulations, transparency regulations, tax laws, export and import restrictions, employment laws, regulatory requirements, and other governmental approvals, permits, and licenses;
- introduction of new health authority requirements and/or changes in health authority expectations;
- failure by us to obtain and maintain regulatory approvals for the use of our products in various countries;
- additional potentially relevant third-party patent rights;
- complexities and difficulties in obtaining protection for, and enforcing, our intellectual property;
- difficulties in staffing and managing foreign operations;
- complexities associated with managing multiple payor reimbursement regimes, government payors, or patient self-pay systems;
- limits in 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, outbreak of disease, boycotts, curtailment of trade, 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.

We may incur additional tax liabilities related to our operations.

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

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

Our business is subject to regulation by various federal, state, local and foreign governmental agencies, including agencies responsible for monitoring and enforcing employment and labor laws, workplace safety, and tax laws and regulations. In certain jurisdictions, these regulatory requirements may be more stringent than those in the United States, and in other circumstances these requirements may be more stringent in the United States. Noncompliance with applicable regulations or requirements could subject us to investigations, sanctions, mandatory recalls, enforcement actions, disgorgement of profits, fines, damages, civil and criminal penalties, or injunctions. 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. Enforcement actions and sanctions could further harm our business, operating results, financial condition, and our reputation.

In particular, our research and development activities 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.

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

We are in the process of implementing a company-wide ERP system to upgrade certain existing business, operational, and financial processes. Our ERP implementation is a complex and time-consuming project that we expect will

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

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

Despite the implementation of security measures, our internal computer systems, and those of our CROs and other third parties on which we rely, are vulnerable to damage from computer viruses, unauthorized access, cyber-attacks, natural disasters, fire, terrorism, war, and telecommunication and electrical failures. If such an event were to occur and interrupt our operations, it could result in a material disruption of our drug development programs. For example, the loss of clinical trial data from ongoing or planned clinical trials could result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce the data. To the extent that any disruption or security breach results in a loss of or damage to our data or applications, loss of trade secrets or inappropriate disclosure of confidential or proprietary information, including protected health information or personal data of employees or former employees, access to our clinical data, or disruption of the manufacturing process, we could incur liability and the further development of our drug candidates could be delayed. We may also be vulnerable to cyber-attacks by hackers or other malfeasance. This type of breach of our cybersecurity may compromise our confidential information and/or our financial information and adversely affect our business or result in legal proceedings.

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

Our corporate headquarters and one of our laboratories are located in the San Francisco Bay Area, and our collaboration partner for Crysvita, KHK, is located in Japan, which have both in the past experienced severe earthquakes and other natural disasters. We do not carry earthquake insurance. Earthquakes or other natural disasters could severely disrupt our operations or those of our collaborators, and have a material adverse effect on our business, results of operations, financial condition, and prospects. If a natural disaster, power outage, or other event occurred that prevented us from using all or a significant portion of our headquarters, that damaged critical infrastructure (such as the manufacturing facilities of our third-party contract manufacturers) or that otherwise disrupted operations, it may be difficult or, in certain cases, impossible for us to continue our business for a substantial period of time. The disaster recovery and business continuity plans we have in place currently are limited and are unlikely to prove adequate 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 other companies or products or engage in strategic transactions, which could divert our management’s attention and cause us to incur various costs and expenses.

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. 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 entering into an agreement for such transactions.

In addition, we may receive inquiries relating to potential strategic transactions, including collaborations, licenses, and acquisitions. Such potential transactions may divert the attention of management and may cause us to incur various costs and expenses in investigating and evaluating such transactions, whether or not they are consummated.

Litigation may substantially increase our costs and harm our business.

We may become party to lawsuits in the future, including, without limitation, actions and proceedings in the ordinary course of business relating to our stockholders, intellectual property, and employment matters, which will cause us to

incur legal fees and other costs related thereto, including potential expenses for the reimbursement of legal fees of officers and directors under indemnification obligations. The expense of defending against such litigation may be significant and there can be no assurance that we will be successful in any defense. Further, the amount of time that may be required to resolve such lawsuits is unpredictable, and these actions may divert management's attention from the day-to-day operations of our business, which could adversely affect our business, results of operations, and cash flows. Litigation is subject to inherent uncertainties, and an adverse result in such matters that may arise from time to time could have a material adverse effect on our business, results of operations, and financial condition.

