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UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 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, 2022

OR

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

For the transition period from_____ to
Commission file number: 001-36167

Karyopharm Therapeutics Inc.
(Exact name of registrant as specified in its charter)

Delaware	**26-3931704**
(State or other jurisdiction of incorporation or organization)	**(I.R.S. Employer Identification Number)**
85 Wells Avenue, 2nd Floor **Newton, MA**	**02459**
(Address of principal executive offices)	**(Zip Code)**

(617) 658-0600
(Registrant's telephone number, including area code)

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

Title of each class	**Trading Symbol(s)**	**Name of each exchange on which registered**
Common Stock, $0.0001 par value	KPTI	Nasdaq Global Select Market

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

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

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

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

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

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

As of April 29, 2022, there were 79,418,349 shares of Common Stock, $0.0001 par value per share, outstanding.

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PART I - FINANCIAL INFORMATION

Item 1. Condensed Consolidated Financial Statements (Unaudited).

KARYOPHARM THERAPEUTICS INC.
CONDENSED CONSOLIDATED BALANCE SHEETS
(unaudited)
(in thousands, except per share amounts)

	March 31, 2022	December 31, 2021
Assets		
Current assets:		
Cash and cash equivalents	$ 153,256	$ 190,459
Short-term investments	52,055	38,156
Accounts receivable, net	24,992	22,497
Inventory	3,874	4,106
Prepaid expenses	12,207	12,511
Other current assets	29,135	1,528
Restricted cash	1,014	6,349
Total current assets	276,533	275,606
Property and equipment, net	1,544	1,642
Operating lease right-of-use assets	7,518	7,915
Other assets	7,802	19,505
Restricted cash	636	637
Total assets	$ 294,033	$ 305,305
Liabilities and stockholders' (deficit) equity		
Current liabilities:		
Accounts payable	$ 3,440	$ 1,603
Accrued expenses	58,371	69,121
Operating lease liabilities	2,463	2,316
Other current liabilities	2,063	678
Total current liabilities	66,337	73,718
Convertible senior notes	169,491	169,293
Deferred royalty obligation	132,998	132,998
Operating lease liabilities, net of current portion	8,286	8,969
Total liabilities	377,112	384,978
Stockholders' (deficit) equity:		
Preferred stock, $0.0001 par value; 5,000 shares authorized; none issued and outstanding	—	—
Common stock, $0.0001 par value; 200,000 shares authorized; 79,419 and 75,746 shares issued and outstanding at March 31, 2022 and December 31, 2021, respectively	8	8
Additional paid-in capital	1,136,873	1,098,776
Accumulated other comprehensive income	87	191
Accumulated deficit	(1,220,047)	(1,178,648)
Total stockholders' deficit	(83,079)	(79,673)
Total liabilities and stockholders' (deficit) equity	$ 294,033	$ 305,305

See accompanying notes to condensed consolidated financial statements.

KARYOPHARM THERAPEUTICS INC.
CONDENSED CONSOLIDATED STATEMENTS OF OPERATIONS
(unaudited)
(in thousands, except per share amounts)

	Three Months Ended March 31,	
	2022	2021
Revenues:		
Product revenue, net	$ 28,300	$ 21,731
License and other revenue	19,370	1,529
Total revenues	47,670	23,260
Operating expenses:		
Cost of sales	1,426	933
Research and development	42,062	37,050
Selling, general and administrative	38,768	37,650
Total operating expenses	82,256	75,633
Loss from operations	(34,586)	(52,373)
Other income (expense):		
Interest income	74	264
Interest expense	(6,684)	(5,095)
Other expense, net	(73)	(61)
Total other expense, net	(6,683)	(4,892)
Loss before income taxes	(41,269)	(57,265)
Income tax provision	(130)	(149)
Net loss	$ (41,399)	$ (57,414)
Net loss per share—basic and diluted	$ (0.53)	$ (0.77)
Weighted-average number of common shares outstanding used to compute net loss per share—basic and diluted	77,570	74,517

See accompanying notes to condensed consolidated financial statements.

KARYOPHARM THERAPEUTICS INC.
CONDENSED CONSOLIDATED STATEMENTS OF COMPREHENSIVE LOSS
(unaudited)
(in thousands)

	Three Months Ended March 31,	
	2022	2021
Net loss	$ (41,399)	$ (57,414)
Other comprehensive loss		
Unrealized loss on investments	(14)	(132)
Foreign currency translation adjustment	(90)	(85)
Comprehensive loss	$ (41,503)	$ (57,631)

See accompanying notes to condensed consolidated financial statements.

KARYOPHARM THERAPEUTICS INC.
CONDENSED CONSOLIDATED STATEMENTS OF CASH FLOWS
(unaudited)
(in thousands)

	Three Months Ended March 31,	
	2022	**2021**
Operating activities		
Net loss	$ (41,399)	$ (57,414)
Adjustments to reconcile net loss to net cash used in operating activities:		
Depreciation and amortization	177	235
Net amortization of premiums and discounts on investments	45	664
Amortization of debt issuance costs	198	191
Stock-based compensation expense	7,336	7,359
Realized and unrealized gains on marketable equity securities	(2)	(14)
Inventory obsolescence charge	—	82
Changes in operating assets and liabilities:		
Accounts receivable, net	(2,495)	(4,962)
Inventory	232	(552)
Prepaid expenses and other current assets	(27,303)	(89)
Operating lease right-of-use assets	397	343
Other noncurrent assets	11,703	—
Accounts payable	1,837	(1,410)
Accrued expenses and other liabilities	(9,387)	3,432
Deferred revenue	—	(297)
Operating lease liabilities	(536)	(456)
Net cash used in operating activities	(59,197)	(52,888)
Investing activities		
Purchases of property and equipment	(79)	—
Proceeds from sales and maturities of investments	21,584	68,950
Purchases of investments	(35,540)	(25,764)
Net cash (used in) provided by investing activities	(14,035)	43,186
Financing activities		
Proceeds from issuance of common stock, net of issuance costs	29,316	9,903
Proceeds from the exercise of stock options and shares issued under employee stock purchase plan	1,467	773
Net cash provided by financing activities	30,783	10,676
Effect of exchange rate on cash, cash equivalents and restricted cash	(90)	(91)
Net (decrease) increase in cash, cash equivalents and restricted cash	(42,539)	883
Cash, cash equivalents and restricted cash at beginning of period	197,445	89,121
Cash, cash equivalents and restricted cash at end of period	$ 154,906	$ 90,004
Reconciliation of cash, cash equivalents and restricted cash reported within the condensed consolidated balance sheets		
Cash and cash equivalents	$ 153,256	$ 88,471
Short-term restricted cash	1,014	815
Long-term restricted cash	636	718
Total cash, cash equivalents and restricted cash	$ 154,906	$ 90,004
Supplemental disclosures:		
Deferred financing costs in accrued expenses	$ 22	$ —
Cash paid for amounts included in the measurement of operating lease liabilities	$ 841	$ 815
Cash paid for interest on deferred royalty obligation	$ 15,784	$ 2,457

See accompanying notes to condensed consolidated financial statements.

KARYOPHARM THERAPEUTICS INC.
CONDENSED CONSOLIDATED STATEMENTS OF STOCKHOLDERS' (DEFICIT) EQUITY
(unaudited)
(in thousands)

	Common Shares		Additional Paid-In Capital	Accumulated Other Comprehensive Income	Accumulated Deficit	Total Stockholders' (Deficit) Equity
	Shares	Amount				
Balance at December 31, 2021	75,746	$ 8	$ 1,098,776	$ 191	$ (1,178,648)	$ (79,673)
Vesting of restricted stock	565	—	—	—	—	—
Exercise of stock options and shares issued under the employee stock purchase plan	167	—	1,467	—	—	1,467
Stock-based compensation expense	—	—	7,336	—	—	7,336
Issuance of common stock, net of issuance costs	2,941	—	29,294	—	—	29,294
Unrealized loss on investments	—	—	—	(14)	—	(14)
Foreign currency cumulative translation adjustment	—	—	—	(90)	—	(90)
Net loss	—	—	—	—	(41,399)	(41,399)
Balance at March 31, 2022	79,419	$ 8	$ 1,136,873	$ 87	$ (1,220,047)	$ (83,079)
Balance at December 31, 2020	73,923	$ 7	$ 1,119,632	$ 518	$ (1,069,611)	$ 50,546
Vesting of restricted stock	409	—	—	—	—	—
Exercise of stock options and shares issued under the employee stock purchase plan	92	—	773	—	—	773
Stock-based compensation expense	—	—	7,359	—	—	7,359
Issuance of common stock, net of issuance costs	638	1	9,902	—	—	9,903
Cumulative effect adjustment for adoption of new accounting guidance	—	—	(65,641)	—	15,051	(50,590)
Unrealized loss on investments	—	—	—	(132)	—	(132)
Foreign currency translation adjustment	—	—	—	(85)	—	(85)
Net loss	—	—	—	—	(57,414)	(57,414)
Balance at March 31, 2021	75,062	$ 8	$ 1,072,025	$ 301	$ (1,111,974)	$ (39,640)

See accompanying notes to condensed consolidated financial statements.

KARYOPHARM THERAPEUTICS INC.
NOTES TO CONDENSED CONSOLIDATED FINANCIAL STATEMENTS

1. Nature of Business and Basis of Presentation

Nature of Business

Karyopharm Therapeutics Inc., a Delaware corporation (collectively with its subsidiaries, the "Company," "we," "us," or "our"), is a commercial-stage pharmaceutical company pioneering novel cancer therapies and dedicated to the discovery, development and commercialization of first-in-class drugs directed against nuclear export for the treatment of cancer and other diseases. We were incorporated in Delaware on December 22, 2008 and have a principal place of business in Newton, Massachusetts.

Our scientific expertise is based upon an understanding of the regulation of intracellular communication between the nucleus and the cytoplasm. Our **S**elective **I**nhibitor of **N**uclear **E**xport ("SINE") compounds function by binding with and inhibiting the nuclear export protein exportin 1 ("XPO1"). Our primary focus is on marketing XPOVIO® (selinexor) in its currently approved indications as well as developing and seeking the regulatory approval of selinexor as an oral agent in multiple myeloma, endometrial cancer, and myelofibrosis, eltanexor in myelodysplastic syndromes and selinexor and eltanexor in additional cancer indications with significant unmet medical need. Our lead asset, XPOVIO, received its initial U.S. approval from the U.S. Food and Drug Administration ("FDA") in July 2019 and is currently approved and marketed for the following indications: (i) in combination with bortezomib and dexamethasone for the treatment of adult patients with multiple myeloma who have received at least one prior therapy; (ii) in combination with dexamethasone for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least four prior therapies and whose disease is refractory to at least two proteasome inhibitors, at least two immunomodulatory agents, and an anti-CD38 monoclonal antibody; and (iii) for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma ("DLBCL"), not otherwise specified, including DLBCL arising from follicular lymphoma, after at least two lines of systemic therapy. In addition, in March 2021 and May 2021, the European Commission and the United Kingdom's Medicines & Healthcare Products Regulatory Agency granted conditional approval, respectively, of NEXPOVIO® (selinexor), the brand name for selinexor in Europe and the United Kingdom, in combination with dexamethasone, to treat adult patients with multiple myeloma who have received at least four prior therapies and whose disease is refractory to at least two proteasome inhibitors, two immunomodulatory agents, and an anti-CD38 monoclonal antibody, and who have demonstrated disease progression on the last therapy. XPOVIO has also received regulatory approval in various indications in Australia, Singapore, Mainland China, South Korea and Israel.

Basis of Presentation

The accompanying unaudited condensed consolidated financial statements of the Company have been prepared in accordance with accounting principles generally accepted in the United States of America ("GAAP") for interim financial reporting and as required by Regulation S-X, Rule 10-01. Accordingly, they do not include all of the information and footnotes required by GAAP for complete financial statements. In the opinion of management, all adjustments (including those which are normal and recurring) considered necessary for a fair presentation of the interim financial information have been included. When preparing financial statements in conformity with GAAP, we must make estimates and assumptions that affect the reported amounts of assets, liabilities, revenues, expenses and related disclosures at the date of the financial statements. Actual results could differ from those estimates. Additionally, operating results for the three months ended March 31, 2022 are not necessarily indicative of the results that may be expected for any other interim period or for the fiscal year ending December 31, 2022. For further information, refer to the financial statements and footnotes included in our Annual Report on Form 10-K for the year ended December 31, 2021 as filed with the Securities and Exchange Commission ("SEC") on March 1, 2022 ("Annual Report").

Basis of Consolidation

The condensed consolidated financial statements at March 31, 2022 include the accounts of Karyopharm Therapeutics Inc. and its wholly-owned subsidiaries. All intercompany balances and transactions have been eliminated in consolidation.

The significant accounting policies used in preparation of these condensed consolidated financial statements in this Form 10-Q are consistent with those discussed in Note 2, "*Summary of Significant Accounting Policies*," in our Annual Report.

2. Product Revenue

To date, our only source of product revenue has been from the U.S. sales of XPOVIO. Net product revenue, including provisions primarily consisting of distribution fees and cash discounts, as well as reserves for chargebacks, rebates and returns, were as follows (in thousands):

	For the Three Months Ended March 31,	
	2022	2021
Gross product revenue	$ 34,910	$ 27,544
Provisions for product revenue	(6,610)	(5,813)
Total product revenue, net	$ 28,300	$ 21,731

As of March 31, 2022 and December 31, 2021, net product revenue of $21.6 million and $20.0 million, respectively, were included in accounts receivable. To date, we have had no bad debt write-offs and we do not currently have credit issues with any customers. There were no credit losses associated with our accounts receivables as of March 31, 2022 and December 31, 2021.

3. Inventory

The following table presents our inventory of XPOVIO (in thousands):

	March 31, 2022	December 31, 2021
Raw materials	$ 2,563	$ 1,797
Work in process	926	1,895
Finished goods	385	414
Total inventory	$ 3,874	$ 4,106

As of March 31, 2022 and December 31, 2021, all of our inventory was related to XPOVIO, which was initially approved by the FDA in July 2019 and at which time we began to capitalize costs to manufacture XPOVIO. Prior to FDA approval of XPOVIO, all costs related to the manufacturing of XPOVIO and related material were charged to research and development expense in the period incurred.

4. License and Asset Purchase Agreements

In prior periods, we entered into out-licensing and asset purchase agreements with Berlin-Chemie AG, an affiliate of the Menarini Group ("Menarini"), Anivive Lifesciences, Inc. ("Anivive"), Biogen MA Inc. ("Biogen"), Antengene Therapeutics Limited ("Antengene"), and FORUS Therapeutics Inc. ("FORUS"), all of which are accounted for within the scope of Accounting Standards Codification 606, *Revenue from Contracts with Customers* ("ASC 606"). For further details on the terms and accounting treatment considerations for these contracts, please refer to Note 10, "*License and Asset Purchase Agreements*," to our consolidated financial statements contained in Item 8 of our Annual Report.

During the three months ended March 31, 2022, we recognized $8.6 million in milestone-related revenue from our partners and $7.1 million related to reimbursement of development related expenses from Menarini. With respect to the $8.6 million in milestone-related revenue, we recognized $7.8 million, net of tax, pursuant to our license agreement with Antengene and $0.8 million pursuant to our distribution agreement with Promedico Ltd. during the three months ended March 31, 2022. We recognized $0.8 million in license and other revenue pursuant to our license agreements with Antengene and others, for the three months ended March 31, 2021.

5. Fair Value of Financial Instruments

Financial instruments, including cash, restricted cash, prepaid expenses and other current assets, accounts payable and accrued expenses, are presented at amounts that approximate fair value at March 31, 2022 and December 31, 2021.

We are required to disclose information on all assets and liabilities reported at fair value that enables an assessment of the inputs used in determining the reported fair values. The fair value hierarchy prioritizes valuation inputs based on the observable nature of those inputs. The fair value hierarchy applies only to the valuation inputs used in determining the reported fair value of the investments and is not a measure of the investment credit quality. The hierarchy defines three levels of valuation inputs:

Level 1 inputs - Quoted prices in active markets for identical assets or liabilities

Level 2 inputs - Inputs other than quoted prices included within Level 1 that are observable for the asset or liability, either directly or indirectly

Level 3 inputs - Unobservable inputs that reflect our own assumptions about the assumptions market participants would use in pricing the asset or liability

Our cash equivalents are comprised of money market funds, U.S. government and agency securities and commercial paper as presented in the tables below. We measure these investments at fair value. The fair value of cash equivalents is determined based on "Level 1" or "Level 2" inputs.

Items classified as Level 2 within the valuation hierarchy consist of corporate debt securities, commercial paper and U.S. government and agency securities. We estimate the fair values of these marketable securities by taking into consideration valuations obtained from third-party pricing sources. These pricing sources utilize industry standard valuation models, including both income and market-based approaches, for which all significant inputs are observable, either directly or indirectly, to estimate fair value. These inputs include market pricing based on real-time trade data for the same or similar securities, issuer credit spreads, benchmark yields, and other observable inputs. We validate the prices provided by our third-party pricing sources by understanding the models used, obtaining market values from other pricing sources and analyzing pricing data in certain instances.

In certain cases where there is limited activity or less transparency around inputs to valuation, the related assets or liabilities are classified as Level 3. The embedded derivative liability associated with our deferred royalty obligation, as discussed further in Note 10, "*Long-Term Obligations*", is measured at fair value using an option pricing Monte Carlo simulation model and is included as a component of the deferred royalty obligation. The embedded derivative liability is subject to remeasurement at the end of each reporting period, with changes in fair value recognized as a component of other expense, net. The assumptions used in the option pricing Monte Carlo simulation model include: (1) our estimates of the probability and timing of related events; (2) the probability-weighted net sales of XPOVIO and any of our other future products, including worldwide net product sales, upfront payments, milestones and royalties; (3) our risk-adjusted discount rate that includes a company specific risk premium; (4) our cost of debt; (5) volatility; and (6) the probability of a change in control occurring during the term of the instrument. Our embedded derivative liability, as well as the estimated fair value of the deferred royalty obligation, is described in Note 2, "*Summary of Significant Accounting Policies*," and Note 16, "*Long-Term Obligations*" to our consolidated financial statements contained in Item 8 of our Annual Report.

The following tables present information about our financial assets and liability that have been measured at fair value and indicate the fair value hierarchy of the valuation inputs utilized to determine such fair value (in thousands):

Description	As of March 31, 2022	Quoted Prices in Active Markets for Identical Assets (Level 1)	Significant Other Observable Inputs (Level 2)	Significant Unobservable Inputs (Level 3)
Financial assets				
Cash equivalents:				
Money market funds	$ 45,209	$ 45,209	$ —	$ —
U.S. government and agency securities	28,994	28,994	—	—
Commercial paper	23,985	—	23,985	—
Investments:				
Short-term:				
Corporate debt securities	11,127	—	11,127	—
Commercial paper	11,984	—	11,984	—
U.S. government and agency securities	28,944	—	28,944	—
	$ 150,243	$ 74,203	$ 76,040	$ —
Financial liability				
Embedded derivative liability	$ 3,080		$ —	$ 3,080

Description	As of December 31, 2021	Quoted Prices in Active Markets for Identical Assets (Level 1)	Significant Other Observable Inputs (Level 2)	Significant Unobservable Inputs (Level 3)
Financial assets				
Cash equivalents:				
Money market funds	$ 32,947	$ 32,947	$ —	$ —
U.S. government and agency securities	12,000	12,000	—	—
Commercial paper	11,998	—	11,998	—
Investments:				
Short-term:				
Corporate debt securities	24,269	—	24,269	—
Commercial paper	12,995	—	12,995	—
U.S. government and agency securities	892	—	892	—
	$ 95,101	$ 44,947	$ 50,154	$ —
Financial liability				
Embedded derivative liability	$ 3,080		$ —	$ 3,080

6. Investments

The following tables summarize our investments in debt securities, classified as available-for-sale (in thousands):

	As of March 31, 2022			
	Amortized Cost	Total Unrealized Gains	Total Unrealized Loss	Aggregate Fair Value
Short-term:				
Corporate debt securities	$ 11,131	$ 3	$ (7)	$ 11,127
Commercial paper	11,990	—	(6)	11,984
U.S. government and agency securities	28,950	2	(8)	28,944
	$ 52,071	$ 5	$ (21)	$ 52,055

	As of December 31, 2021			
	Amortized Cost	Total Unrealized Gains	Total Unrealized Loss	Aggregate Fair Value
Short-term:				
Corporate debt securities	$ 24,272	$ 3	$ (6)	$ 24,269
Commercial paper	12,998	—	(3)	12,995
U.S. government and agency securities	891	1	—	892
	$ 38,161	$ 4	$ (9)	$ 38,156

We determine the appropriate classification of our investments in debt securities at the time of purchase. All of our securities are classified as available-for-sale and are reported as short-term investments or long-term investments based on maturity dates and whether such assets are reasonably expected to be realized in cash or sold or consumed during the normal cycle of business. Available-for-sale investments are recorded at fair value. Short-term and long-term investments are composed of corporate debt securities, commercial paper and U.S. government and agency securities. We review investments whenever the fair value of an investment is less than the amortized cost and evidence indicates that an investment's carrying amount is not recoverable within a reasonable period of time. We evaluate whether the decline in fair value has resulted from credit losses or other factors. In making this assessment, we consider the extent to which fair value is less than amortized cost, any changes to the rating of the security by a rating agency, and adverse conditions specifically related to the security, among other factors. If this assessment indicates that a credit loss exists, the present value of cash flows expected to be collected from the security is compared to the amortized cost basis of the security. If the present value of cash flows expected to be collected is less than the amortized cost basis, a credit loss exists and an allowance for credit losses is recorded on our condensed consolidated balance sheet, limited by the amount that the fair value is less than the amortized cost basis. Any impairment that is not related to a credit loss is recognized in other comprehensive income.