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 product candidates in countries where they have the right to commercialize the product candidates;
- decisions by our collaboration partners regarding market access and pricing in countries where they have the right to commercialize our product candidates;
- failure to successfully develop and commercialize our product candidates;
- the level of any revenue we receive 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;
- failure to meet or exceed financial projections we may provide to the public;
- failure to meet or exceed the financial projections of the investment community;
- the perception of the pharmaceutical industry 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 acquire;
- disputes or other developments relating to proprietary rights, including patents, litigation matters, and our ability to obtain patent protection for our technologies;
- additions or departures of key scientific or management personnel;
- significant lawsuits, including patent or stockholder litigation;
- securities or industry analysts' reports regarding our stock, or their failure to issue such reports;
- changes in the market valuations of similar companies;
- general market or macroeconomic conditions;
- 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.

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Pursuant to our 2014 Incentive Plan, or the 2014 Plan, our management is authorized to grant stock options and other equity-based awards to our employees, directors, and consultants. At March 31, 2018, 1,828,073 shares were available for future grants under the 2014 Plan. The number of shares available for future grant under the 2014 Plan will automatically increase on January 1 of each year by the lesser of 2,500,000 shares or 4% of all shares of our capital stock outstanding as of December 31 of the prior calendar year, subject to the ability of our compensation committee to take action to reduce the size of the increase in any given year.

Pursuant to our 2014 Employee Stock Purchase Plan, or 2014 ESPP, eligible employees can acquire shares of our common stock at a discount to the prevailing market price. At March 31, 2018, 2,292,906 shares were available for issuance under the 2014 ESPP. 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.

Currently we plan to register the increased number of shares available under the 2014 Plan and the 2014 ESPP each year. If our board of directors elects to increase the number of shares available for future grant under the 2014 Plan or the 2014 ESPP, our stockholders may experience additional dilution, which could cause our stock price to fall.

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 and do not expect to become profitable in the near future nor may we ever achieve profitability. To the extent that we continue to generate taxable losses, unused taxable losses will, subject to certain limitations, carry forward to offset future taxable income, if any, until such unused losses expire. Under Sections 382 and 383 of the Internal Revenue Code of 1986, as amended, or the IRC, if a corporation undergoes an “ownership change,” generally defined as a greater than 50% change (by value) in its equity ownership over a three-year period, the corporation’s ability to use its pre-change net operating loss carryforwards, or NOL carryforwards, and other pre-change tax attributes (such as research tax credits) to offset its post-change income may be limited. An analysis to determine limitations upon our NOL carryforwards and other pre-change tax attributes for ownership changes that have occurred previously has been performed, resulting in a permanent decrease of federal and state NOL carryforwards in the amount of $7.2 million and a permanent decrease in federal research tax credit carryforwards in the amount of $0.2 million. As a result of these decreases and others that may occur as a result of future ownership changes, our ability to use our pre-change NOL carryforwards and other tax attribute carryforwards to offset U.S. federal taxable income and tax liabilities is limited and may become subject to even greater limitations, which could potentially accelerate or permanently increase future federal tax liabilities for us. In addition, there may be periods during which the use of state income tax NOL carryforwards and other state tax attribute carryforwards (such as state research tax credits) are suspended or otherwise limited, which could potentially accelerate or permanently increase future state tax liabilities for us.

The recently enacted comprehensive tax reform legislation could adversely affect our business and financial condition.

On December 22, 2017, the U.S. government enacted comprehensive tax legislation commonly referred to as the Tax Cuts and Jobs Act (Tax Act). The Tax Act makes broad and complex changes to the U.S. tax code, including, but not limited to, (1) reducing the U.S. federal corporate tax rate from 35% to 21%; (2) requiring companies to pay a one-time transition tax on certain unrepatriated earnings of foreign subsidiaries; (3) generally eliminating U.S. federal income taxes on dividends from foreign subsidiaries; (4) requiring a current inclusion in U.S. federal taxable income of certain earnings of controlled foreign corporations; (5) eliminating the corporate alternative minimum tax (AMT) and changing how existing AMT credits can be realized; (6) creating the base erosion anti-abuse tax (BEAT), a new minimum tax; (7) creating a new limitation on deductible interest expense; and (8) changing rules related to uses and limitations of net operating loss carryforwards created in tax years beginning after December 31, 2017. Notwithstanding the reduction in the corporate income tax rate, the overall impact of the new federal tax law is uncertain and our business and financial condition could be adversely affected. In addition, it is uncertain if and to

what extent various states will conform to the newly enacted federal tax law. The determination of the benefit from (provision for) income taxes requires complex estimations, significant judgments and significant knowledge and experience concerning the applicable tax laws. Given that we are still in the transition period for the accounting for income tax effects of the Tax Act, the current assessment on deferred tax assets (liabilities) is based on the currently available information and guidance. If in the future any element of the tax reform changes the related accounting guidance for income tax, it could affect our income tax position and we may need to adjust the benefit from (provision for) income taxes accordingly.