Changes in the allowance for credit losses are recorded as a provision for (or reversal of) credit loss expense. Losses are charged against the allowance when we believe the uncollectability of an available-for-sale security is confirmed or when either of the criteria

regarding intent or requirement to sell is met. The unrealized losses at March 31, 2022 and December 31, 2021 were attributable to changes in interest rates, and we do not believe any unrealized losses represent credit losses.

We held 16 and 37 commercial paper and corporate debt securities at March 31, 2022 and December 31, 2021, respectively, that were in an unrealized loss position. We do not intend to sell the investments before recovery of their amortized cost bases, which may be at maturity. The following tables summarize our available-for-sale securities in an unrealized loss position for which an allowance for credit losses has not been recorded, aggregated by major security type and length of time in a continuous unrealized loss position (in thousands):

	As of March 31, 2022					
	Less than 12 Months		12 Months or Longer		Total	
	Aggregate Related Fair Value	Unrealized Losses	Aggregate Related Fair Value	Unrealized Losses	Aggregate Related Fair Value	Unrealized Losses
Corporate debt securities	$ 8,123	$ (7)	$ —	$ —	$ 8,123	$ (7)
Commercial paper	11,984	(6)	—	—	11,984	(6)
U.S. government and agency securities	21,949	(8)	—	—	21,949	(8)
Total	$ 42,056	$ (21)	$ —	$ —	$ 42,056	$ (21)

	As of December 31, 2021					
	Less than 12 Months		12 Months or Longer		Total	
	Aggregate Related Fair Value	Unrealized Losses	Aggregate Related Fair Value	Unrealized Losses	Aggregate Related Fair Value	Unrealized Losses
Corporate debt securities	$ 16,655	$ (6)	$ —	$ —	$ 16,655	$ (6)
Commercial paper	9,995	(3)	—	—	9,995	(3)
Total	$ 26,650	$ (9)	$ —	$ —	$ 26,650	$ (9)

7. Net Loss Per Share

Basic and diluted net loss per common share is calculated by dividing net loss by the weighted-average number of common shares outstanding for the period. Diluted net loss per share is computed by dividing the diluted net loss by the weighted average number of common shares, including potential dilutive common shares assuming the dilutive effect of outstanding stock options and unvested restricted common stock. For periods in which the Company has reported net losses, diluted net loss per common share is the same as basic net loss per share, since dilutive common shares are not assumed to have been issued if their effect is anti-dilutive.

The following potentially dilutive securities were excluded from the calculation of diluted net loss per share due to their anti-dilutive effect (in thousands):

	As of March 31,	
	2022	2021
Outstanding stock options	13,477	12,900
Unvested restricted stock units	3,798	2,517

We have the option to settle the conversion obligation for our 3.00% convertible senior notes due 2025 (the “Notes”) in cash, shares or any combination of the two. Based on our net loss position, there was no impact on the calculation of dilutive loss per share during the three months ended March 31, 2022 and 2021.

8. Stock-based Compensation Expense

The following table summarizes stock-based compensation expense included in operating expenses (in thousands):

	For the Three Months Ended March 31,	
	2022	2021
Cost of sales	$ 55	$ 44
Research and development	2,968	2,932
Selling, general and administrative	4,313	4,383
Total	$ 7,336	$ 7,359

9. Stockholders' Equity

Open Market Sale Agreement

On August 17, 2018, we entered into an Open Market Sale Agreement (the "Open Market Sale Agreement") with Jefferies LLC, as agent ("Jefferies"), pursuant to which we may issue and sell shares of our common stock having an aggregate offering price of up to $75.0 million from time to time through Jefferies (the "Open Market Offering"). On May 5, 2020, we entered into Amendment No. 1 to the Open Market Sale Agreement, pursuant to which we increased the maximum aggregate offering price of shares of our common stock that we may issue and sell from time to time through Jefferies, by $100.0 million, from $75.0 million to up to $175.0 million (the "Open Market Shares").

Under the Open Market Sale Agreement, Jefferies may sell the Open Market Shares by methods deemed to be an "at the market offering" as defined in Rule 415(a)(4) promulgated under the Securities Act of 1933, as amended (the "Securities Act"). We may sell the Open Market Shares in amounts and at times to be determined by us from time to time subject to the terms and conditions of the Open Market Sale Agreement, but we have no obligation to sell any of the Open Market Shares in an Open Market Offering.

We or Jefferies may suspend or terminate the offering of Open Market Shares upon notice to the other party and subject to other conditions. We have agreed to pay Jefferies commissions for its services in acting as agent in the sale of the Open Market Shares in the amount of up to 3.0% of gross proceeds from the sale of the Open Market Shares pursuant to the Open Market Sale Agreement. We have also agreed to provide Jefferies with customary indemnification and contribution rights.

We sold an aggregate of 2,941,517 Open Market Shares under the Open Market Sale Agreement, for net proceeds of approximately $29.3 million, during the three months ended March 31, 2022. We sold an aggregate of 638,341 Open Market Shares under the Open Market Sale Agreement, for net proceeds of approximately $9.9 million, during the three months ended March 31, 2021. As of March 31, 2022, $70.7 million of Open Market Shares may be issued and sold under the Open Market Sale Agreement.

10. Long-Term Obligations

3.00% Convertible Senior Notes due 2025

On October 16, 2018, we completed an offering of $150.0 million aggregate principal amount of the Notes. In addition, on October 26, 2018, we issued an additional $22.5 million aggregate principal amount of the Notes pursuant to the full exercise of the option to purchase additional Notes granted to the initial purchasers in the offering. The Notes were sold in a private offering to qualified institutional buyers in reliance on Rule 144A under the Securities Act. In connection with the issuance of the Notes, we incurred approximately $5.6 million of debt issuance costs, which primarily consisted of underwriting, legal and other professional fees. Debt issuance costs are being amortized to interest expense using the effective interest method over seven years.

The Notes are senior unsecured obligations and bear interest at a rate of 3.00% per year payable semiannually in arrears on April 15 and October 15 of each year, beginning on April 15, 2019. Upon conversion, the Notes will be converted into cash, shares of our common stock, or a combination of cash and shares of our common stock, at our election. The Notes will be subject to redemption at our option, on or after October 15, 2022, in whole or in part, if the conditions described below are satisfied. The Notes will mature on October 15, 2025, unless earlier converted, redeemed or repurchased in accordance with their terms. Subject to satisfaction of certain conditions and during the periods described below, the Notes may be converted at an initial conversion rate of 63.0731 shares of common stock per $1 principal amount of the Notes (equivalent to an initial conversion price of approximately $15.85 per share of common stock).

Holders of the Notes may convert all or any portion of their Notes, in multiples of $1 principal amount, at their option at any time prior to the close of business on the business day immediately preceding June 15, 2025 only under the following circumstances:

(1) during any calendar quarter commencing after the calendar quarter ending on December 31, 2018 (and only during such calendar quarter), if the last reported sale price of our common stock for at least 20 trading days (whether or not consecutive) during the period of 30 consecutive trading days ending on, and including, the last trading day of the immediately preceding calendar quarter is greater than or equal to 130% of the conversion price for the Notes on each applicable trading day;

(2) during the five business day period immediately after any five consecutive trading day period (the "Measurement Period") in which the trading price per $1,000 principal amount of Notes for each trading day of the Measurement Period was less than 98% of the product of the last reported sale price of our common stock and the conversion rate on each such trading day;

(3) if we call the Notes for redemption, until the close of business on the business day immediately preceding the redemption date; or

(4) upon the occurrence of specified corporate events as described within the indenture governing the Notes.

As of March 31, 2022, none of the above circumstances had occurred and as such, the Notes could not have been converted.

We may not redeem the Notes prior to October 15, 2022. On or after October 15, 2022, we may redeem for cash all or part of the Notes at our option if the last reported sale price of our common stock equals or exceeds 130% of the conversion price then in effect for at least 20 trading days (whether or not consecutive) during any 30 consecutive trading day period ending within five trading

days prior to the date on which we send any notice of redemption. The redemption price will be 100% of the principal amount of the Notes to be redeemed, plus accrued and unpaid interest, if any. In addition, calling any convertible note for redemption will constitute a make-whole fundamental change with respect to that convertible note, in which case the conversion rate applicable to the conversion of that convertible note, if it is converted in connection with the redemption, will be increased in certain circumstances.

The outstanding balances of the Notes consisted of the following (in thousands):

	March 31, 2022	December 31, 2021
Principal	$ 172,500	$ 172,500
Less: debt issuance costs	(3,009)	(3,207)
Net carrying amount	$ 169,491	$ 169,293

We determined the expected life of the Notes was equal to its seven-year term. The effective interest rate on the Notes was 11.85%. As of March 31, 2022, the "if-converted value" did not exceed the remaining principal amount of the Notes. The fair value of the Notes was determined based on data points other than quoted prices that are observable, either directly or indirectly, and has been classified as Level 2 within the fair value hierarchy. The fair value of the Notes, which differs from their carrying value, is influenced by market interest rates, our stock price and stock price volatility. The estimated fair value of the Notes as of March 31, 2022 and December 31, 2021 was approximately $141.9 million and $139.2 million, respectively.

The following table sets forth total interest expense recognized related to the Notes for the periods indicated (in thousands):

	For the Three Months Ended March 31,	
	2022	2021
Contractual interest expense	$ 1,294	$ 1,294
Amortization of debt issuance costs	198	191
Total	$ 1,492	$ 1,485

Future minimum payments on the Notes as of March 31, 2022 were as follows (in thousands):

Years ended December 31,	Future Minimum Payments
2022	$ 5,175
2023	5,175
2024	5,175
2025	177,675
Total minimum payments	$ 193,200
Less: interest and issuance costs	(23,709)
Convertible senior notes	$ 169,491

Deferred Royalty Obligation

In September 2019, we entered into a Revenue Interest Financing Agreement ("the Revenue Interest Agreement") with HealthCare Royalty Partners III, L.P. and HealthCare Royalty Partners IV, L.P. ("HCR"). In June 2021, we, and certain of our subsidiaries, entered into an amendment of the Revenue Interest Agreement (the "Amended Revenue Interest Agreement") with, among others, HCR. We received $75.0 million, less certain transaction expenses, upon closing of the Revenue Interest Agreement (the "First Investment Amount") and $60.0 million upon closing of the Amended Revenue Interest Agreement (the "Second Investment Amount" and together with the First Investment Amount, the "deferred royalty obligation").

In exchange for the above payments, HCR receives payments from us at a tiered percentage (the "Applicable Tiered Percentage") of net revenues of selinexor and any of our other future products, including worldwide net product sales and upfront payments, milestones, and royalties. The Applicable Tiered Percentage is subject to reduction in the future if a target based on cumulative U.S. net sales of selinexor is met. Total payments to HCR are capped at 185% of the Investment Amount.

If HCR has not received 65% of the First Investment Amount by December 31, 2022, 100% of the First Investment Amount and 65% of the Second Investment amount by December 31, 2024, or 100% of both the First Investment Amount and the Second Investment Amount by September 30, 2026, we must make a cash payment sufficient to gross up the payments to such minimum amounts.

As the repayment of the funded amount is contingent upon worldwide net product sales and upfront payments, milestones, and royalties, the repayment term may be shortened or extended depending on actual worldwide net product sales and upfront payments, milestones, and royalties. The repayment period commenced on October 1, 2019 for the First Investment Amount and on July 1, 2021 for the Second Investment Amount, and expires on the earlier of (i) the date in which HCR has received cash payments totaling an

aggregate of 185% of the Investment Amount or (ii) the legal maturity date of October 1, 2031. If HCR has not received payments equal to 185% of the Investment Amount by the twelve-year anniversary of the initial closing date, we will be required to pay an amount equal to the Investment Amount plus a specific annual rate of return less payments previously received by HCR. In the event of a change of control, we are obligated to pay HCR an amount equal to 185% of the Investment Amount less payments previously received by HCR. In addition, upon the occurrence of an event of default, including, among others, our failure to pay any amounts due to HCR under the deferred royalty obligation, insolvency, our failure to pay indebtedness when due, the revocation of regulatory approval of XPOVIO in the U.S. or our breach of any covenant contained in the Amended Revenue Interest Agreement and our failure to cure the breach within the prescribed time frame, we are obligated to pay HCR an amount equal to 185% of the Investment Amount less payments previously received by HCR. In addition, upon an event of default, HCR may exercise all other rights and remedies available under the Amended Revenue Interest Agreement, including foreclosing on the collateral that was pledged to HCR, which consists of all of our present and future assets relating to XPOVIO. As of March 31, 2022, we have made $32.2 million in payments to HCR.

We have evaluated the terms of the deferred royalty obligation and concluded that the features of both the First Investment Amount and Second Investment Amount are similar to those of a debt instrument. Accordingly, we have accounted for the transaction as long-term debt and presented it as a deferred royalty obligation on our condensed consolidated balance sheet.

We have further evaluated the terms of the debt and determined that the repayment of 185% of the Investment Amount, less any payments made to date, upon a change of control is an embedded derivative that requires bifurcation from the debt instrument and fair value recognition. We determined the fair value of the derivative using an option pricing Monte Carlo simulation model taking into account the probability of change of control occurring and potential repayment amounts and timing of such payments that would result under various scenarios, as further described in Note 5, "*Fair Value of Financial Instruments"* to our condensed consolidated financial statements. The aggregate fair value of the embedded derivative liability was $3.1 million as of both March 31, 2022 and December 31, 2021. We remeasure the embedded derivative to fair value each reporting period until the time the features lapse and/or termination of the deferred royalty obligation.

The effective interest rate as of March 31, 2022 was approximately 16.5%. In connection with the First Investment Amount, we incurred debt issuance costs totaling $1.4 million. Debt issuance costs have been netted against the debt and are being amortized over the estimated term of the debt using the effective interest method, adjusted on a prospective basis for changes in the underlying assumptions and inputs. The assumptions used in determining the expected repayment term of the debt and amortization period of the issuance costs requires that we make estimates that could impact the short and long-term classification of these costs, as well as the period over which these costs will be amortized.

The carrying value of the deferred royalty obligation at both March 31, 2022 and December 31, 2021 was $129.9 million based on $135.0 million of proceeds, net of the fair value of the bifurcated embedded derivative liability upon execution of the Revenue Interest Agreement and the Amended Revenue Interest Agreement, and debt issuance costs incurred. The carrying value of the deferred royalty obligation approximated fair value at March 31, 2022 and December 31, 2021 and was measured using Level 3 inputs. The estimated fair market value was calculated using an option pricing Monte Carlo simulation model with inputs consistent with those used in determining the embedded derivative values as described in Note 5, "*Fair Value of Financial Instruments"* to our condensed consolidated financial statements.

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

You should read the following discussion and analysis of our financial condition and results of operations together with our financial statements and related notes appearing elsewhere in this quarterly report and the audited financial information and the notes thereto included in our Annual Report on Form 10-K for the year ended December 31, 2021, as filed with the Securities and Exchange Commission ("SEC") on March 1, 2022 ("Annual Report").

FORWARD-LOOKING STATEMENTS

This Quarterly Report on Form 10-Q, contains forward-looking statements regarding the expectations of Karyopharm Therapeutics Inc., herein referred to as "Karyopharm," the "Company," "we," or "our," with respect to the possible achievement of discovery and development milestones, our future discovery and development efforts, including regulatory submissions and approvals, our commercialization efforts, our partnerships and collaborations with third parties, our future operating results and financial position, our business strategy, and other objectives for future operations. We often use words such as "anticipate," "believe," "estimate," "expect," "intend," "may," "plan," "predict," "project," "target," "potential," "will," "would," "could," "should," "continue," and other words and terms of similar meaning to help identify forward-looking statements, although not all forward-looking statements contain these identifying words. You also can identify these forward-looking statements by the fact that they do not relate strictly to historical or current facts. There are a number of important risks and uncertainties that could cause actual results or events to differ materially from those indicated by forward-looking statements. These risks and uncertainties include, but are not limited to, those described in Part II, Item 1A - Risk Factors of this Quarterly Report on Form 10-Q. As a result of these and other factors, we may not actually achieve the plans, intentions, expectations or results disclosed in our forward-looking statements, and you should not place undue reliance on our forward-looking statements. Our forward-looking statements do not reflect the potential impact of any future acquisitions, mergers, dispositions, joint ventures or investments we may make. We do not assume any obligation to update any forward-looking statements, whether as a result of new information, future events or otherwise, except as required by law.

References to XPOVIO® (selinexor) also refer to NEXPOVIO®(selinexor) when discussing its approval and commercialization outside of the U.S.

OVERVIEW

We are a commercial-stage pharmaceutical company pioneering novel cancer therapies and dedicated to the discovery, development and commercialization of first-in-class drugs directed against nuclear export for the treatment of cancer and other diseases. Our scientific expertise is based upon an understanding of the regulation of intracellular communication between the nucleus and the cytoplasm. We have discovered and are developing and commercializing novel, small molecule **S**elective **I**nhibitor of **N**uclear **E**xport ("SINE") compounds that inhibit the nuclear export protein exportin 1 ("XPO1"). These SINE compounds represent a new class of drug candidates with a novel mechanism of action that have the potential to treat a variety of diseases with high unmet medical need. Our lead asset, XPOVIO® (selinexor), was the first oral XPO1 inhibitor to receive marketing approval, receiving its initial U.S. approval from the U.S. Food and Drug Administration ("FDA") in July 2019, and is currently approved and marketed in the U.S. for the following indications:

- In combination with bortezomib and dexamethasone for the treatment of adult patients with multiple myeloma who have received at least one prior therapy. Approval in this indication was supported by data from the BOSTON (**Bo**rtezomib, **S**elinexor and Dexame**t**has**on**e) study (the "BOSTON Study");
- In combination with dexamethasone for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least four prior therapies and whose disease is refractory to at least two proteasome inhibitors ("Pls"), at least two immunomodulatory agents ("IMiDs"), and an anti-CD38 monoclonal antibody ("mAB"). We refer to myeloma that is refractory to these five agents as penta-refractory. Approval in this indication was supported by data from the STORM (**S**elinexor **T**reatment **o**f **R**efractory **M**yeloma) study (the "STORM Study"); and
- For the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma ("DLBCL"), not otherwise specified, including DLBCL arising from follicular lymphoma, after at least two lines of systemic therapy. This indication was approved under accelerated approval based on response rate and was supported by data from the SADAL (**S**elinexor **A**gainst **D**iffuse **A**ggressive **L**ymphoma) study. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).

The commercialization of XPOVIO in the U.S., for both the multiple myeloma and DLBCL indications, is currently supported by sales representatives, nurse liaisons, and a market access team as well as KaryForward™, an extensive patient and healthcare provider support program. Our commercial efforts are also supplemented by patient support initiatives coordinated by our dedicated

network of participating specialty pharmacy providers. We plan to continue to educate physicians, other healthcare providers and patients about XPOVIO's clinical profile and unique mechanism of action as we continue to expand XPOVIO use.

The commercialization of XPOVIO and NEXPOVIO (the brand name for selinexor in Europe and the United Kingdom) outside of the U.S. is managed by our partners in their respective territories. We have received the following regulatory approval for NEXPOVIO outside of the U.S.:

- **European Union**: Conditional approval received in March 2021 from the European Commission for NEXPOVIO in combination with dexamethasone for the treatment of adult patients with penta-refractory multiple myeloma in 27 European Union member countries as well as the European Economic Area countries of Iceland, Liechtenstein and Norway. In December 2021, we entered into a license agreement (the "Menarini Agreement") with Berlin-Chemie AG, an affiliate of the Menarini Group ("Menarini"), pursuant to which we granted Menarini a non-exclusive license to develop, and an exclusive license to commercialize, products containing selinexor for all human oncology indications in Europe and other key global territories.
- **United Kingdom**: Conditional approval received in May 2021 from the United Kingdom's Medicines & Healthcare Products Regulatory Agency for NEXPOVIO in combination with dexamethasone for the treatment of adult patients with penta-refractory multiple myeloma. Under the terms of the Menarini Agreement, Menarini obtained the exclusive rights to commercialize NEXPOVIO in the United Kingdom.

Our partners have received the following regulatory approvals for XPOVIO outside of the U.S.:

- **Australia:** Approval received in March 2022 for XPOVIO (a) in combination with bortezomib and dexamethasone for the treatment of adult patients with multiple myeloma who have received at least one prior therapy; and (b) in combination with dexamethasone for the treatment of adult patients with relapsed and/or refractory multiple myeloma who have received at least three prior therapies and whose disease is refractory to at least one PI, at least one IMiD, and an anti-CD38 mAb.
- **Singapore**: Approval received in March 2022 for XPOVIO (a) in combination with bortezomib and dexamethasone for the treatment of adult patients with multiple myeloma who have received at least one prior therapy; (b) in combination with dexamethasone for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least four prior therapies and whose disease is refractory to at least two PIs, at least two IMiDs, and an anti-CD38 mAb; and (c) for the treatment of adult patients with relapsed or refractory DLBCL, not otherwise specified, including DLBCL arising from follicular lymphoma, after at least two lines of therapy who are not eligible for haematopoietic cell transplant.
- **Mainland China**: Conditional approval received in December 2021 for XPOVIO in combination with dexamethasone in patients with relapsed or refractory multiple myeloma who have received prior therapies and whose disease is refractory to at least a PI, an IMiD, and an anti-CD38 mAb.
- **South Korea**: Approval received in July 2021 for XPOVIO (a) in combination with dexamethasone for the treatment of adult patients with penta-refractory multiple myeloma; and (b) as a monotherapy for the treatment of adult patients with relapsed or refractory DLBCL who have received at least two prior lines of treatment.
- **Israel**: Approval received in February 2021 for XPOVIO (a) in combination with dexamethasone for the treatment of adult patients with relapsed refractory multiple myeloma who have received at least three prior therapies and whose disease is refractory to at least one PI, at least one IMiD, and an anti-CD38 mAb; and (b) for the treatment of adult patients with relapsed or refractory DLBCL, not otherwise specified, including DLBCL arising from follicular lymphoma, after at least two lines of systemic therapy. In January 2022, approval was also received for XPOVIO in combination with bortezomib and dexamethasone for the treatment of adult patients with multiple myeloma who have received at least one prior therapy.

In addition, in April 2021, the European Medicines Agency ("EMA") validated our Type II variation to the marketing authorization application ("MAA") based on the data from the Phase 3 BOSTON Study, which evaluated once-weekly administration of selinexor in combination with once-weekly administration of Velcade® (bortezomib) and low-dose dexamethasone compared to standard twice-weekly administration of Velcade® plus low-dose dexamethasone in patients with multiple myeloma who have received one to three prior lines of therapy. In January 2022, as part of the MAA approval process, the EMA conducted a preapproval good clinical practices ("GCP") inspection at our corporate headquarters, which was also attended by the FDA. In addition, an inspection of one of the clinical trial sites that participated in the BOSTON Study took place in late 2021. In February 2022, the EMA issued its initial GCP inspection reports, which included certain questions and findings. We promptly addressed the questions and findings included in the inspection reports. We have since received and responded to additional questions and requests from the CHMP. The Type II variation is currently under review by the Committee for Medicinal Products for Human Use ("CHMP"). An opinion by the CHMP could be issued in the first half of 2022. There can be no assurances that our responses will be acceptable to the EMA.

Our primary focus is on marketing XPOVIO in its currently approved indications as well as developing and seeking the regulatory approval of selinexor as an oral agent in multiple myeloma, endometrial cancer, and myelofibrosis ("MF"), eltanexor in myelodysplastic syndromes ("MDS") and selinexor and eltanexor in additional cancer indications with significant unmet medical need. We plan to continue to conduct clinical trials and to seek additional approvals for the use of selinexor and eltanexor as single agents or in combination with other oncology therapies to expand the patient populations that are eligible for treatment with selinexor or eltanexor. In addition to selinexor and eltanexor, we continue to advance our pipeline of novel drug candidates, including verdinexor, our other oral SINE compound, KPT-9274 and a proprietary recombinant human interleukin 12 ("IL-12").

On February 8, 2022, we announced top-line results from our Phase 3 SIENDO study evaluating the efficacy and safety of selinexor for front-line maintenance therapy in patients with advanced or recurrent endometrial cancer (the "SIENDO Study"). On February 25, 2022, we attended a pre-supplemental New Drug Application ("sNDA") submission meeting with the FDA during which we received feedback, including that the top-line results from the SIENDO Study are unlikely to support an sNDA approval. Considering the FDA's feedback and based on the promising study results in a prespecified exploratory subgroup of patients with p53 wild-type tumors, we are planning to initiate a new placebo-controlled randomized clinical study of selinexor in patients with p53 wild-type with advanced or recurrent endometrial cancer. To that end, we are currently in discussions with the FDA regarding the design of this new study. Pending the outcome of those discussions, we are planning to initiate this study in the second half of 2022.

In the first half of 2022, we expect the first patient to be enrolled in a randomized global Phase 3 study evaluating selinexor in combination with pomalidomide and dexamethasone ("SPd") versus elotuzumab, pomalidomide, and dexamethasone ("EloPd") in patients with relapsed or refractory multiple myeloma (NCT05028348//EMN29). Patients in this Phase 3 study will have received one to four prior lines of therapy, including a PI, lenalidomide and an anti-CD38 mAb. Sixty patients will be randomized to SPd 40, SPd 60 or EloPd (Part 1) followed by Part 2, with 240 patients randomized to SPd (at the identified optimal dose from Part 1) versus EloPd in a 1:1 fashion. This global study is sponsored by the European Myeloma Network. The primary endpoint of this study is progression-free survival and secondary endpoints include overall response rate, overall survival and duration of response.

As of March 31, 2022, we had an accumulated deficit of $1.2 billion. We had net losses of $41.4 million and $57.4 million for the three months ended March 31, 2022 and 2021, respectively.

Uncertainty Relating to the COVID-19 Pandemic

The COVID-19 pandemic has and will continue to affect economies, healthcare systems, and businesses around the world. We continue to closely monitor the impact of the COVID-19 pandemic on all aspects of our business, including the impact on our employees, patients and business operations. We have experienced and may continue to experience, disruptions that could impact clinical trial enrollment and/or our results of operations, including product revenue and our financial condition. These uncertainties include the availability, administration rates and effectiveness of vaccines and therapeutics against any variants as new strains of the virus evolve, the continued duration and severity of the pandemic, governmental, business or other actions, changes to our operations and how quickly and to what extent normal economic and operation conditions can resume, among others. We will continue to monitor the COVID-19 situation closely and intend to follow health and safety guidelines as they evolve. Further, the impacts of a potential worsening of global economic conditions and the continued disruptions to, and volatility in, the credit and financial markets, as well as other unanticipated consequences, remain unknown. The situation surrounding the COVID-19 pandemic remains fluid and we are actively managing our response and assessing potential impacts to our operating results and financial condition, as well as adverse developments in our business. For further information regarding the impact of the COVID-19 pandemic on us, see Part II, Item 1A - Risk Factors included in this Quarterly Report on Form 10-Q.

CRITICAL ACCOUNTING ESTIMATES

We believe that several accounting policies are important to understanding our historical and future performance. We refer to these policies as "critical" because these specific areas generally require us to make judgments and estimates about matters that are uncertain at the time we make the estimate, and different estimates - which also would have been reasonable - could have been used, which would have resulted in different financial results.

There have been no changes to the critical accounting estimates we identified in Item 7. Management's Discussion and Analysis of Financial Condition and Results of Operations in our Annual Report.

RESULTS OF OPERATIONS

The following table summarizes our results of operations (in thousands except for percentages):

	Three Months Ended March 31,			
	2022	2021	$ Change	% Change
Product revenue, net	$ 28,300	$ 21,731	$ 6,569	30 %
License and other revenue	19,370	1,529	17,841	1167 %
Total revenues	47,670	23,260	24,410	105 %
Operating expenses:				
Cost of sales	1,426	933	493	53 %
Research and development	42,062	37,050	5,012	14 %
Selling, general and administrative	38,768	37,650	1,118	3 %
Loss from operations	(34,586)	(52,373)	17,787	(34)%
Other expense, net	(6,683)	(4,892)	(1,791)	37 %
Loss before income taxes	(41,269)	(57,265)	15,996	(28)%
Income tax provision	(130)	(149)	19	(13)%
Net loss	$ (41,399)	$ (57,414)	$ 16,015	(28)%

Product Revenue, net (in thousands, except for percentages)

	Three Months Ended March 31,			
	2022	2021	$ Change	% Change
Product revenue, net	$ 28,300	$ 21,731	$ 6,569	30 %

Net product revenue from U.S. commercial sales of XPOVIO for the three months ended March 31, 2022 increased 30% as compared to the three months ended March 31, 2021 due to an increasing number of patients treated in earlier lines of therapy and the increasing utilization of XPOVIO by physicians in the first quarter of 2022 compared to the first quarter of 2021. We expect this trend to continue, resulting in increased net product revenue in 2022 as compared to 2021.

License and Other Revenue (in thousands, except for percentages)

	Three Months Ended March 31,			
	2022	2021	$ Change	% Change
Antengene Therapeutics Limited ("Antengene")	$ 9,014	$ 492	$ 8,522	1732 %
Menarini	7,086	—	7,086	100 %
Other	3,270	1,037	2,233	215 %
Total	$ 19,370	$ 1,529	$ 17,841	1167 %

License and other revenue for the three months ended March 31, 2022 increased as compared to the three months ended March 31, 2021, due to $7.8 million that we recognized in development/regulatory milestones from Antengene and $7.1 million that we earned for reimbursement of development expenses from Menarini in the first quarter of 2022.

We expect license and other revenue will decrease in the second quarter of 2022 as compared to the first quarter of 2022, due primarily to the recognition of milestones earned in the first quarter of 2022 related to our license agreement with Antengene.

Operating Expenses (in thousands, except for percentages)

	Three Months Ended March 31,			
	2022	2021	$ Change	% Change
Cost of sales	$ 1,426	$ 933	$ 493	53 %
Research and development	42,062	37,050	5,012	14 %
Selling, general and administrative	38,768	37,650	1,118	3 %
Total	$ 82,256	$ 75,633	$ 6,623	9 %

Cost of Sales

During the three months ended March 31, 2022 and 2021, we recorded $1.4 million and $0.9 million, respectively, of cost of sales, including $0.3 million and $0.1 million, respectively, related to royalties. The cost of sales during the three months ended March 31, 2022 and 2021 only reflects a portion of the costs related to the manufacturing of XPOVIO and related materials, since,

prior to the July 2019 FDA approval, these costs were expensed. The manufacturing costs of XPOVIO on-hand upon FDA approval amounted to approximately $2.8 million. At March 31, 2022, we had $2.0 million of previously expensed XPOVIO costs and related material on-hand. We expect to utilize zero cost inventory with respect to XPOVIO for an extended period of time. We do not expect cost of sales to materially change in the second quarter of 2022, as compared to the first quarter of 2022.

Research and Development Expense (in thousands, except for percentages)

	Three Months Ended March 31,			
	2022	2021	$ Change	% Change
Clinical trial costs	$ 18,230	$ 16,750	$ 1,480	9%
Personnel costs	17,240	14,107	3,133	22%
Stock-based compensation	2,968	2,932	36	1%
Consulting, professional and other costs	3,624	3,261	363	11%
Total	$ 42,062	$ 37,050	$ 5,012	14%

Research and development expense for the three months ended March 31, 2022 increased as compared to the three months ended March 31, 2021, primarily due to an increase in personnel costs, including $1.6 million related to severance charges recognized in the quarter. In addition, clinical trial costs increased by approximately $1.5 million, primarily related to an increase of $4.0 million in costs related to our Phase 3 study evaluating selinexor in combination with pomalidomide and dexamethasone in patients with relapsed or refractory multiple myeloma. This increase was partially offset by a $2.3 million decrease in costs related to our BOSTON, SIENDO, SEAL and SADAL studies.

We expect our research and development expense to increase in the second quarter of 2022 as compared to the first quarter of 2022, due primarily to severance-related stock-based compensation expense.

Selling, General and Administrative Expense (in thousands, except for percentages)

	Three Months Ended March 31,			
	2022	2021	$ Change	% Change
Personnel costs	$ 19,448	$ 18,285	$ 1,163	6%
Consulting, professional and other costs	11,807	12,259	(452)	(4)%
Stock-based compensation	4,313	4,383	(70)	(2)%
Facility and information technology infrastructure costs	3,200	2,723	477	18%
Total	$ 38,768	$ 37,650	$ 1,118	3%

Selling, general and administrative expense for the three months ended March 31, 2022 increased as compared to the three months ended March 31, 2021, primarily due to an increase of $1.2 million in personnel costs, largely attributable to severance-related charges recognized in the quarter.

We expect our selling, general and administrative expenses to increase in the second quarter of 2022 as compared to the first quarter of 2022, due primarily to severance-related stock-based compensation expense.

Other Expense, net (in thousands, except for percentages)

	Three Months Ended March 31,			
	2022	2021	$ Change	% Change
Interest expense	$ (6,684)	$ (5,095)	$ (1,589)	31%
Interest income	74	264	(190)	(72)%
Other income (expense):				
Realized gains on marketable equity securities	—	14	(14)	(100)%
Foreign currency translation	(73)	(75)	2	(3)%
Total other expense, net	$ (6,683)	$ (4,892)	$ (1,791)	37%

Other expense, net for the three months ended March 31, 2022 increased as compared to the three months ended March 31, 2021 primarily due to an increase in interest expense of $1.6 million related to our Revenue Interest Agreement that we entered into with HealthCare Royalty Partners III, L.P. and HealthCare Royalty Partners IV, L.P. (“HCR”) and was amended in June 2021 (“Amended Revenue Interest Agreement”) resulting in an increased deferred royalty obligation following the closing of the Amended Revenue Interest Agreement. We expect other expense, net to remain relatively consistent in the second quarter of 2022, as compared to the first quarter of 2022.

LIQUIDITY AND CAPITAL RESOURCES

Cash Flows

To date, we have financed our operations through a combination of product revenue sales, through private placements of our preferred stock, proceeds from our initial public offering and follow-on offerings of common stock, proceeds from the issuance of convertible debt, proceeds pursuant to the deferred royalty obligation, proceeds from sales of common stock under our Open Market Sale Agreement (as defined below), and cash generated from our business development activities. As of March 31, 2022, our principal source of liquidity was $205.3 million of cash, cash equivalents and investments. We have had recurring losses since inception and incurred a loss of $41.4 million for the three months ended March 31, 2022. Net cash used in operations for the three months ended March 31, 2022 was $59.2 million. We expect that our cash, cash equivalents and investments at March 31, 2022 will be sufficient to fund our current operating plans and capital expenditure requirements for at least twelve months from the date of issuance of the financial statements contained in this Quarterly Report on Form 10-Q.

The following table provides information regarding our cash flows (in thousands):

	Three Months Ended March 31,	
	2022	2021
Net cash used in operating activities	$ (59,197)	$ (52,888)
Net cash (used in) provided by investing activities	(14,035)	43,186
Net cash provided by financing activities	30,783	10,676
Effect of exchange rate	(90)	(91)
Net (decrease) increase in cash, cash equivalents and restricted cash	$ (42,539)	$ 883

Operating activities. The net cash used in operating activities in each of the three months ended March 31, 2022 and March 31, 2021 primarily reflects our net losses adjusted for non-cash charges and changes in the components of working capital. The increase in cash used in operating activities during the quarter ended March 31, 2022 as compared to the quarter ended March 31, 2021 was driven by a $16.0 million decrease in our net loss that was more than offset by a $21.6 million increase in the change in operating assets and liabilities.

Investing activities. The net cash used in investing activities during the three months ended March 31, 2022, compared to the net cash provided by investing activities during the three months ended March 31, 2021, primarily reflects a $47.4 million decrease in proceeds from the sales and maturities of investments coupled with a $9.8 million increase in the purchases of investments.

Financing activities. The $20.1 million increase in net cash provided by financing activities for the three months ended March 31, 2022 compared to the three months ended March 31, 2021 was primarily due to the net cash proceeds of $29.3 million from the sale of shares of our common stock under our Open Market Sale Agreement in the first quarter of 2022, compared to net cash proceeds of $9.9 million during the first quarter of 2021.

Sources of Liquidity

On June 23, 2021, we and certain of our subsidiaries entered into an amendment to the Revenue Interest Agreement with HCR. Pursuant to the Revenue Interest Agreement, HCR paid us $75.0 million, less certain transaction expenses, on September 27, 2019 and pursuant to the Amended Revenue Interest Agreement, HCR paid us $60.0 million, less certain transaction expenses, on June 23, 2021. For additional information on the Amended Revenue Interest Agreement, see Note 10, "*Long-Term Obligations*", to the condensed consolidated financial statements included under Part I, Item I of this Quarterly Report on Form 10-Q.

On May 5, 2020, we entered into Amendment No. 1 to the Open Market Sale Agreement, dated August 17, 2018 (the "Open Market Sale Agreement") with Jefferies LLC, as agent ("Jefferies") pursuant to which we increased the maximum aggregate offering price of shares of our common stock that we may issue and sell from time to time through Jefferies, by $100.0 million from $75.0 million to up to $175.0 million. As of March 31, 2022, $70.7 million of shares of our common stock may be issued and sold under the Open Market Sale Agreement. We sold an aggregate of 2,941,517 shares under the Open Market Sale Agreement, for net proceeds of approximately $29.3 million during the three months ended March 31, 2022.

During the quarter ended March 31, 2022, we received $1.6 million in milestone payments under our license and distribution arrangements pursuant to which we are entitled to receive additional milestone payments, if certain development goals and sales milestones are achieved, as well as royalties on future net sales of the licensed and sold products in the territories under such arrangements. In addition, under our license agreement with Menarini, Menarini will reimburse us for 25% of all documented expenses we incur for the global development of selinexor during 2022 through 2025, provided that such reimbursements shall not exceed $15.0 million per calendar year.

Commitments, Contingencies and Contractual Obligations

Operating Leases

We are party to an operating lease of 98,502 square feet of office and research space in Newton, Massachusetts with a term through September 30, 2025 (the "Newton, MA Lease"). Pursuant to the Newton, MA Lease, we have provided a security deposit in the form of a cash-collateralized letter of credit in the amount of $0.6 million. The amount is classified within long-term restricted cash. We expect lease costs under this commitment to total $3.4 million in 2022 and increase annually; we expect total future lease costs to be approximately $13.1 million.

In addition, we are party to certain short-term leases having a term of twelve months or less at the commencement date. We recognize short-term lease expense on a straight-line basis and do not record a related right-of use asset or lease liability for such leases. These costs were insignificant for the three months ended March 31, 2022.

Contractual Obligations

We have contractual obligations under our Notes and under our Amended Revenue Interest Agreement as disclosed in Note 10, "*Long-Term Obligations*", to the condensed consolidated financial statements included under Part I, Item 1 of this Quarterly Report on Form 10-Q.

Funding Requirements

We expect our expenses, excluding stock-based compensation, to remain relatively consistent in 2022 as compared to 2021. We expect to continue to incur costs related to our clinical development programs as well as commercialization expenses related to sales, marketing, manufacturing and distribution of any of our approved products, to the extent that these functions are not the responsibility of our collaborators.