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.

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

None.

Item 3. Defaults Upon Senior Securities

None.

Item 4. Mine Safety Disclosures

Not applicable.

Item 5. Other Information

None.

Item 6. Exhibits

Exhibit Number	Exhibit Description	Incorporated by Reference			Furnished or Filed Herewith
		Form	Date	Number	
3.1	Amended and Restated Certificate of Incorporation	8-K	2/5/2014	3.1	
3.2	Amended and Restated Bylaws	8-K	2/5/2014	3.2	
10.1§	Amendment No. 4 to Collaboration and License Agreement, effective as of January 29, 2018, between Ultragenyx Pharmaceutical Inc. and Kyowa Hakko Kirin Co., Ltd.	10-K	2/21/2018	10.5	
10.2§	Commercial Supply and Services Agreement – Drug Substance, effective December 7, 2017, between Ultragenyx Europe Gmbh and Rentschler Biopharma SE	10-K	2/21/2018	10.18	
10.3§	Commercial Supply and Services Agreement – Drug Product, effective January 31, 2018, between Ultragenyx Europe Gmbh and Rentschler Biopharma SE	10-K	2/21/2018	10.19	
10.4#	Offer Letter, dated as of January 15, 2018, between Ultragenyx Pharmaceutical Inc. and Camille Bedrosian, M.D.	10-K	2/21/2018	10.46	
10.5	Lease Agreement, by and between Dimension Therapeutics, Inc. and ARE-MA Region No. 20, LLC, dated November 2, 2015, and Consent to Assignment to Ultragenyx Pharmaceutical Inc.	10-K	2/21/2018	10.66	
10.6	First Amendment to Lease Agreement, dated March 20, 2018, between ARE-MA Region No. 20, LLC and Ultragenyx Pharmaceutical Inc.				X
10.7	Underwriting Agreement, dated as of January 23, 2018, among Ultragenyx Pharmaceutical Inc. and J.P. Morgan Securities LLC, Merrill Lynch, Pierce, Fenner & Smith Incorporated, Goldman Sachs & Co. LLC, and Cowen and Company, LLC	8-K	1/26/2018	1.1	
10.8	Amendment No. 1 to Sales Agreement, dated as of March 30, 2018, between Ultragenyx Pharmaceutical Inc. and Cowen and Company, LLC	8-K	3/30/2018	1.1	
31.1	Certification of Principal Executive Officer Required Under Rule 13a-14(a) or Rule 15d-14(a) of the Exchange Act				X
31.2	Certification of Principal Financial Officer Required Under Rule 13a-14(a) or Rule 15d-14(a) of the Exchange Act				X
32.1*	Certification of Principal Executive Officer and Principal Financial Officer Required Under Rule 13a-14(b) or Rule 15d-14(b) of the Exchange Act and 18 U.S.C. 1350				X
101.INS	XBRL Instance Document				X
101.SCH	XBRL Taxonomy Extension Schema Document				X
101.CAL	XBRL Taxonomy Extension Calculation Linkbase Document				X
101.DEF	XBRL Taxonomy Extension Definition Linkbase Document				X
101.LAB	XBRL Taxonomy Extension Labels Linkbase Document				X

101.PRE	XBRL Taxonomy Extension Presentation Linkbase Document	X

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

#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: May 7, 2018 By: /s/ Emil D. Kakkis
Emil D. Kakkis, M.D., Ph.D.
President and Chief Executive Officer

(Duly Authorized Officer)

Date: May 7, 2018 By: /s/ Shalini Sharp
Shalini Sharp
Executive Vice President and Chief Financial Officer

(Principal Financial Officer)

Date: May 7, 2018 By: /s/ Theodore A. Huizenga
Theodore A. Huizenga
Vice President and Corporate Controller

(Principal Accounting Officer)