Identifying potential product candidates and conducting preclinical studies and clinical trials is a time-consuming, expensive and uncertain process that takes years to complete. In addition, our product candidates for which we receive marketing approval may not achieve commercial success. Our ability to become and remain profitable depends on our ability to generate revenue. There can be no assurance as to the amount or timing of any such revenue, and we may not achieve profitability for several years, if at all, as described more fully in the risk factor entitled "*We have incurred significant losses since inception, expect to continue to incur significant losses, and may never achieve or maintain profitability*," under the heading "*Risk Factors*" in this Quarterly Report on Form 10-Q. Accordingly, we will need to continue to rely on additional financing to achieve our business objectives. Adequate additional financing may not be available to us on acceptable terms, or at all. We may seek additional capital due to favorable market conditions or strategic considerations, even if we believe we have sufficient funds for our current or future operating plans. If we are unable to raise capital when needed or on attractive terms, we would be forced to delay, reduce or eliminate our research and development programs or commercialization efforts.

We currently expect that cash, cash equivalents and short- and long-term investments at March 31, 2022 will be sufficient to fund our current operating plans and capital expenditure requirements for at least twelve months from the date of issuance of the financial statements contained in this Quarterly Report on Form 10-Q while we continue to commercialize XPOVIO in the U.S. and continue the clinical trials of our product candidates. Our future long-term capital requirements will depend on many factors, as described more fully in the risk factor entitled "*We will need additional funding to achieve our business objectives. If we are unable to raise capital when needed or on acceptable terms, we would be forced to delay, reduce or eliminate our research and development programs and/or commercialization efforts*," under the heading *"Risk Factors*" in this Quarterly Report on Form 10-Q.

In addition to the expenses required to fund our operations described above, our funding requirements also include the following:

- Lease costs for our headquarters in Newton, Massachusetts with a term through September 30, 2025, which totaled $2.8 million in 2021 and increase annually; we expect total future lease costs to be approximately $13.1 million;
- Increased cash operating expenditures over our 2021 totals of $107.1 million;
- Future long-term debt obligations related to the Notes of $169.5 million over the next four years; and
- Future royalty obligations to HCR under our Revenue Interest Financing Agreement of approximately $217.6 million.

Item 3. Quantitative and Qualitative Disclosures About Market Risk.

We are exposed to market risk related to changes in interest rates. We had cash, cash equivalents and investments of $205.3 million as of March 31, 2022. Our primary exposure to market risk is interest rate sensitivity, which is affected by changes in the general level of U.S. interest rates, particularly because our investments are short-term securities. Due to the short-term duration of our investment portfolio and the low risk profile of our investments, an immediate 100 basis point shift in interest rates would not have a material effect on the fair market value of our investment portfolio.

We do not believe our cash, cash equivalents and investments have significant risk of default or illiquidity. While we believe our cash, cash equivalents and investments do not contain excessive risk, we cannot provide absolute assurance that in the future our investments will not be subject to adverse changes in securities at one or more financial institutions that are in excess of federally insured limits. Given the potential instability of financial institutions, we cannot provide assurance that we will not experience losses on these deposits and investments.

We are also exposed to market risk related to changes in foreign currency exchange rates. We contract with contract research organizations and contract manufacturing organizations that are located in Canada and Europe, which are denominated in foreign currencies. We also contract with a number of clinical trial sites outside of the U.S., and our budgets for those studies are frequently denominated in foreign currencies. We are subject to fluctuations in foreign currency rates in connection with these agreements. We do not currently hedge our foreign currency exchange rate risk.

Item 4. Controls and Procedures.

Evaluation of Disclosure Controls and Procedures

Our management, with the participation of our President and Chief Executive Officer (principal executive officer) and Executive Vice President, Chief Financial Officer and Treasurer (principal financial officer), evaluated the effectiveness of our disclosure controls and procedures as of March 31, 2022. The term “disclosure controls and procedures,” as defined in Rules 13a-15(e) and 15d-15(e) under the Securities Exchange Act of 1934, as amended (the “Exchange Act”), means controls and other procedures of a company that are designed to ensure that information required to be disclosed by a company in the reports that it files or submits under the Exchange Act is recorded, processed, summarized and reported, within the time periods specified in the SEC’s rules and forms. Disclosure controls and procedures include, without limitation, controls and procedures designed to ensure that information required to be disclosed by a company in the reports that it files or submits under the Exchange Act is accumulated and communicated to our management, including our principal executive and principal financial officers, as appropriate to allow timely decisions regarding required disclosure. Management recognizes that any controls and procedures, no matter how well designed and operated, can provide only reasonable assurance of achieving their objectives and management necessarily applies our judgment in evaluating the cost-benefit relationship of possible controls and procedures. Based on the evaluation of our disclosure controls and procedures as of March 31, 2022, our President and Chief Executive Officer and our Executive Vice President, Chief Financial Officer and Treasurer concluded that, as of such date, our disclosure controls and procedures were effective at the reasonable assurance level.

Changes in Internal Control Over Financial Reporting

There were no changes in our internal control over financial reporting identified in connection with the evaluation required by Rule 13a-15(d) and 15d-15(d) of the Exchange Act that occurred during the fiscal quarter ended March 31, 2022 that have materially affected, or are reasonably likely to materially affect, our internal control over financial reporting.

PART II - OTHER INFORMATION

Item 1. Legal Proceedings.

From time to time we may face legal claims or actions in the normal course of business. We were named as a defendant in a securities class action litigation filed on July 23, 2019 in the U.S. District Court for the District of Massachusetts. The complaint was filed by the Allegheny County Employees' Retirement System, against us and certain of our current and former executive officers and directors as well as the underwriters of our public offerings of common stock conducted in April 2017 and May 2018. This complaint was voluntarily dismissed on March 12, 2020. A second complaint was filed by Heather Mehdi on September 17, 2019, in the same court and against the same defendants with the exception of the underwriters. In April 2020, the court appointed a lead plaintiff, Myo Thant ("Plaintiff"), who filed an amended complaint on June 29, 2020. The amended complaint alleges violations of federal securities laws based on our disclosures related to the results from the Phase 2 SOPRA study and Part 2 of the Phase 2b STORM study, and seeks unspecified compensatory damages, including interest; reasonable costs and expenses, including attorneys' and expert fees; and such equitable/injunctive relief or other relief as the court may deem just and proper. We have reviewed the allegations and believe they are without merit. We moved to dismiss the complaint on July 31, 2020 and concluded related briefing in September 2020. Before the court ruled on this motion to dismiss, Plaintiff filed a second amended complaint. We moved to dismiss the second amended complaint on November 2, 2020 and completed related briefing on December 3, 2020. On July 21, 2021, the court issued a decision dismissing the securities class action complaint, and an order of dismissal was issued on the same date. On August 20, 2021, Plaintiff filed a Notice of Appeal. Appellate briefing before the First Circuit was completed on December 30, 2021, and oral argument took place on February 8, 2022. While we cannot predict the outcome of the appeal, we believe the appeal is without merit and intend to defend vigorously against this litigation.

On December 14, 2020, we were named as a defendant in a shareholder derivative suit based on allegations substantially similar to those in the class action litigation. The suit was filed in the U.S. District Court for the District of Massachusetts, by Plaintiff Vladimir Gusinsky Revocable Trust, against us and certain of our current and former executive officers and directors. On January 12, 2021, the shareholder derivative suit was stayed pending the outcome of further proceedings in the securities class action and currently remains stayed.

Item 1A. Risk Factors.

Careful consideration should be given to the following material risk factors, in addition to the other information set forth in this Quarterly Report on Form 10-Q and in other documents that we file with the U.S. Securities and Exchange Commission ("SEC") in evaluating us and our business. Investing in our common stock involves a high degree of risk. If any of the following risks and uncertainties actually occurs, our business, prospects, financial condition and results of operations could be materially and adversely affected. The risks described below are not intended to be exhaustive and are not the only risks we face. New risk factors can emerge from time to time, and it is not possible to predict the impact that any factor or combination of factors may have on our business, prospects, financial condition and results of operations.

References to XPOVIO® (selinexor) also refer to NEXPOVIO® (selinexor) when discussing its approval and commercialization outside of the U.S.

Risks Related to Commercialization and Product Development

Our business is substantially dependent on the commercial success of XPOVIO. If we, either alone or with our collaborators, are unable to successfully commercialize current and future indications of XPOVIO or other products or product candidates on a timely basis, including achieving widespread market acceptance by physicians, patients, third-party payors and others in the medical community, our business, financial condition and future profitability will be materially harmed.

Our business and our ability to generate product revenue from the sales of drugs that treat cancer and other diseases in humans depend heavily on our and our collaborators' ability to successfully commercialize our lead drug, XPOVIO® (selinexor) on a global basis, in currently approved and future indications and the level of market adoption for, and the continued use of, our products and product candidates, if approved. XPOVIO is currently approved and marketed in the U.S. in multiple hematologic malignancy indications, including in combination with Velcade® (bortezomib) and dexamethasone for the treatment of patients with multiple myeloma after at least one prior therapy, in combination with dexamethasone for the treatment of patients with heavily pretreated multiple myeloma and as a monotherapy for the treatment of patients with relapsed or refractory diffuse large B-cell lymphoma ("DLBCL"). Efforts to drive adoption within the medical community and third-party payors based on the benefits of our products and product candidates require significant resources and may not be successful. The success of XPOVIO and any current or future product candidates, whether alone or in collaboration with third-parties, including achieving and maintaining an adequate level of market adoption, depends on several factors, including:

- our ability to successfully launch and achieve broad adoption of our approved products in earlier lines of therapy following the approval of the expanded XPOVIO indication based on the results from our Phase 3 BOSTON study or

based on any future indications for which XPOVIO may be approved, or any product candidates for which we obtain marketing approval;

- actual or perceived advantages or disadvantages of our products or product candidates as compared to alternative treatments, including their respective safety, tolerability and efficacy profiles, the potential convenience and ease of administration, access or cost effectiveness;
- the effectiveness of our sales, marketing, manufacturing and distribution strategies and operations;
- the competitive landscape for our products, including the timing of new competing products entering the market and the level and speed at which these products achieve market acceptance;
- the consistency of any new data we collect and analyses we conduct with prior results, whether they support a favorable safety, efficacy and effectiveness profile of XPOVIO and any potential impact on our U.S. Food and Drug Administration ("FDA") approvals and/or FDA package insert for XPOVIO and comparable foreign regulatory approvals and package inserts;
- our ability to comply with the FDA's and comparable foreign regulatory authorities' post-marketing requirements and commitments, including through successfully conducting, on a timely basis, additional studies that confirm clinical efficacy, effectiveness and safety of XPOVIO and acceptance of the same by the FDA, such as requirements in connection with the FDA's June 2020 approval of XPOVIO based on the results of the SADAL study to treat patients with DLBCL, which was approved under the FDA's Accelerated Approval Program;
- acceptance of current and future indications of XPOVIO and, if approved, our product candidates, by patients, the medical community and third-party payors;
- obtaining and maintaining coverage, adequate pricing and reimbursement by third-party payors, including government payors, for XPOVIO and our product candidates, if approved;
- the willingness of patients to pay out-of-pocket in the absence of third-party coverage or as co-pay amounts under third-party coverage;
- our ability to enforce intellectual property rights in and to our products to prohibit a third-party from marketing a competing product and our ability to avoid third-party patent interference or intellectual property infringement claims;
- current and future restrictions or limitations on our approved or future indications and patient populations or other adverse regulatory actions;
- the performance of our manufacturers, license partners, distributors, providers and other business partners, over which we have limited control;
- any significant misestimations of the size of the market and market potential for any of our products or product candidates;
- establishing and maintaining commercial manufacturing capabilities or making arrangements with third-party manufacturers;
- the willingness of the target patient population to try new therapies and of physicians to prescribe these therapies, based, in part, on their perception of our clinical trial data and/or the actual or perceived safety, tolerability and effectiveness profile;
- maintaining an acceptable safety and tolerability profile of our approved products, including the prevalence and severity of any side effects;
- the ability to offer our products for sale at competitive prices;
- adverse publicity about our products or favorable publicity about competitive products;
- our ability to maintain compliance with existing and new health care laws and regulations, including government pricing, price reporting and other disclosure requirements related to such laws and regulations and the potential impact of such requirements on physician prescribing practices and payor coverage; and
- the impact of the novel coronavirus disease ("COVID-19") pandemic on the above factors, including the limitation of our sales professionals to meet in person with healthcare professionals as the result of travel restrictions or limitations on access for non-patients.

If we do not achieve one or more of these factors in a timely manner, or at all, either on our own or with our collaborators, we could experience significant delays or an inability to successfully commercialize XPOVIO or our product candidates, if approved, which would materially harm our business.

We face substantial competition, which may result in others discovering, developing or commercializing drugs before or more successfully than we do.

The discovery, development and commercialization of new drugs is highly competitive, particularly in the cancer field. We and our collaborators face competition with respect to XPOVIO and will face competition with respect to any product candidates that we may seek to discover and develop or commercialize in the future, from major pharmaceutical companies, specialty pharmaceutical companies, biotechnology companies, academic institutions and governmental agencies as well as public and private research institutions worldwide, many of which have significantly greater financial resources and expertise in research and development, manufacturing, preclinical studies, conducting clinical trials, obtaining regulatory approvals and marketing approved products than we do. There are a number of major pharmaceutical, specialty pharmaceutical and biotechnology companies that currently market and sell drugs and/or are pursuing the development of drugs for the treatment of cancer and the other disease indications for which we, and our collaborators, are developing our product candidates. For example, BLENREP (belantamab mafodotin), ABECMA® (idecabtagene vicleucel) and CARVYKTI™ (ciltacabtagene autoleucel) were approved for the treatment of multiple myeloma by the FDA in 2020, 2021, and 2022, respectively. In addition, several new novel therapeutics such as bispecific T-Cell engagers and a BCL-2 inhibitor are in clinical development and may be introduced into the multiple myeloma market beginning in 2022. The approval of these anti-cancer agents, or any others which may receive regulatory approval, may have a significant impact on the therapeutic landscape and our product revenues. See Item 1 under the heading *Business—Competition* in our Annual Report on Form 10-K for the year ended December 31, 2021 as filed with the SEC on March 1, 2022 ("Annual Report") for more information on competition.

We are initially focused on developing and commercializing our current products and product candidates for the treatment of cancer and there are a variety of available therapies marketed for cancer. In many cases, cancer drugs are administered in combination to enhance efficacy. Some of these drugs are branded and subject to patent protection, and others are available on a generic basis. Many of these approved drugs are well-established therapies and are widely accepted by physicians, patients and third-party payors. Insurers and other third-party payors may also encourage the use of generic drugs. Our products are priced at a significant premium over competitive generic drugs, which may make it difficult for us to achieve our business strategy of using our products in combination with existing therapies or replacing existing therapies with our products.

Further, our commercial opportunity could be reduced or eliminated if our competitors develop and commercialize drugs that are or are perceived to be more effective, safer, more tolerable, more convenient and/or less costly than any of our currently approved products or product candidates or that would render our products obsolete or non-competitive. Our competitors may also obtain marketing approval from the FDA or other regulatory authorities for their products more rapidly than we, or our collaborators, may obtain approval for ours, which could result in our competitors establishing a stronger market position before we, or our collaborators, are able to enter the market or preventing us, or our collaborators, from entering into a particular indication at all.

Mergers and acquisitions in the pharmaceutical and biotechnology industries may result in even more resources being concentrated among a smaller number of our competitors. Smaller and other early-stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies. These third parties compete with us in recruiting and retaining qualified scientific and management personnel, establishing clinical trial sites and patient registration for clinical trials, as well as in acquiring technologies complementary to, or that may be necessary for, our programs.

If we are not able to compete effectively against current or potential competitors, our business will not grow and our financial condition and operations will suffer.

Clinical development is a lengthy and expensive process, with uncertain timelines and outcomes. If clinical trials of our product candidates fail to demonstrate safety and efficacy to the satisfaction of regulatory authorities or do not otherwise produce positive results, we, or our collaborators, may incur additional costs or experience delays in completing, or ultimately be unable to complete, the development and commercialization of such product candidates.

Our long-term success depends in a large part on our ability to continue to successfully develop new indications of selinexor, our product candidates, including eltanexor, or any new product candidates we may develop or acquire. Clinical testing is expensive, time consuming, difficult to design and implement, inherently uncertain as to outcome and can fail at any stage of testing. Furthermore, the failure of any product candidates to demonstrate safety and efficacy in any clinical trial could negatively impact the perception of selinexor, eltanexor or our product candidates and/or cause the FDA or other regulatory authorities to require additional testing before any of our product candidates are approved.

We may experience numerous unforeseen events during, or as a result of, clinical trials that could delay or prevent our or our collaborators' ability to receive marketing approval of our product candidates, including, but not limited to, the following:

- delays or failure to reach agreement with regulatory authorities on a trial design or the receipt of feedback requiring us to modify the design of our clinical trials, perform additional or unanticipated clinical trials to obtain approval or alter our regulatory strategy, as is the case in connection with the recent feedback we received from the FDA on our SIENDO Study;
- clinical trials of our product candidates may produce negative or inconclusive results or other patient safety concerns, including undesirable side effects or other unexpected characteristics, and we may decide, or regulatory authorities may require us, to conduct additional clinical trials, suspend ongoing clinical trials or abandon drug development programs, including as a result of a finding that the participants are being exposed to unacceptable health risks;
- enrollment in our clinical trials may be slower than we anticipate, including as a result of competition with other ongoing clinical trials for the same indications as our product candidates;
- regulators may revise the requirements for approving our product candidates, even after providing a positive opinion on or otherwise reviewing and providing comments to a clinical trial protocol, or such requirements may not be as we anticipate;
- delays or failure in obtaining the necessary authorization from regulatory authorities or institutional review boards to permit us or our investigators to commence a clinical trial, conduct a clinical trial at a prospective trial site, or the suspension or termination of a clinical trial once commenced;
- delays or failure to reach agreement on acceptable terms with prospective clinical trial sites or contract research organizations ("CROs");
- the number of patients required for clinical trials of our product candidates may be larger than we anticipate or participants may drop out of these clinical trials at a higher rate than we anticipate;
- our third-party contractors, including manufacturers or CROs, may fail to comply with regulatory requirements, perform effectively, or meet their contractual obligations to us in a timely manner, or at all;
- we or our investigators might be found to be non-compliant with regulatory requirements;
- the cost of clinical trials of our product candidates may be greater than we anticipate;
- the supply or quality of our product candidates or other materials necessary to conduct clinical trials may be insufficient or inadequate;
- any partners or collaborators that help us conduct clinical trials may face any of the above issues, and may conduct clinical trials in ways they view as advantageous to them but that are suboptimal for us; and
- negative impacts resulting from the ongoing COVID-19 pandemic, including impacts to healthcare systems and our trial sites' ability to conduct trials.

The COVID-19 pandemic has had and may continue to have an impact on our clinical trials. For more information, please see the risk factor entitled, "*The COVID-19 pandemic has adversely disrupted, and is expected to continue to adversely disrupt, our operations, including our clinical trial activities and commercial operations, which could have an adverse effect on our business and financial results*." At this time, however, we cannot fully forecast the scope of the impact that the COVID-19 pandemic may continue to have on our ability to, among other things, initiate and oversee trial sites, enroll and assess patients, supply study drug and report trial results. In addition, we have and may continue to experience delays in the regulatory process as a result of the COVID-19 pandemic, which may impact our approval timelines. For example, inspections conducted by the European Medicines Agency ("EMA") in connection with regulatory reviews have recently been subject to scheduling delays due to certain COVID-19 related restrictions and impacts.

Further, in response to the COVID-19 pandemic, the FDA issued guidance on March 18, 2020, and updated it on July 2, 2020, January 27, 2021 and August 30, 2021, to address the conduct of clinical trials during the pandemic. The guidance sets out a number of considerations for sponsors of clinical trials impacted by the pandemic, including the requirement to include in the clinical study report (or as a separate document) contingency measures implemented to manage the study, and any disruption of the study as a result of COVID-19; a list of all study participants affected by COVID-19-related study disruptions by a unique subject identifier and by investigational site, and a description of how the individual's participation was altered; and analyses and corresponding discussions that address the impact of implemented contingency measures (e.g., participant discontinuation from investigational product and/or study, alternative procedures used to collect critical safety and/or efficacy data) on the safety and efficacy results reported for the study. In its most recent update to this guidance, the FDA addresses questions received during the past year from clinical practitioners who are adapting their operations in a pandemic environment. These questions focused on, among other things, when to suspend,

continue or initiate a trial and how to submit changes to protocols for investigational new drug applications and handle remote site monitoring visits.

If we, or our collaborators, are required to conduct additional clinical trials or other testing of our product candidates beyond those that we currently contemplate or are unable to successfully complete clinical trials of our product candidates or other testing, on a timely basis or at all, and/or if the results of these trials or tests are not positive or are only modestly positive or if there are safety concerns, we, or our collaborators, may:

- be delayed in obtaining, or not obtain at all, marketing approval for the indication or product candidate;
- obtain marketing approval in some countries and not in others;
- obtain approval for indications or patient populations that are not as broad as intended or desired;
- obtain approval with labeling that includes significant use or distribution restrictions or safety warnings, including boxed warnings;
- be subject to additional post-marketing testing requirements;
- not receive royalty or milestone revenue under our collaboration agreements for several years, or at all; or
- have the product removed from the market after obtaining marketing approval.

Further, we do not know whether clinical trials will begin as planned, will need to be restructured or will be completed on schedule, or at all, particularly as a result of the COVID-19 pandemic. Significant clinical trial delays also could shorten any periods during which we may have the exclusive right to commercialize our products, allow our competitors to bring products to market before we do or impair our ability to successfully commercialize our products, which would harm our business and results of operations. In addition, many of the factors that cause, or lead to, clinical trial delays may ultimately lead to the denial of regulatory approval of our product candidates.

Serious adverse or unacceptable side effects related to XPOVIO or future products or product candidates may delay or prevent their regulatory approval, cause us or our collaborators to suspend or discontinue clinical trials, limit the commercial value of approved indications or result in significant negative financial consequences following any marketing approval.

We currently have four product candidates in clinical development for the treatment of human diseases: selinexor, eltanexor, verdinexor and KPT-9274. Their risk of failure is high. If our current or future indications of XPOVIO or any of our product candidates are associated with undesirable side effects or have characteristics that are unexpected in clinical trials or following approval and/or commercialization, we may need to abandon or limit their development or limit marketing to certain uses or subpopulations in which the undesirable side effects or other characteristics are less prevalent, less severe or more acceptable from a risk-benefit perspective.

Adverse events (“AEs”) in our clinical trials to date have been generally predictable and typically manageable, including through prophylactic care or dose reductions, although some patients have experienced more serious AEs. The most common drug-related AEs in our clinical trials for XPOVIO were fatigue, nausea, anorexia, diarrhea, peripheral neuropathy, upper respiratory tract infection, vomiting, cytopenias, hyponatremia, weight loss, decreased appetite, cataract, dizziness, syncope, depressed level of consciousness, and mental status changes. These side effects were generally mild or moderate in severity. The most common AEs that were Grade 3 or Grade 4, meaning they were more than mild or moderate in severity, included thrombocytopenia, lymphopenia, hypophosphatemia, anemia, hyponatremia and neutropenia. To date, the most common AEs in the multiple myeloma patient population have been managed with supportive care and dose modifications. However, a number of patients have withdrawn from our clinical trials as a result of AEs and some patients across our clinical trials have experienced serious AEs deemed by us and the clinical investigator to be related to selinexor. Serious AEs generally refer to AEs that result in death, are life threatening, require hospitalization or prolonging of hospitalization, or cause a significant and permanent disruption of normal life functions, congenital anomalies or birth defects, or require intervention to prevent such an outcome.

The occurrence of AEs in either our clinical trials or following regulatory approval could result in a more restrictive label for any product candidates approved for marketing or could result in the delay or denial of approval to market any product candidates by the FDA or comparable foreign regulatory authorities, which could prevent us from generating sufficient revenue from product sales or ultimately achieving profitability. Treatment-related side effects could also affect patient recruitment or the ability of enrolled patients to complete the trial, result in potential product liability claims or cause patients and/or healthcare providers to elect alternative courses of treatment. In addition, these side effects may not be appropriately recognized or managed by the treating medical staff. Inadequate training or education of healthcare professionals to recognize or manage the potential side effects of XPOVIO or our product candidates, if approved, could result in increased treatment-related side effects and cause patients to discontinue treatment. Any of these occurrences may harm our business, financial condition and prospects significantly.

Results of our trials could reveal an unacceptably high severity and prevalence of side effects. In such an event, our trials could be suspended or terminated and the FDA or comparable foreign regulatory authorities could order us or our collaborators to cease further development of or deny approval of our product candidates for any or all targeted indications. Many compounds that initially showed promise in early-stage trials for treating cancer or other diseases have later been found to cause side effects that prevented further development of the compound. If such an event occurs after any of our or our collaborators' product candidates are approved and/or commercialized, a number of potentially significant negative consequences may result, including:

- regulatory authorities may withdraw the approval of such drug;
- regulatory authorities may require additional warnings on the label or impose distribution or use restrictions;
- patients and/or healthcare providers may elect to utilize other treatment options that have or are perceived to have more tolerable side effects;
- regulatory authorities may require one or more post-marketing studies;
- we may be required to create a medication guide outlining the risks of such side effects for distribution to patients;
- we could be sued and held liable for harm caused to patients; and
- our reputation may suffer.

Further, we, our collaborators and our clinical trial investigators, currently determine if serious adverse or unacceptable side effects are drug-related. The FDA or foreign regulatory authorities may disagree with our, our collaborators' or our clinical trial investigators' interpretation of data from clinical trials and the conclusion by us, our collaborators or our clinical trial investigators that a serious adverse effect or unacceptable side effect was not drug-related. The FDA or foreign regulatory authorities may require more information related to the safety of our products or product candidates, including additional preclinical or clinical data to support approval, which may cause us to incur additional expenses, delay or prevent the approval of one of our product candidates, and/or delay or cause us to change our commercialization plans, or we may decide to abandon the development of the product candidate altogether.

Any of these events could prevent us or our collaborators from achieving or maintaining market acceptance of the affected product candidate, if approved, or could substantially increase costs and expenses of development or commercialization, which could delay or prevent us from generating sufficient revenue from the sale of our products and harm our business and results of operations.

The COVID-19 pandemic has adversely disrupted, and is expected to continue to adversely disrupt, our operations, including our clinical trial activities and commercial operations, which could have an adverse effect on our business and financial results.

As a result of the COVID-19 pandemic that has affected many segments of the global economy, we have experienced, and we expect to continue to experience, disruptions that could adversely impact our business, clinical trial activities and commercial operations, including:

- negative impact to revenue for XPOVIO, which may continue as the COVID-19 pandemic persists, including as a result of decreased new patient starts due to the decreased ability of our sales force and our patients to meet with healthcare professionals in person;
- delays or difficulties in enrolling patients in our clinical trials;
- delays or difficulties in initiating new clinical studies, including clinical site initiation and oversight as well as difficulties in recruiting clinical site investigators and clinical site staff;
- reduction or diversion of healthcare resources away from the conduct of clinical trials, including the diversion of hospitals serving as our clinical trial sites and hospital staff supporting the conduct of our clinical trials;
- interruption of key clinical trial activities, such as clinical trial site data monitoring, due to limitations on travel imposed or recommended by government officials or entities, employers and others or interruption of clinical trial patient visits and study procedures (particularly any procedures that may be deemed non-essential), which may impact the integrity of clinical trial data and clinical study endpoints;
- interruption or delays in the operations of the FDA and comparable foreign regulatory agencies, including the EMA, which has and may impact regulatory review and approval timelines, such as the EMA review of our Type II variation to our Marketing Authorization for selinexor in multiple myeloma based on the results of the BOSTON study or any future Marketing Authorization Applications ("MAA");

- negative impacts on any or all aspects of our operations due to business disruptions related to COVID-19 at our third-party vendors who we rely upon in the conduct of our business. including supply chain disruptions; and
- limitations on employee resources that would otherwise be focused on the conduct of our business, including because of sickness of employees or their families, the desire of employees to avoid contact with large groups of people, and an increased reliance on working from home.

The full extent of the impact of the disruptions to our business, including commercial sales and clinical trials, as a result of the pandemic will depend on the availability, administration rates and effectiveness of vaccines and their effectiveness against variants as new strains of the virus evolve, and therapeutics and future developments, all of which are highly uncertain and cannot be predicted with confidence, such as the duration and severity of the pandemic, and the effectiveness of actions taken in the U.S. and other countries to contain and treat the disease. In addition, in October 2021, we began to require that all of our employees be fully vaccinated, subject to limited medical and religious exemptions. We cannot currently predict the impact on our operations of the vaccine mandate on our business or on third parties with whom we conduct business. Our business may be negatively impacted in the event that large numbers of employees or key employees do not comply with the mandate and we may experience workforce attrition or difficulties securing future employees as a result of our vaccine mandate policy. Due to the ongoing uncertainty regarding the severity and duration of the COVID-19 pandemic, including the emergence of new variants of COVID-19, we cannot predict whether our response to date or the actions we may take in the future will be effective in mitigating the effects of the COVID-19 pandemic on our business, results of operations or financial condition. Accordingly, we are unable at this time to predict the future impact of the COVID-19 pandemic on our operations, liquidity, and financial results.

The results of previous clinical trials may not be predictive of future trial results and interim or top-line data may be subject to change or qualification based on the complete analyses of data.

Clinical failure can occur at any stage of the clinical development process and, therefore, the outcome of preclinical studies and early-stage clinical trials may not be predictive of the success of later stage clinical trials. For example, certain data from our Phase 1 and Phase 2 clinical trials of selinexor are based on unaudited data provided by our clinical trial investigators. Finalization and cleaning of this data may change the conclusions drawn from this unaudited data provided by our clinical trial investigators indicating less promising results than we currently anticipate. Further, there can be significant variability in safety and/or efficacy results between different trials of the same product candidate due to numerous factors, including changes in trial protocols, differences in size and type of the patient populations, adherence to the dosing regimen and other trial protocols and the dropout rate among clinical trial participants. We do not know whether any Phase 2, Phase 3 or other clinical trials we may conduct will demonstrate consistent or adequate efficacy and safety data sufficient to obtain regulatory approval to market our product candidates, if approved. Moreover, preclinical and clinical data are often susceptible to varying interpretations and analyses, and many companies have suffered significant setbacks in late-stage clinical trials after achieving positive results in earlier development, and we could face similar setbacks.

We may publicly disclose preliminary, interim or top-line data from our clinical trials. These interim updates are based on a preliminary analysis of then-available data, and the results and related findings and conclusions are subject to change as further patient data become available and following a more comprehensive review of the data related to the particular study or trial. For example, on February 8, 2022, we announced positive top-line data results for our Phase 3 SIENDO study. On February 25, 2022, we discussed these data with the FDA in a pre-sNDA meeting. We and the FDA meeting participants had differing views on the statistical significance of the study and the overall clinical benefit for the whole study population. For this study or any other that we report preliminary, interim or top-line data, we make assumptions, estimations, calculations and conclusions as part of our analyses of data. We may not have received or had the opportunity to fully and carefully evaluate all data or our conclusions may differ from those of the FDA or other regulatory authorities. Consequently, the preliminary, interim or top-line data results that we report may differ from future results of the same studies, or different conclusions or considerations may qualify such results, once additional data have been received and fully evaluated or based on differing views from regulatory agencies, such as in the SIENDO Study. Preliminary, interim or top-line data also remain subject to audit and verification procedures that may result in the final data being materially different from the preliminary data we previously published. As a result, these early data points should be viewed with caution until the final data are available. Adverse differences between previous preliminary or interim data and future interim or final data could significantly harm our business.

We expect that in any later phase clinical trial where patients are randomized to receive either selinexor or eltanexor on the one hand, or standard of care, supportive care or placebo on the other hand, the primary endpoint will be either overall response rate or progression-free survival, meaning the length of time on treatment until objective tumor progression, or overall survival, while the primary endpoint in any later phase clinical trial that is not similarly randomized may be different. In some instances, the FDA and other regulatory bodies have accepted overall response rate as a surrogate for a clinical benefit and have granted regulatory approvals based on this or other surrogate endpoints, such as in our SADAL study and our STORM study. These clinical trials were not randomized against control arms and the primary endpoints of these trials were overall response rate. If selinexor does not demonstrate sufficient overall response rates for any other indication for which a clinical trial has overall response rate as a primary endpoint, or if

the FDA or foreign regulatory authorities do not deem overall response rate a sufficient endpoint, or deem a positive overall response rate to be insufficient, selinexor or eltanexor will likely not be approved for that indication based on the applicable study. Further, others, including regulatory agencies, may not accept or agree with our assumptions, estimates, calculations, conclusions or analyses or may interpret or weigh the importance of data differently, which could impact the value of the particular program, the approvability or commercialization of the particular product candidate or product and our company in general.

In addition, the information we choose to publicly disclose regarding a particular study or clinical trial is typically selected from a more extensive amount of available information. Furthermore, we may report interim analyses of only certain endpoints rather than all endpoints. Investors may not agree with what we determine is the material or otherwise appropriate information to include in our disclosure, and any information we determine not to disclose may ultimately be deemed significant with respect to future decisions, conclusions, views, activities or otherwise regarding a particular product, product candidate or our business.

If the interim or top-line data that we report differ from future or more comprehensive data, or if others, including regulatory authorities, disagree with the conclusions reached, our ability to obtain approval for and commercialize our product candidates, our business, operating results, prospects, or financial condition may be harmed.

We may not be successful in our efforts to identify or discover additional potential product candidates or our decisions to prioritize the development of certain product candidates over others may later prove wrong.

Part of our strategy involves identifying and developing product candidates to build a pipeline of product candidates. Our drug discovery efforts may not be successful in identifying compounds that are useful in treating cancer or other diseases. Our research programs may initially show promise in identifying potential product candidates, yet fail to yield product candidates for clinical development for a number of reasons, including:

- the research methodology used may not be successful in identifying potential product candidates;
- potential product candidates may, on further study, be shown to have harmful side effects or other characteristics that indicate that they are unlikely to be drugs that will receive marketing approval and/or achieve market acceptance; or
- potential product candidates may not be effective in treating their targeted diseases.

We are currently advancing multiple clinical development studies of selinexor, eltanexor and other product candidates, which may create a strain on our limited human and financial resources. As a result, we may not be able to provide sufficient resources to any single product candidate to permit the successful development and commercialization of such product candidate, which could result in material harm to our business. Further, because we have limited financial and managerial resources, we focus on research programs and product candidates that we identify for specific indications. As a result, we may forego or delay pursuit of opportunities with other product candidates or for other indications that later prove to have greater commercial potential. Our resource allocation decisions may cause us to fail to capitalize on viable commercial products or profitable market opportunities. Our spending on current and future research and development programs and product candidates for specific indications may not yield any additional commercially-viable products. If we do not accurately evaluate the commercial potential or target market for a particular product candidate, we may relinquish valuable rights to that product candidate through collaboration, licensing or other royalty arrangements in cases in which it would have been more advantageous for us to retain sole development and commercialization rights to such product candidate.

If we are unable to maintain or expand our sales, marketing and distribution capabilities, we may not be successful in commercializing XPOVIO or any of our products or product candidates, if approved, that we may acquire or develop.

We have built a commercial infrastructure in the U.S. for XPOVIO, our first commercial product, in hematological malignancies and our company did not previously have any prior experience in the sales, marketing or distribution of pharmaceutical drugs. If XPOVIO or any of our product candidates is approved for additional indications beyond hematological malignancies, such as solid tumors, we may need to evolve our sales, marketing and distribution capabilities and we may not be able to do so successfully or on a timely basis. In the future, we may choose to expand our sales, marketing and distribution infrastructure to market or co-promote one or more of our product candidates, if and when they are approved, or enter into additional collaborations with respect to the sale, marketing and distribution of our product candidates. We are working with existing and potential partners to establish the commercial infrastructure to support potential launches of selinexor outside of the U.S. For example, in December 2021, we entered into a license agreement with the Menarini Group ("Menarini") to, among other things, develop and commercialize NEXPOVIO® (selinexor) for all human oncology indications in Europe (including the United Kingdom ("UK")), Latin America and other key countries. For additional risks associated with commercializing our products outside of the U.S., please see the risk factor entitled "*We depend on collaborations with third parties for certain aspects of the development, marketing and/or commercialization of XPOVIO and/or our product candidates. If those collaborations are not successful, or if we are not able to maintain our existing collaborations or establish additional collaborations, we may have to alter our development and commercialization plans and may not be able to capitalize on the market potential of XPOVIO or our product candidates*" below.

There are risks involved with establishing and maintaining our own sales, marketing and distribution capabilities. For example, recruiting and training a sales force is expensive and time-consuming and could delay any commercial launch of a product candidate. Further, we may underestimate the size of the sales force required for a successful product launch and we may need to expand our sales force earlier and at a higher cost than we anticipated. If the commercial launch of any of our product candidates is delayed or does not occur for any reason, including if we do not receive marketing approval in the timeframe we expect, we may have prematurely or unnecessarily incurred commercialization expenses. This may be costly, and our investment would be lost if we cannot retain or reposition our sales and marketing personnel.

Factors that may inhibit our efforts to successfully commercialize XPOVIO or any product candidates, if approved, on our own include:

- our inability to recruit, train and retain adequate numbers of effective sales, market access, market analytics, operations and marketing personnel;
- the inability of sales personnel to obtain access to physicians or persuade adequate numbers of physicians to prescribe current or future products;
- the lack of complementary drugs, which may put us at a competitive disadvantage relative to companies with more extensive drug lines;
- unforeseen costs and expenses associated with creating an independent sales, marketing and distribution organization;
- our inability to obtain sufficient coverage and reimbursement from third-party payors and governmental agencies;
- our ability to supply sufficient inventory of our products for commercial sale; and
- existing or new competitors taking share from XPOVIO or any other future product or preventing XPOVIO or any other future product from gaining share in its approved indications.

Even if we, or our collaborators, are able to effectively commercialize XPOVIO or any approved product candidate that we may develop or acquire, the products may not receive coverage or may become subject to unfavorable pricing regulations, third-party reimbursement practices or healthcare reform initiatives, all of which would harm our business.

The legislation and regulations that govern marketing approvals, pricing and reimbursement for new drug products vary widely from country to country. As a result, we or our collaborators might obtain marketing approval for a drug in a particular country, but then be subject to price regulations that delay the commercial launch of the product, possibly for lengthy time periods, and negatively impact the revenues we, or our collaborators, are able to generate from product sales in that country. In the U.S., approval and reimbursement decisions are not linked directly, but there is increasing scrutiny from the Congress, regulatory authorities, payers, patients and pathway organizations of the pricing of pharmaceutical products. Adverse pricing limitations may also hinder our ability to recoup our investment in one or more product candidates, even if our product candidates obtain marketing approval.

Our, and our collaborators', ability to successfully commercialize XPOVIO or any of our product candidates that we may develop or acquire will depend, in part, on the extent to which reimbursement for these products is available from government health administration authorities, private health insurers and other organizations. Government authorities and third-party payors, such as private health insurers and health maintenance organizations, decide which medications they will pay for and establish reimbursement levels. Obtaining and maintaining adequate reimbursement for XPOVIO and any of our product candidates, if approved, may be difficult. Moreover, the process for determining whether a third-party payor will provide coverage for a product may be separate from the process for setting the price of a product or for establishing the reimbursement rate that such a payor will pay for the product. Further, one payor's determination to provide coverage for a product does not assure that other payors will also provide coverage and reimbursement for our products by third-party payors. Even with payer coverage, patients may be unwilling or unable to pay the copay required and may choose not to take XPOVIO.

A primary trend in the healthcare industry in the U.S. and elsewhere is cost containment. Government authorities and third-party payors have attempted to control costs by limiting coverage and the amount of reimbursement for particular medications. Increasingly, third-party payors are requiring that drug companies provide them with predetermined discounts from list prices and are challenging the prices charged for medical products. Third-party payors may also seek, with respect to an approved product, additional clinical evidence that goes beyond the data required to obtain marketing approval. They may require such evidence to demonstrate clinical benefits and value in specific patient populations or they may call for costly pharmaceutical studies to justify coverage and reimbursement or the level of reimbursement relative to other therapies before covering our products. Accordingly, we cannot be sure that reimbursement will be or will continue to be available for XPOVIO and any product that we, or our collaborators, commercialize and, if reimbursement is available, we cannot be sure as to the level of reimbursement and whether it will be adequate. Coverage and reimbursement may impact the demand for or the price of XPOVIO or any product candidate for which we, or our collaborators, obtain marketing approval. If reimbursement is not available or is available only at limited levels, we, or our collaborators, may not be able to successfully commercialize XPOVIO or any other approved products.

There may be significant delays in obtaining reimbursement for newly-approved drugs, and coverage may be more limited than the indications for which the drug is approved by the FDA or comparable foreign regulatory authorities. Moreover, eligibility for reimbursement does not imply that any drug will be paid for in all cases or at a rate that covers our costs, including research, development, manufacture, sale and distribution. Interim reimbursement levels for new drugs, if applicable, may also not be sufficient to cover our costs and may not be made permanent. Reimbursement rates may vary according to the use of the drug and the clinical setting in which it is used, may be based on reimbursement levels already set for lower cost drugs and may be incorporated into existing payments for other services. Net prices for drugs may be reduced by mandatory discounts or rebates required by government healthcare programs or private payors and by any future relaxation of laws that presently restrict imports of drugs from countries where they may be sold at lower prices than in the U.S. Third-party payors often rely upon Medicare coverage policy and payment limitations in setting their own reimbursement policies. Our inability to promptly obtain coverage and profitable payment rates from both government-funded and private payors for any approved drugs that we develop could have a material adverse effect on our operating results, our ability to raise capital needed to commercialize our products and our overall financial condition.

Product liability lawsuits against us could divert our resources, cause us to incur substantial liabilities and limit commercialization of XPOVIO or any other products that we may develop or acquire.

We face an inherent risk of product liability exposure related to our commercialization of XPOVIO and the testing of our product candidates in human clinical trials as the administration of our products to humans may expose us to liability claims, whether or not our products are actually at fault for causing any harm or injury. As XPOVIO is used over longer periods of time by a wider group of patients taking numerous other medicines or by patients with additional underlying conditions, the likelihood of adverse drug reactions or unintended side effects, including death, may increase. For example, we may be sued if any drug we develop allegedly causes injury or is found to be otherwise unsuitable during clinical testing, manufacturing, marketing or sale. Any such product liability claims may include allegations of defects in manufacturing, defects in design, a failure to warn of dangers inherent in the product, negligence, strict liability or a breach of warranties. Claims could also be asserted under state consumer protection acts. If we cannot successfully defend ourselves against claims that our products or product candidates caused injuries, we will incur substantial liabilities or be required to limit commercialization of our products. Regardless of merit or eventual outcome, liability claims may result in:

- decreased demand for XPOVIO and any other products that we may develop or acquire;
- injury to our reputation and significant negative media attention;
- withdrawal of clinical trial participants;
- initiation of investigations by regulators;
- product recalls, withdrawals or labeling, marketing or promotional restrictions;
- significant costs to defend the related litigation;
- substantial monetary awards to trial participants or patients;
- loss of revenue;
- reduced resources of our management to pursue our business strategy; and
- the inability to successfully commercialize XPOVIO and any other products that we may develop or acquire.

We currently hold clinical trial and general product liability insurance coverage, but that coverage may not be adequate to cover any and all liabilities that we may incur. Insurance coverage is increasingly expensive. We may not be able to maintain insurance coverage at a reasonable cost or in an amount adequate to satisfy any liability that may arise.

The business that we or our collaborators conduct outside of the U.S. may be adversely affected by international risks and uncertainties.

Although our operations are primarily based in the U.S., we conduct business outside of the U.S. and expect to continue to do so in the future. For instance, many of the sites at which our clinical trials are being conducted are located outside of the U.S. In addition, we and our collaborators are seeking and continue to plan to seek approvals to sell our and their products in foreign countries. Any business that we, or our collaborators, conduct outside of the U.S. will be subject to additional risks that may materially adversely affect our or their ability to conduct business in international markets, including:

- potentially reduced protection of our intellectual property rights;
- the potential for so-called parallel importing, which is what happens when a local seller, faced with high or higher local prices, opts to import goods from a foreign market (with low or lower prices) rather than buying them locally;

- unexpected changes in tariffs, trade barriers or regulatory requirements;
- economic weakness, including inflation, volatility in currency exchange rates or political instability in particular foreign economies and markets, including as a result of the current economic situation stemming from the COVID-19 pandemic and the adoption of comprehensive sanctions by, among others, the European Union (the "EU"), the U.S. and the UK in response to Russia's invasion of Ukraine, which sanctions restrict a wide range of trade and financial dealings with Russia and Russian persons, as well as certain regions in Ukraine;
- workforce uncertainty in countries where labor unrest is more common than in the U.S.;
- production shortages resulting from any events affecting a product candidate and/or finished drug product supply or manufacturing capabilities abroad;
- business interruptions resulting from pandemics (including the COVID-19 pandemic), geo-political actions, including war and terrorism, such as the ongoing conflict between Russia and Ukraine, climate change or natural disasters, including earthquakes, hurricanes, typhoons, floods and fires; and
- failure to comply with Office of Foreign Asset Control rules and regulations and the Foreign Corrupt Practices Act ("FCPA").

Risks Related to Regulatory Matters

Even if we, or our collaborators, complete the necessary preclinical studies and clinical trials for our product candidates, the regulatory approval process is expensive, time-consuming and uncertain and we or they may not receive approvals for the commercialization of some or all of our or their product candidates in a timely manner, or at all.

Our long-term success and ability to sustain and grow revenue depends on our and our collaborators' ability to continue to successfully develop our product candidates and obtain regulatory approval to market our or their products both in and outside of the U.S. In order to market and sell our products in the EU and many other jurisdictions, we and our collaborators must obtain separate marketing approvals and comply with numerous and varying regulatory requirements. The FDA and comparable foreign regulatory authorities, whose laws and regulations may differ from country to country, impose substantial requirements on the development of product candidates to become eligible for marketing approval and have substantial discretion in the process and may refuse to accept any application or may decide that the data are insufficient for approval and require additional preclinical studies, clinical trials or other studies and testing. The time required to obtain approval outside of the U.S. may differ substantially from that required to obtain FDA approval. For example, in many countries outside of the U.S., it is required that the drug be approved for reimbursement before the drug can be approved for sale in that country. Approval by the FDA does not ensure approval by regulatory authorities in other countries or jurisdictions, and approval by one regulatory authority outside of the U.S. does not ensure approval by regulatory authorities in other countries or jurisdictions or by the FDA. However, a failure or delay in obtaining regulatory approval in one country may have a negative effect on the regulatory process in other countries. For additional risks related to conducting business outside of the U.S., please see the risk factor below entitled "*The business that we conduct outside of the U.S. may be adversely affected by international risks and uncertainties*."

In addition, the FDA and foreign regulatory authorities retain broad discretion in evaluating the results of our clinical trials and in determining whether the results demonstrate that selinexor or any of our product candidates is safe and effective. If we are required to conduct additional clinical trials of selinexor or our product candidates prior to approval of additional indications in earlier lines of therapy or in combination with other drugs, including additional earlier phase clinical trials that may be required prior to commencing any later phase clinical trials, or additional clinical trials following completion of our current and planned later phase clinical trials, we may need substantial additional funds, and there is no assurance that the results of any such additional clinical trials will be sufficient for approval.

The process of obtaining marketing approvals, both in the U.S. and abroad, is lengthy, expensive and uncertain. It may take many years, if approval is obtained at all, and can vary substantially based upon a variety of factors, including the type, complexity and novelty of the product candidates involved. Securing marketing approval requires the submission of extensive preclinical and clinical data and supporting information, including manufacturing information, to regulatory authorities for each therapeutic indication to establish the product candidate's safety and efficacy. The FDA or other regulatory authorities may determine that our product candidates are not safe and effective, only moderately effective or have undesirable or unintended side effects, toxicities or other characteristics that preclude our obtaining marketing approval or prevent or limit commercial use.

Further, under the Pediatric Research Equity Act ("PREA"), an NDA or supplement to an NDA for certain drugs must contain data to assess the safety and effectiveness of the drug in all relevant pediatric subpopulations and to support dosing and administration for each pediatric subpopulation for which the product is safe and effective, unless the sponsor receives a deferral or waiver from the FDA. A deferral may be granted for several reasons, including a finding that the product or therapeutic candidate is ready for approval for use in adults before pediatric trials are complete or that additional safety or effectiveness data needs to be collected before the pediatric trials begin. The law requires the FDA to send a PREA Non-Compliance letter to sponsors who have failed to submit their

pediatric assessments required under PREA, have failed to seek or obtain a deferral or deferral extension or have failed to request approval for a required pediatric formulation. It further requires the FDA to publicly post the PREA Non-Compliance letter and sponsor's response. The applicable legislation in the EU also requires applicants to either conduct clinical trials in a pediatric population in accordance with a Pediatric Investigation Plan approved by the Pediatric Committee of the EMA or to obtain a waiver or deferral from the conduct of these studies by this Committee. For any of our product candidates for which we are seeking regulatory approval in the U.S. or the EU, we cannot guarantee that we will be able to obtain a waiver or alternatively complete any required studies and other requirements in a timely manner, or at all, which could result in in issuance and publication of a PREA Non-Compliance letter and associated reputational harm, our product candidate being considered misbranded and subject to relevant enforcement action, invalidation of the marketing application, and/or financial penalties.

We have limited experience in conducting and managing the clinical trials necessary to obtain marketing approvals. The approval of our and our collaborators' current or future product candidates for commercial sale could be delayed, limited or denied or we or they may be required to conduct additional studies for a number of reasons, including, but not limited to, the following:

- regulatory authorities may determine that our or our collaborators' product candidates do not demonstrate safety and effectiveness in accordance with regulatory agency standards based on a number of considerations, including AEs that are reported during clinical trials;
- regulatory authorities could analyze and/or interpret data from clinical trials and preclinical testing in different ways than we, or our collaborators, interpret them and determine that our data is insufficient for approval;
- regulatory authorities may require more information, including additional preclinical or clinical data or trials, to support approval, as in the case of our intention to conduct a new trial for selinexor in endometrial cancer following recent discussions with the FDA on our SIENDO Study;
- regulatory authorities could determine that our manufacturing processes are not properly designed, are not conducted in accordance with federal or other laws or otherwise not properly managed and we may be unable to obtain regulatory approval for a commercially viable manufacturing process for our product candidates in a timely manner, or at all;
- the supply or quality of our or our collaborators' product candidates for our clinical trials may be insufficient, inadequate or delayed;
- the size of the patient population required to establish the efficacy of our or our collaborators' product candidates to the satisfaction of regulatory agencies may be larger than we or they anticipated;
- our failure or the failure of clinical investigational sites and the records kept at the respective locations, including clinical trial data, to be in compliance with the FDA's current good clinical practices regulations ("GCP") or comparable regulations outside of the U.S., including the failure to pass inspections of our corporate site or our clinical trial sites, such as the January 2022 preapproval GCP inspection conducted by the EMA at our corporate headquarters and an inspection that took place in late 2021 at one of the clinical sites that participated in the BOSTON Study;
- regulatory authorities may change their approval policies or adopt new regulations;
- regulatory authorities may not be able to undertake reviews or approval processes in a timely manner, including delays as a result of the ongoing COVID-19 pandemic, such as with the EMA review of the MAA for selinexor in multiple myeloma based on the results of the BOSTON study;
- the results of our earlier clinical trials may not be representative of our future, larger trials;
- regulatory authorities may not agree with our or our collaborators' regulatory approval strategies or components of our or their regulatory filings, such as the design or implementation of the relevant clinical trials; or
- a product may not be approved for the indications that we, or our collaborators, request or may be limited or subject to restrictions or post-approval commitments that render the approved drug not commercially viable.

Further, we could face heightened risks with respect to seeking marketing approval in the UK as a result of the withdrawal of the UK from the EU, commonly referred to as Brexit. The UK is no longer part of the European Single Market and European Union Customs Union. As of January 1, 2021, the Medicines and Healthcare products Regulatory Agency ("MHRA") became responsible for supervising medicines and medical devices in Great Britain, comprising England, Scotland and Wales under domestic law, whereas Northern Ireland will continue to be subject to EU rules under the Northern Ireland Protocol. The MHRA will rely on the Human Medicines Regulations 2012 (SI 2012/1916) (as amended) ("HMR") as the basis for regulating medicines. The HMR has incorporated into the domestic law of the body of EU law instruments governing medicinal products that pre-existed prior to the UK's withdrawal from the EU. Any delay in obtaining, or an inability to obtain, any marketing approvals, as a result of Brexit or otherwise, may force us to restrict or delay efforts to seek regulatory approval in the UK for our product candidates, which could significantly and materially harm our business.

We, or our collaborators, may not be able to file for marketing approvals and may not receive necessary approvals to commercialize our or their products in any market. Any failure, delay or setback in obtaining regulatory approval for our or our collaborators' product candidates could materially adversely affect our or our collaborators' ability to generate revenue from a particular product candidate, which could result in significant harm to our financial position and adversely impact our stock price.

We, or our collaborators, may seek approval from the FDA or comparable foreign regulatory authorities to use accelerated development pathways for our product candidates. If we, or our collaborators, are not able to use such pathways, we, or they, may be required to conduct additional clinical trials beyond those that are contemplated, which would increase the expense of obtaining, and delay the receipt of, necessary marketing approvals, if we, or they, receive them at all. In addition, even if an accelerated approval pathway is available to us, or our collaborators, it may not lead to expedited approval of our product candidates, or approval at all.

Under the Federal Food, Drug and Cosmetic Act ("FDCA") and implementing regulations, the FDA may grant accelerated approval to a product candidate to treat a serious or life-threatening condition that provides meaningful therapeutic benefit over available therapies, upon a determination that the product has an effect on a surrogate endpoint or intermediate clinical endpoint that is reasonably likely to predict clinical benefit. The FDA considers a clinical benefit to be a positive therapeutic effect that is clinically meaningful in the context of a given disease, such as irreversible morbidity or mortality. For the purposes of accelerated approval, a surrogate endpoint is a marker, such as a laboratory measurement, radiographic image, physical sign, or other measure that is thought to predict clinical benefit, but is not itself a measure of clinical benefit. An intermediate clinical endpoint is a clinical endpoint that can be measured earlier than an effect on irreversible morbidity or mortality that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit measurement of a therapeutic effect that is considered reasonably likely to predict the clinical benefit of a drug. The accelerated approval pathway may be used in cases in which the advantage of a new drug over available therapy may not be a direct therapeutic advantage, but is a clinically important improvement from a patient and public health perspective. Prior to seeking such accelerated approval, we, or our collaborators, will continue to seek feedback from the FDA or comparable foreign regulatory agencies and otherwise evaluate our, or their, ability to seek and receive such accelerated approval.

There can be no assurance that the FDA or foreign regulatory agencies will agree with our, or our collaborators', surrogate endpoints or intermediate clinical endpoints in any of our, or their, clinical trials, or that we, or our collaborators, will decide to pursue or submit any additional New Drug Applications ("NDA") for accelerated approval or any other form of expedited development, review or approval. Similarly, there can be no assurance that, after feedback from the FDA or comparable foreign regulatory agencies, we, or our collaborators, will continue to pursue or apply for accelerated approval or any other form of expedited development, review or approval. Furthermore, for any submission of an application for accelerated approval or application under another expedited regulatory designation, there can be no assurance that such submission or application will be accepted for filing or that any expedited development, review or approval will be granted on a timely basis, or at all.

A failure to obtain accelerated approval or any other form of expedited development, review or approval for our product candidates, or withdrawal of a product candidate, would result in a longer time period until commercialization of such product candidate, could increase the cost of development of such product candidate and could harm our competitive position in the marketplace.

Under accelerated or conditional approval regulations of the FDA or comparable foreign regulatory authorities, we, and our collaborators, must comply with post-approval development and regulatory requirements to maintain the approval of XPOVIO or any future approved products and, if we, or our collaborators, fail to do so, the FDA or comparable foreign regulatory authorities could withdraw its approval of XPOVIO or any future approved products for the indication that received accelerated or conditional approval, which would lead to substantially lower revenues.

For drugs approved under the FDA's Accelerated Approval Program, the FDA typically requires post-marketing confirmatory trials to evaluate the anticipated effect on irreversible morbidity or mortality or other clinical benefit. These confirmatory trials must be completed with due diligence. For example, in June 2020, the FDA approved XPOVIO to treat DLBCL under the FDA's accelerated approval regulations and as a condition of the accelerated approval for this indication we are required to (i) complete and submit a final report with full datasets from a randomized, double-blind, placebo-controlled Phase 3 trial that verifies and describes the clinical benefit of selinexor in patients with relapsed or refractory DLBCL and (ii) provide the interim and final analyses of a randomized Phase 2 clinical trial of selinexor to characterize the safety and efficacy of at least two different dosing regimens of selinexor monotherapy in patients with relapsed or refractory DLBCL after at least two prior lines of systemic therapy. We intend to satisfy the Phase 3 trial requirement though our XPORT-DLBCL-030 study and we may not be able to successfully and timely complete this study or any other post-marketing confirmatory study as required to maintain approval or achieve full approval, including as a result of adverse impacts from the ongoing COVID-19 pandemic. If the required post-approval studies fail to verify the clinical benefits of XPOVIO or confirm that the surrogate marker used for accelerated approval of XPOVIO to treat DLBCL showed an adequate correlation with clinical outcomes, if a sufficient number of participants cannot be enrolled, or if we fail to perform the required post-approval studies with due diligence or on a timely basis, the FDA has the authority to withdraw approval of the drug following a hearing conducted under the FDA's regulations, which could have a material adverse impact on our business. We cannot

be certain of the results of the confirmatory clinical studies for the DLBCL indication or any other future conditional approval we receive or what action the FDA may take if the results of those studies are not as expected based on clinical data that FDA has already reviewed.

Similar risks to those described above are also applicable to any application that we, or our collaborators, have submitted or may submit to the EMA to support conditional approval of selinexor to treat heavily pretreated multiple myeloma, relapsed or refractory DLBCL, or any other cancer indication. For medicinal products where the benefit of immediate availability outweighs the risk of less comprehensive data than normally required, based on the scope and criteria defined in legislation and guidelines, it is possible to obtain a conditional marketing authorization in the EU with a 12-month validity period and annual renewal pursuant to Regulation No 507/2006. These are granted only if the EMA's Committee for Medicinal Products for Human Use ("CHMP") finds that all four of the following requirements are met: (i) the benefit-risk balance of the product is positive; (ii) it is likely that the applicant will be able to provide comprehensive data; (iii) unmet medical needs will be fulfilled; and (iv) the benefit to public health of the medicinal product's immediate availability on the market outweighs the risks due to need for further data. Once a conditional marketing authorization has been granted, the marketing authorization holder must fulfil specific obligations within defined timelines. These obligations could include completing ongoing or new studies or collecting additional data to confirm the medicine's benefit-risk balance remains positive.

In March 2021, we received conditional marketing authorization from the European Commission ("EC") for NEXPOVIO to treat adult patients with multiple myeloma who have received at least four prior therapies and whose disease is refractory to at least two proteasome inhibitors, two immunomodulatory agents, and an anti-CD38 monoclonal antibody, and who have demonstrated disease progression on the last therapy. This marketing authorization, or any others we, or our collaborators, obtain from the EC in the future, is valid for a period of one year and could be renewed/prolonged if the conditions set out in the conditional marketing authorization are met. If we, or our collaborators, are not able to fulfill these specific obligations set out in the conditional marketing authorization requirements (which include the presentation of additional clinical data on the safety and efficacy for NEXPOVIO), the marketing authorization for the EU may not be prolonged and we, or our collaborators, will no longer be able to market NEXPOVIO in the EU.

XPOVIO and any of our product candidates for which we, or our collaborators, obtain marketing approval in the future are subject to post-marketing regulatory requirements and could be subject to post-marketing restrictions or withdrawal from the market, and we, and our collaborators, may be subject to substantial penalties if we, or they, fail to comply with regulatory requirements or if we, or they, experience unanticipated problems with our products following approval.

Once marketing approval has been granted, an approved product and its manufacturer and marketer are subject to ongoing review and extensive regulation. XPOVIO and any of our product candidates for which we, or our collaborators, obtain marketing approval in the future, as well as the manufacturing processes, post-approval studies and measures, labeling, advertising and promotional activities for such drug, among other things, will be subject to continual requirements of and review by the FDA and other U.S. and foreign regulatory authorities. These requirements include submissions of safety and other post-marketing information and reports, registration and listing requirements, requirements relating to manufacturing, quality control, quality assurance and corresponding maintenance of records and documents, and requirements regarding the distribution of samples to physicians and recordkeeping. For example, as a condition of the XPOVIO approval by the FDA for the multiple myeloma and DLBCL indications, we are required to complete certain post-marketing commitments. Even if marketing approval of a product candidate is granted, the approval may be subject to limitations on the indicated uses for which the drug may be marketed or to the conditions of approval, including the requirement to implement a Risk Evaluation and Mitigation Strategy, which could include requirements for a restricted distribution system.

The FDA and comparable foreign regulatory authorities may also impose requirements for costly post-marketing studies or clinical trials and surveillance to monitor the safety or efficacy of a drug. The FDA and other U.S. or foreign agencies, including the Department of Justice (the "DOJ"), closely regulate and monitor the post-approval marketing and promotion of drugs to ensure that they are manufactured, marketed and distributed only for the approved indications and in accordance with the provisions of the approved labeling. The FDA imposes stringent restrictions on manufacturers' communications regarding off-label use, and if we, or our collaborators communicate about any of our product candidates for which we, or they, receive marketing approval in a way that regulators assert goes beyond their approved indications, we, or they, may be subject to warnings or enforcement action for off-label marketing. Alleged violations of the FDCA or other statutes, including the False Claims Act (the "FCA"), relating to the promotion and advertising of prescription drugs may lead to investigations or allegations of violations of federal and state health care fraud and abuse laws and state consumer protection laws. In September 2021, the FDA published final regulations which describe the types of evidence that the agency will consider in determining the intended use of a drug or biologic.

In addition, manufacturers of approved products and those manufacturers' facilities are required to comply with extensive requirements by the FDA and comparable foreign regulatory authorities, including ensuring that quality control and manufacturing procedures conform to current Good Manufacturing Practice ("cGMP"), which include requirements relating to quality control and quality assurance as well as the corresponding maintenance of records and documentation and reporting requirements. We, our

contract manufacturers, our collaborators and their contract manufacturers could be subject to periodic unannounced inspections by the FDA or foreign regulatory authorities to monitor and ensure compliance with cGMPs or other regulations.

Post-approval discovery of previously unknown problems with our products, including AEs of unanticipated severity or frequency, or relating to our manufacturing processes, data integrity issues with regulatory filings, or failure to comply with regulatory requirements, may yield various results, including:

- litigation involving patients taking our drug;
- restrictions on our manufacturers or manufacturing processes;
- restrictions on the labeling or marketing of our products;
- restrictions on the distribution or use of our products;
- requirements to conduct post-marketing studies or clinical trials;
- warning letters or untitled letters;
- withdrawal, recall or seizure of our products from the market;
- refusal to approve pending applications or supplements to approved applications that we submit;
- fines, restitution or disgorgement of profits or revenues;
- suspension or withdrawal of marketing approvals;
- damage to relationships with our current or potential collaborators;
- unfavorable press coverage and damage to our reputation;
- refusal to permit the import or export of our products; or
- injunctions or the imposition of civil or criminal penalties.

Similar restrictions apply to the approval of our products in the EU. The holder of the marketing authorization is required to comply with a range of requirements applicable to the manufacturing, marketing, promotion and sale of medicinal products. These include:

- compliance with the EU's stringent pharmacovigilance or safety reporting rules, which can impose post-authorization studies and additional monitoring obligations;
- the manufacturing of authorized medicinal products, for which a separate manufacturer's license is mandatory, must also be conducted in strict compliance with the applicable EU laws, regulations and guidance, including Directive 2001/83/EC, Directive 2003/94/EC, Regulation (EC) No 726/2004 and the European Commission Guidelines for Good Manufacturing Practice. These requirements include compliance with EU cGMP standards when manufacturing medicinal products and active pharmaceutical ingredients, including the manufacture of active pharmaceutical ingredients outside of the EU with the intention to import the active pharmaceutical ingredients into the EU; and
- the marketing and promotion of authorized drugs, including industry-sponsored continuing medical education and advertising directed toward the prescribers of drugs and/or the general public, are strictly regulated in the EU notably under Directive 2001/83/EC, as amended, and are also subject to EU Member State laws. Direct-to-consumer advertising of prescription medicines is prohibited across the EU.

Accordingly, in connection with our currently approved products and assuming we, or our collaborators, receive marketing approval for one or more of our product candidates, we, and our collaborators, and our and their contract manufacturers will continue to expend time, money and effort in all areas of regulatory compliance, including manufacturing, production, product surveillance and quality control. If we, and our collaborators, are not able to comply with post-approval regulatory requirements, our or our collaborators' ability to market any future products could be limited, which could adversely affect our ability to achieve or sustain profitability. Further, the cost of compliance with post-approval regulations may have a negative effect on our operating results and financial condition.

We may seek certain designations for our product candidates in or outside of the U.S., including Breakthrough Therapy, Fast Track and Priority Review designations, and PRIME Designation in the EU, but we might not receive such designations, and even if we do, such designations may not lead to a faster development or regulatory review or approval process.

We may seek certain designations for one or more of our product candidates that could expedite review and approval by the FDA. A Breakthrough Therapy product is defined as a product that is intended, alone or in combination with one or more other

products, to treat a serious condition, and preliminary clinical evidence indicates that the product may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. For products that have been designated as breakthrough therapies, interaction and communication between the FDA and the sponsor of the trial can help to identify the most efficient path for clinical development while minimizing the number of patients placed in ineffective control regimens.

The FDA may also designate a product for Fast Track review if it is intended, whether alone or in combination with one or more other products, for the treatment of a serious or life-threatening disease or condition, and it demonstrates the potential to address unmet medical needs for such a disease or condition. For Fast Track products, sponsors may have greater interactions with the FDA and the FDA may initiate review of sections of a Fast-Track product's application before the application is complete. This rolling review may be available if the FDA determines, after preliminary evaluation of clinical data submitted by the sponsor, that a Fast-Track product may be effective.

We may also seek a priority review designation for one or more of our product candidates. If the FDA determines that a product candidate offers major advances in treatment or provides a treatment where no adequate therapy exists, the FDA may designate the product candidate for priority review. A priority review designation means that the goal for the FDA to review an application is six months, rather than the standard review period of ten months.

These designations are within the discretion of the FDA. Accordingly, even if we believe that one of our product candidates meets the criteria for these designations, the FDA may disagree and instead determine not to make such designation. Further, even if we receive a designation, the receipt of such designation for a product candidate may not result in a faster development or regulatory review or approval process compared to products considered for approval under conventional FDA procedures and does not assure ultimate approval by the FDA. For example, in connection with our NDA for XPOVIO, in March 2019, the FDA extended the Prescription Drug User Fee Act action date by three months following our submission of additional, existing clinical information as an amendment to the NDA, which resulted in a nine-month review cycle despite the priority review designation. In addition, even if one or more of our product candidates qualifies for these designations, the FDA may later decide that the product candidates no longer meet the conditions for qualification or decide that the time period for FDA review or approval will not be shortened.

In the EU, we or our collaborators may seek PRIME designation for some of our product candidates in the future. PRIME is a voluntary program aimed at enhancing the EMA's role to reinforce scientific and regulatory support in order to optimize development and enable accelerated assessment of new medicines that are of major public health interest with the potential to address unmet medical needs. The program focuses on medicines that target conditions for which there exists no satisfactory method of treatment in the EU or even if such a method exists, it may offer a major therapeutic advantage over existing treatments. PRIME is limited to medicines under development and not authorized in the EU and the applicant intends to apply for an initial MAA through the centralized procedure. To be accepted for PRIME, a product candidate must meet the eligibility criteria with respect to its major public health interest and therapeutic innovation based on information that is capable of substantiating the claims. The benefits of a PRIME designation include the appointment of a CHMP rapporteur to provide continued support and help to build knowledge ahead of a MAA, early dialogue and scientific advice at key development milestones, and the potential to qualify products for accelerated review, meaning reduction in the review time for an opinion on approvability to be issued earlier in the application process. PRIME enables an applicant to request parallel EMA scientific advice and health technology assessment advice to facilitate timely market access. Even if we or our collaborators receive PRIME designation for any of our product candidates, the designation may not result in a materially faster development process, review or approval compared to conventional EMA procedures. Further, obtaining PRIME designation does not assure or increase the likelihood of the EMA's grant of a marketing authorization.

We may not be able to obtain orphan drug exclusivity for any product candidates we may develop, and even if we do, that exclusivity may not prevent the FDA or the EMA from approving other competing products.

Under the Orphan Drug Act, the FDA may designate a product as an orphan drug if it is a drug or biologic intended to treat a rare disease or condition. A similar regulatory scheme governs approval of orphan products by the EMA in the EU. Generally, if a product candidate with an orphan drug designation subsequently receives the first marketing approval for the indication for which it has such designation, the product is entitled to a period of marketing exclusivity, which precludes the FDA or the EMA from approving another marketing application for the same product for the same therapeutic indication for that time period. The applicable period is seven years in the U.S. and ten years in the EU. The exclusivity period in the EU can be reduced to six years if a product no longer meets the criteria for orphan drug designation, in particular if the product is sufficiently profitable so that market exclusivity is no longer justified.

In order for the FDA to grant orphan drug exclusivity to one of our products, the agency must find that the product is indicated for the treatment of a condition or disease with a patient population of fewer than 200,000 individuals annually in the U.S. The FDA may conclude that the condition or disease for which we seek orphan drug exclusivity does not meet this standard. Even if we obtain orphan drug exclusivity for a product, that exclusivity may not effectively protect the product from competition because different products can be approved for the same condition. In addition, even after an orphan drug is approved, the FDA and comparable foreign regulatory authorities such as the EMA can subsequently approve the same product for the same condition if the FDA or such other

authorities conclude that the later product is clinically superior in that it is shown to be safer, more effective or makes a major contribution to patient care. Orphan drug exclusivity may also be lost if the FDA or EMA determines that the request for designation was materially defective or if the manufacturer is unable to assure sufficient quantity of the product to meet the needs of the patients with the rare disease or condition.

In 2017, the Congress passed the FDA Reauthorization Act of 2017 ("FDARA"). FDARA, among other things, codified the FDA's pre-existing regulatory interpretation, to require that a drug sponsor demonstrate the clinical superiority of an orphan drug that is otherwise the same as a previously approved drug for the same rare disease in order to receive orphan drug exclusivity. Under omnibus legislation signed by former President Trump in December 2020, the requirement for a product to show clinical superiority applies to drugs and biologics that received orphan drug designation before enactment of FDARA in 2017, but have not yet been approved or licensed by the FDA.

The FDA may further reevaluate the Orphan Drug Act and its regulations and policies. This may be particularly true in light of a decision from the Court of Appeals for the 11th Circuit in September 2021 finding that, for the purpose of determining the scope of exclusivity, the term "same disease or condition" means the designated "rare disease or condition" and could not be interpreted by the FDA to mean the "indication or use." Thus, the court concluded, orphan drug exclusivity applies to the entire designated disease or condition rather than the "indication or use." We do not know if, when, or how the FDA may change the orphan drug regulations and policies in the future, and it is uncertain how any changes might affect our business. Depending on what changes the FDA may make to its orphan drug regulations and policies, our business could be adversely impacted.

Inadequate funding for the FDA, the SEC and other government agencies, including from government shut downs, or other disruptions to these agencies' operations, could hinder their ability to hire and retain key leadership and other personnel, prevent new products and services from being developed or commercialized in a timely manner or otherwise prevent those agencies from performing normal business functions on which the operation of our business may rely, which could negatively impact our business.

The ability of the FDA to review and approve new products can be affected by a variety of factors, including government budget and funding levels, ability to hire and retain key personnel and accept the payment of user fees, and statutory, regulatory and policy changes. Average review times at the agency have fluctuated in recent years as a result. Disruptions at the FDA and other agencies may also slow the time necessary for new product candidates to be reviewed and/or approved by necessary government agencies, which would adversely affect our business. In addition, government funding of the SEC and other government agencies on which our operations may rely, including those that fund research and development activities, is subject to the political process, which is inherently fluid and unpredictable.

Disruptions at the FDA and other agencies may also slow the time necessary for new product candidates to be reviewed and/or approved by necessary government agencies, which would adversely affect our business. For example, over the last several years the U.S. government has shut down several times and certain regulatory agencies, such as the FDA and the SEC, have had to furlough critical employees and stop critical activities. If a prolonged government shutdown occurs, it could significantly impact the ability of the FDA to timely review and process our regulatory submissions, which could have a material adverse effect on our business. Further, future government shutdowns could impact our ability to access the public markets and obtain necessary capital in order to properly capitalize and continue our operations.

Separately, in response to the COVID-19 pandemic, a number of companies announced receipt of complete response letters due to the FDA's inability to complete required inspections for their applications. As of May 26, 2021, the FDA noted it was continuing to ensure timely reviews of applications for medical products during the ongoing COVID-19 pandemic in line with its user fee performance goals and conducting mission critical domestic and foreign inspections to ensure compliance of manufacturing facilities with FDA quality standards. Following a period of false starts, the FDA announced on February 2, 2022 that it would resume domestic inspections beginning on February 7, 2022. As for foreign inspections, the FDA indicated that it would continue planned inspections in countries that have received country clearance and are within the CDC's level 1 or level 2 COVID-19 travel recommendation. However, the FDA may not be able to continue its current pace and review timelines could be extended, including where a pre-approval inspection or an inspection of clinical sites is required and due to the ongoing COVID-19 pandemic and travel restrictions, the FDA is unable to complete such required inspections during the review period. Regulatory authorities outside the U.S. may adopt similar restrictions or other policy measures in response to the COVID-19 pandemic and may experience delays in their regulatory activities. If a prolonged government shutdown or other disruption occurs, it could significantly impact the ability of the FDA to timely review and process our regulatory submissions, which could have a material adverse effect on our business. Future shutdowns or other disruptions could also affect other government agencies such as the SEC, which may also impact our business by delaying review of our public filings, to the extent such review is necessary, and our ability to access the public markets.

Current and future legislation may increase the difficulty and cost for us, or any collaborators, to obtain marketing approval and commercialize our or their product candidates, if approved, and affect the prices we, or they, may obtain.

In the U.S. and some foreign jurisdictions, there have been a number of legislative and regulatory changes and proposed changes regarding the healthcare system that could, among other things, prevent or delay marketing approval of our or our collaborators' product candidates, restrict or regulate post-approval activities and affect our ability, or the ability of any collaborators, to profitably sell or commercialize XPOVIO or any product candidate for which we, or they, obtain marketing approval. We expect that current laws, as well as other healthcare reform measures that may be adopted in the future, may result in more rigorous coverage criteria and in additional downward pressure on the price that we, or any collaborators, may receive for any approved products. If reimbursement of our products is unavailable or limited in scope, our business could be materially harmed.

In March 2010, President Obama signed into law the Patient Protection and Affordable Care Act (the "PPACA"), as amended by the Health Care and Education Affordability Reconciliation Act (collectively the "ACA"). In addition, other legislative changes have been proposed and adopted since the ACA was enacted. In August 2011, the Budget Control Act of 2011, among other things, created measures for spending reductions by Congress. A Joint Select Committee on Deficit Reduction, tasked with recommending a targeted deficit reduction of at least $1.2 trillion for the years 2013 through 2021, was unable to reach required goals, thereby triggering the legislation's automatic reduction to several government programs. These changes included aggregate reductions to Medicare payments to providers of up to 2% per fiscal year, which went into effect in April 2013 and will remain in effect through 2031 under the Coronavirus Aid, Relief, and Economic Security Act (the "CARES Act"). Pursuant to subsequent legislation, however, these Medicare sequester reductions were suspended through the end of March 2022. From April 2022 through June 2022, a 1% sequester cut will be in effect, with the full 2% cut resuming thereafter. The American Taxpayer Relief Act of 2012, among other things, reduced Medicare payments to several providers and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. These laws may result in additional reductions in Medicare and other healthcare funding and otherwise affect the prices we may obtain for any of our products or product candidates for which we may obtain regulatory approval or the frequency with which any such product is prescribed or used.

Since enactment of the PPACA, there have been, and continue to be, numerous legal challenges and Congressional actions to repeal and replace provisions of the law. For example, with enactment of the Tax Cuts and Jobs Act of 2017 (the "TCJA"), Congress repealed the "individual mandate." The repeal of this provision, which requires most Americans to carry a minimal level of health insurance, became effective in 2019. Further, in December 2018, a U.S. District Court judge in the Northern District of Texas ruled that the individual mandate portion of the PPACA is an essential and inseverable feature of the PPACA, and therefore because the mandate was repealed as part of the TCJA, the remaining provisions of the PPACA are invalid as well. The U.S. Supreme Court heard this case in November 2020 and, in June 2021, dismissed this action after finding that the plaintiffs do not have standing to challenge the constitutionality of the PPACA. Litigation and legislation over the PPACA are likely to continue, with unpredictable and uncertain results.

The Trump Administration also took executive actions to undermine or delay implementation of the ACA, including directing federal agencies with authorities and responsibilities under the ACA to waive, defer, grant exemptions from, or delay the implementation of any provision of the ACA that would impose a fiscal or regulatory burden on states, individuals, healthcare providers, health insurers, or manufacturers of pharmaceuticals or medical devices. On January 28, 2021, however, President Biden issued a new Executive Order which directs federal agencies to reconsider rules and other policies that limit Americans' access to health care, and consider actions that will protect and strengthen that access. Under this Executive Order, federal agencies are directed to re-examine: policies that undermine protections for people with pre-existing conditions, including complications related to COVID-19; demonstrations and waivers under Medicaid and the ACA that may reduce coverage or undermine the programs, including work requirements; policies that undermine the health insurance marketplace or other markets for health insurance; policies that make it more difficult to enroll in Medicaid and the ACA; and policies that reduce affordability of coverage or financial assistance, including for dependents.

We expect that these healthcare reforms, as well as other healthcare reform measures that may be adopted in the future, may result in additional reductions in Medicare and other healthcare funding, more rigorous coverage criteria and new payment methodologies that govern XPOVIO or any other approved product and/or the level of reimbursement physicians receive for administering XPOVIO or any other approved product we, or our collaborators, might bring to market. Reductions in reimbursement levels may negatively impact the prices we receive or the frequency with which our products are prescribed or administered. Any reduction in reimbursement from Medicare or other government programs may result in a similar reduction in payments from private payors. Accordingly, such reforms, if enacted, could have an adverse effect on anticipated revenue from XPOVIO or from product candidates for which we may obtain marketing approval and may affect our overall financial condition and ability to develop or commercialize product candidates.

Further, outside of the US, including the countries of the EU, the pricing of prescription pharmaceuticals is subject to governmental control. In these countries, pricing negotiations with governmental authorities can take considerable time after the receipt of marketing approval for a drug. To obtain reimbursement or pricing approval in some countries, we, or our collaborators, may be required to conduct a clinical trial that compares the cost-effectiveness of our products to other available therapies. If reimbursement of our products is unavailable or limited in scope or amount, or if pricing is set at unsatisfactory levels, our business could be materially harmed.

The prices of prescription pharmaceuticals in the U.S. and foreign jurisdictions are subject to considerable legislative and executive actions and could impact the prices we obtain for our products, if and when licensed.

The prices of prescription pharmaceuticals have also been the subject of considerable discussion in the U.S. There have been several recent U.S. congressional inquiries, as well as proposed and enacted state and federal legislation designed to, among other things, bring more transparency to pharmaceutical pricing, review the relationship between pricing and manufacturer patient programs, and reduce the costs of pharmaceuticals under Medicare and Medicaid. In 2020, former President Trump issued several executive orders intended to lower the costs of prescription products and certain provisions in these orders have been incorporated into regulations. These regulations include an interim final rule implementing a most favored nation model for prices that would tie Medicare Part B payments for certain physician-administered pharmaceuticals to the lowest price paid in other economically advanced countries, effective January 1, 2021. That rule, however, has been subject to a nationwide preliminary injunction and, on December 29, 2021, the Centers for Medicare & Medicaid Services ("CMS") issued a final rule to rescind it. With issuance of this rule, CMS stated that it will explore all options to incorporate value into payments for Medicare Part B pharmaceuticals and improve beneficiaries' access to evidence-based care.

In addition, in October 2020, the Department of Health and Human Services (the "HHS") and the FDA published a final rule allowing states and other entities to develop a Section 804 Importation Program ("SIP") to import certain prescription drugs from Canada into the U.S. The final rule is currently the subject of ongoing litigation, but at least six states (Vermont, Colorado, Florida, Maine, New Mexico, and New Hampshire) have passed laws allowing for the importation of drugs from Canada with the intent of developing SIPs for review and approval by the FDA. Further, in November 2020, the HHS finalized a regulation removing safe harbor protection for price reductions from pharmaceutical manufacturers to plan sponsors under Part D, either directly or through pharmacy benefit managers, unless the price reduction is required by law. The implementation of the rule has been delayed by the Biden administration from January 1, 2022 to January 1, 2023 in response to ongoing litigation. The rule also creates a new safe harbor for price reductions reflected at the point-of-sale, as well as a new safe harbor for certain fixed fee arrangements between pharmacy benefit managers and manufacturers, the implementation of which has been delayed until January 1, 2026 by the Infrastructure Investment and Jobs Act.

In July 2021, President Biden signed Executive Order 14063, which focuses on, among other things, the price of pharmaceuticals. The Order directs the HHS to create a plan within 45 days to combat "excessive pricing of prescription pharmaceuticals and enhance domestic pharmaceutical supply chains, to reduce the prices paid by the federal government for such pharmaceuticals, and to address the recurrent problem of price gouging." In September 2021, the HHS released its plan to reduce pharmaceutical prices. The key features of that plan are to: (a) make pharmaceutical prices more affordable and equitable for all consumers and throughout the health care system by supporting pharmaceutical price negotiations with manufacturers; (b) improve and promote competition throughout the prescription pharmaceutical industry by supporting market changes that strengthen supply chains, promote biosimilars and generic drugs, and increase transparency; and (c) foster scientific innovation to promote better healthcare and improve health by supporting public and private research and making sure that market incentives promote discovery of valuable and accessible new treatments.

At the state level, individual states are increasingly aggressive in passing legislation and implementing regulations designed to control pharmaceutical and biological product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing. In addition, regional healthcare organizations and individual hospitals are increasingly using bidding procedures to determine what pharmaceutical products and which suppliers will be included in their prescription drug and other healthcare programs. These measures could reduce the ultimate demand for our products, once approved, or put pressure on our product pricing. We expect that additional state and federal healthcare reform measures will be adopted in the future, any of which could limit the amounts that federal and state governments will pay for healthcare products and services, which could result in reduced demand for our product candidates or additional pricing pressures.

Finally, outside of the U.S., in some nations, including those of the EU, the pricing of prescription pharmaceuticals is subject to governmental control and access. In these countries, pricing negotiations with governmental authorities can take considerable time after the receipt of marketing approval for a product. To obtain reimbursement or pricing approval in some countries, we, or our collaborators, may be required to conduct a clinical trial that compares the cost-effectiveness of our product to other available therapies.

These measures, as well as others adopted in the future, may result in additional downward pressure on the price that we receive for XPOVIO or any other approved product we or our collaborators might bring to market. Accordingly, such reforms, if enacted, could have an adverse effect on anticipated revenue from XPOVIO or from product candidates that we, or our collaborators, may successfully develop and for which we, or they, may obtain marketing approval and may affect our overall financial condition and ability to develop or commercialize product candidates.

Our relationships with healthcare providers, physicians and third-party payers will be subject to applicable anti-kickback, fraud and abuse, and other healthcare laws and regulations, which could expose us to criminal sanctions, civil penalties, contractual damages, reputational harm and diminished profits and future earnings.

Healthcare professionals, including but not limited to physicians, nurses, medical directors, hospitals, pharmacies, pharmacy benefit managers, group purchasing organizations, wholesalers, insurers, and all individuals employed by such entities (collectively, "HCPs"), may influence the recommendation and prescription of our approved products. Our arrangements with HCPs and others who have the ability to influence the recommendation and prescription of our products may expose us to broadly applicable fraud and abuse and other healthcare laws and regulations that may constrain the business or financial arrangements and relationships through which we market, sell and distribute our medicines for which we obtain marketing approval. Restrictions under applicable federal and state healthcare laws and regulations include the following:

- the federal healthcare anti-kickback statute prohibits, among other things, persons from knowingly and willfully soliciting, offering, receiving or providing remuneration, directly or indirectly, in cash or in kind, to induce or reward either the referral of an individual for, or the purchase, order, or recommendation of, any good or service, for which payment may be made under federal and state healthcare programs such as Medicare and Medicaid;
- the FCA imposes criminal and civil penalties, including civil whistleblower or qui tam actions, against individuals or entities for knowingly presenting or causing to be presented, to the federal government, claims for payment or approval from Medicare, Medicaid or other government payers that are false or fraudulent or making a false statement to avoid, decrease or conceal an obligation to pay money to the federal government, with potential liability including mandatory treble damages and significant per-claim penalties;
- the federal Health Insurance Portability and Accountability Act of 1996 ("HIPAA"), as further amended by the Health Information Technology for Economic and Clinical Health Act, which imposes certain requirements, including mandatory contractual terms, with respect to safeguarding the privacy, security and transmission of individually identifiable health information without appropriate authorization by entities subject to the rule, such as health plans, healthcare clearinghouses and healthcare providers;
- the federal false statements statute, which prohibits knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false statement in connection with the delivery of or payment for healthcare benefits, items or services;
- the federal transparency requirements under the federal Physician Payment Sunshine Act, which requires manufacturers of drugs, devices, biologics and medical supplies to report to the HHS, information related to payments and other transfers of value to physicians, other healthcare providers and teaching hospitals and ownership and investment interests held by physicians and their immediate family members and applicable group purchasing organizations; and
- analogous state laws and regulations, such as state anti-kickback and false claims laws, which may apply to sales or marketing arrangements and claims involving healthcare items or services reimbursed by non-governmental third-party payers, including private insurers, and certain state laws that require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government in addition to requiring drug manufacturers to report information related to payments to physicians and other healthcare providers or marketing expenditures.

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 government regulations that apply to us, we may be subject to penalties, including civil and criminal penalties, damages, fines, exclusion from participation in government healthcare programs, such as Medicare and Medicaid, imprisonment and the curtailment or restructuring of our operations, any of which could adversely affect our business, financial condition, results of operations and prospects.

Efforts to ensure that our business arrangements with third parties will comply with applicable healthcare laws and regulations will involve substantial costs. It is possible that governmental authorities will conclude that our business practices may not comply with current or future statutes, regulations or case law involving applicable fraud and abuse or other healthcare laws and regulations. If our operations are found to be in violation of any of these laws or any other governmental regulations that may apply to us, we may be subject to significant civil, criminal and administrative penalties, damages, fines, exclusion from government funded healthcare

programs, such as Medicare and Medicaid, and the curtailment or restructuring of our operations. If any of the physicians or other providers or entities with whom we expect to do business are found to be not in compliance with applicable laws, they may be subject to criminal, civil or administrative sanctions, including exclusions from government funded healthcare programs. Liabilities they incur pursuant to these laws could result in significant costs or an interruption in operations, which could have a material adverse effect on our business, financial condition, results of operations and prospects.

Our reporting and payment obligations under the Medicaid Drug Rebate Program and other governmental drug pricing programs are complex and may involve subjective decisions. Any failure to comply with those obligations could subject us to penalties and sanctions.

As a condition of reimbursement by various federal and state health insurance programs, we are required to calculate and report certain pricing information to federal and state agencies. The regulations governing the calculations, price reporting and payment obligations are complex and subject to interpretation by various government and regulatory agencies, as well as the courts. Reasonable assumptions have been made where there is lack of regulations or clear guidance and such assumptions involve subjective decisions and estimates. We are required to report any revisions to our calculation, price reporting and payment obligations previously reported or paid. Such revisions could affect our liability to federal and state payers and also adversely impact our reported financial results of operations in the period of such restatement.

Uncertainty exists as new laws, regulations, judicial decisions, or new interpretations of existing laws, or regulations related to our calculations, price reporting or payments obligations increases the chances of a legal challenge, restatement or investigation. If we become subject to investigations, restatements, or other inquiries concerning our compliance with price reporting laws and regulations, we could be required to pay or be subject to additional reimbursements, penalties, sanctions or fines, which could have a material adverse effect on our business, financial condition and results of operations. In addition, it is possible that future healthcare reform measures could be adopted, which could result in increased pressure on pricing and reimbursement of our products and thus have an adverse impact on our financial position or business operations.

Further, state Medicaid programs may be slow to invoice pharmaceutical companies for calculated rebates resulting in a lag between the time a sale is recorded and the time the rebate is paid. This results in us having to carry a liability on our consolidated balance sheets for the estimate of rebate claims expected for Medicaid patients. If actual claims are higher than current estimates, our financial position and results of operations could be adversely affected.

In addition to retroactive rebates and the potential for 340B Program refunds, if we are found to have knowingly submitted any false price information related to the Medicaid Drug Rebate Program to CMS, we may be liable for civil monetary penalties. Such failure could also be grounds for CMS to terminate our Medicaid drug rebate agreement, pursuant to which we participate in the Medicaid program. In the event that CMS terminates our rebate agreement, federal payments may not be available under government programs, including Medicaid or Medicare Part B, for our covered outpatient drugs.

Additionally, if we overcharge the government in connection with the Federal Supply Schedule pricing program or Tricare Retail Pharmacy Program, whether due to a misstated Federal Ceiling Price or otherwise, we are required to refund the difference to the government. Failure to make necessary disclosures and/or to identify contract overcharges can result in allegations against us under the FCA and other laws and regulations. Unexpected refunds to the government, and responding to a government investigation or enforcement action, would be expensive and time-consuming, and could have a material adverse effect on our business, financial condition, results of operations and growth prospects.

Our collaborators are also subject to similar requirements outside of the U.S. and thus the attendant risks and uncertainties. If our collaborators suffer material and adverse effects from such risks and uncertainties, our rights and benefits for our licensed products could be negatively impacted, which could have a material and adverse impact on our revenues.

We are subject to stringent privacy laws, information security laws, regulations, policies and contractual obligations related to data privacy and security and changes in such laws, regulations, policies, contractual obligations and failure to comply with such requirements could subject us to significant fines and penalties, which may have a material adverse effect on our business, financial condition or results of operations.

We are subject to data privacy and protection laws and regulations that apply to the collection, transmission, storage and use of personally-identifying information, which among other things, impose certain requirements relating to the privacy, security and transmission of personal information, including comprehensive regulatory systems in the U.S., EU and UK. The legislative and regulatory landscape for privacy and data protection continues to evolve in jurisdictions worldwide, and there has been an increasing focus on privacy and data protection issues with the potential to affect our business. Failure to comply with any of these laws and regulations could result in enforcement action against us, including fines, imprisonment of company officials and public censure, claims for damages by affected individuals, damage to our reputation and loss of goodwill, any of which could have a material adverse effect on our business, financial condition, results of operations or prospects.

There are numerous U.S. federal and state laws and regulations related to the privacy and security of personal information. In particular, regulations promulgated pursuant to HIPAA establish privacy and security standards that limit the use and disclosure of individually identifiable health information, or protected health information, and require the implementation of administrative, physical and technological safeguards to protect the privacy of protected health information and ensure the confidentiality, integrity and availability of electronic protected health information. Determining whether protected health information has been handled in compliance with applicable privacy standards and our contractual obligations can be complex and may be subject to changing interpretation. These obligations may be applicable to some or all of our business activities now or in the future.

If we are unable to properly protect the privacy and security of protected health information, we could be found to have breached our contracts. Further, if we fail to comply with applicable privacy laws, including applicable HIPAA privacy and security standards, we could face civil and criminal penalties. HHS enforcement activity can result in financial liability and reputational harm, and responses to such enforcement activity can consume significant internal resources. In addition, state attorneys general are authorized to bring civil actions seeking either injunctions or damages in response to violations that threaten the privacy of state residents. We cannot be sure how these regulations will be interpreted, enforced or applied to our operations. In addition to the risks associated with enforcement activities and potential contractual liabilities, our ongoing efforts to comply with evolving laws and regulations at the federal and state level may be costly and require ongoing modifications to our policies, procedures and systems.

In 2018, California passed into law the California Consumer Privacy Act (the "CCPA"), which took effect on January 1, 2020 and imposed many requirements on businesses that process the personal information of California residents. Many of the CCPA's requirements are similar to those found in the General Data Protection Regulation (the "GDPR"), including requiring businesses to provide notice to data subjects regarding the information collected about them and how such information is used and shared, and providing data subjects the right to request access to such personal information and, in certain cases, request the erasure of such personal information. The CCPA also affords California residents the right to opt-out of "sales" of their personal information. The CCPA contains significant penalties for companies that violate its requirements. In November 2020, California voters passed a ballot initiative for the California Privacy Rights Act (the "CPRA"), which will significantly expand the CCPA to incorporate additional GDPR-like provisions including requiring that the use, retention, and sharing of personal information of California residents be reasonably necessary and proportionate to the purposes of collection or processing, granting additional protections for sensitive personal information, and requiring greater disclosures related to notice to residents regarding retention of information. Most CPRA provisions will take effect on January 1, 2023, though the obligations will apply to any personal information collected after January 1, 2022. These provisions may apply to some of our business activities. In addition, other states, including Virginia and Colorado, already have passed state privacy laws. Other states will be considering these laws in the future. These laws may impact our business activities, including our identification of research subjects, relationships with business partners and ultimately the marketing and distribution of our products.

Similar to the laws in the U.S., there are significant privacy and data security laws that apply in Europe and other countries. The collection, use, disclosure, transfer, or other processing of personal data, including personal health data, regarding individuals who are located in the European Economic Area ("EEA"), and the processing of personal data that takes place in the EEA, is regulated by the GDPR, which went into effect in May 2018 and which imposes obligations on companies that operate in our industry with respect to the processing of personal data and the cross-border transfer of such data. The GDPR imposes onerous accountability obligations requiring data controllers and processors to maintain a record of their data processing and policies. If our or our partners' or service providers' privacy or data security measures fail to comply with the GDPR requirements, we may be subject to litigation, regulatory investigations, enforcement notices requiring us to change the way we use personal data and/or fines of up to 20 million Euros or up to 4% of the total worldwide annual turnover of the preceding financial year, whichever is higher, as well as compensation claims by affected individuals, negative publicity, reputational harm and a potential loss of business and goodwill.

The GDPR places restrictions on the cross-border transfer of personal data from the EU to countries that have not been found by the EC to offer adequate data protection legislation, such as the U.S. There are ongoing concerns about the ability of companies to transfer personal data from the EU to other countries. In July 2020, the Court of Justice of the European Union (the "CJEU") invalidated the EU-U.S. Privacy Shield, one of the mechanisms used to legitimize the transfer of personal data from the EEA to the U.S. The CJEU decision also drew into question the long-term viability of an alternative means of data transfer, the standard contractual clauses, for transfers of personal data from the EEA to the U.S. While we were not self-certified under the Privacy Shield, this CJEU decision may lead to increased scrutiny on data transfers from the EEA to the U.S. generally and increase our costs of compliance with data privacy legislation as well as our costs of negotiating appropriate privacy and security agreements with our vendors and business partners.

Following the withdrawal of the UK from the EU, the UK Data Protection Act 2018 applies to the processing of personal data that takes place in the UK and includes parallel obligations to those set forth by GDPR. As with other issues related to Brexit, there are open questions about how personal data will be protected in the UK and whether personal information can transfer from the EU to the UK. While the Data Protection Act of 2018 in the UK that "implements" and complements the GDPR, has achieved Royal Assent on May 23, 2018 and is now effective in the UK, it is still unclear whether transfer of data from the EEA to the UK will remain lawful under GDPR. The UK government has already determined that it considers all EU 27 and EEA member states to be adequate for the purposes of data protection, ensuring that data flows from the UK to the EU/EEA remain unaffected. In addition, a recent decision

from the EC appears to deem the UK as being "essentially adequate" for purposes of data transfer from the EU to the UK, although this decision may be re-evaluated in the future.

Beyond GDPR, there are privacy and data security laws in a growing number of countries around the world. While many loosely follow GDPR as a model, other laws contain different or conflicting provisions. These laws will impact our ability to conduct our business activities, including both our clinical trials and any eventual sale and distribution of commercial products, through increased compliance costs, costs associated with contracting and potential enforcement actions.

While we continue to address the implications of the recent changes to data privacy regulations, data privacy remains an evolving landscape at both the domestic and international level, with new regulations coming into effect and continued legal challenges, and our efforts to comply with the evolving data protection rules may be unsuccessful. It is possible that these laws may be interpreted and applied in a manner that is inconsistent with our practices. We must devote significant resources to understanding and complying with this changing landscape. Failure to comply with laws regarding data protection would expose us to risk of enforcement actions taken by data protection authorities in the EEA and elsewhere and carries with it the potential for significant penalties if we are found to be non-compliant. Similarly, failure to comply with federal and state laws in the U.S. regarding privacy and security of personal information could expose us to penalties under such laws. Any such failure to comply with data protection and privacy laws could result in government-imposed fines or orders requiring that we change our practices, claims for damages or other liabilities, regulatory investigations and enforcement action, litigation and significant costs for remediation, any of which could adversely affect our business. Even if we are not determined to have violated these laws, government investigations into these issues typically require the expenditure of significant resources and generate negative publicity, which could harm our business, financial condition, results of operations or prospects.

Our employees, independent contractors, consultants, collaborators and vendors may engage in misconduct or other improper activities, including non-compliance with regulatory standards and/or requirements and insider trading, which could cause significant liability for us and harm our reputation.

We are exposed to the risk of fraud or other misconduct by our employees, independent contractors, consultants, collaborators and vendors. Misconduct by these partners could include intentional failures to comply with FDA regulations or similar regulations of comparable foreign regulatory authorities, provide accurate information to the FDA or comparable foreign regulatory authorities, comply with manufacturing standards, comply with federal and state healthcare fraud and abuse laws and regulations and similar laws and regulations established and enforced by comparable foreign regulatory authorities, report financial information or data accurately or disclose unauthorized activities to us. Employee misconduct could also involve the improper use of information obtained in the course of clinical trials, which could result in regulatory sanctions and serious harm to our reputation. This could include violations of HIPAA, other U.S. federal and state laws, and requirements of foreign jurisdictions, including the GDPR. We are also exposed to risks in connection with any insider trading violations by employees or others affiliated with us. It is not always possible to identify and deter employee or third-party misconduct, and the precautions we take to detect and prevent these activities may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to be in compliance with such laws, standards, regulations, guidance or codes of conduct. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business and results of operations, including the imposition of significant fines or other sanctions.

If we fail to comply with environmental, health and safety laws and regulations, we could become subject to fines or penalties or incur costs that could have a material adverse effect on our business.

We are subject to numerous environmental, health and safety laws and regulations, including those governing laboratory procedures and the handling, use, storage, treatment and disposal of hazardous materials and wastes. Our operations involve the use of hazardous and flammable materials, including chemicals and biological and radioactive materials. Our operations also produce hazardous waste products. We generally contract with third parties for the disposal of these materials and wastes. We cannot eliminate the risk of contamination or injury from these materials. In the event of contamination or injury resulting from our use of hazardous materials, we could be held liable for any resulting damages, and any liability could exceed our resources. We also could incur significant costs associated with civil or criminal fines and penalties.

Although we maintain workers' compensation insurance to cover us for costs and expenses we may incur due to injuries to our employees resulting from the use of hazardous materials, this insurance may not provide adequate coverage against potential liabilities. We do not maintain insurance for environmental liability or toxic tort claims that may be asserted against us in connection with our storage or disposal of biological, hazardous or radioactive materials.

In addition, we may incur substantial costs in order to comply with current or future environmental, health and safety laws and regulations. These current or future laws and regulations may impair our research, development or commercialization efforts. Failure to comply with these laws and regulations also may result in substantial fines, penalties or other sanctions.

Laws and regulations governing international operations we may have in the future may preclude us from developing, manufacturing and selling certain products outside of the U.S. and require us to develop and implement costly compliance programs.

We are subject to numerous laws and regulations in each jurisdiction outside of the U.S. in which we operate. The creation, implementation and maintenance of international business practices compliance programs is costly and such programs are difficult to enforce, particularly where reliance on third parties is required.

The FCPA prohibits any U.S. individual or business from paying, offering, authorizing payment or offering of anything of value, directly or indirectly, to any foreign official, political party or candidate for the purpose of influencing any act or decision of the foreign entity in order to assist the individual or business in obtaining or retaining business. The FCPA also obligates companies whose securities are listed in the U.S. to comply with certain accounting provisions requiring us to maintain books and records that accurately and fairly reflect all transactions of the corporation, including international subsidiaries, and to devise and maintain an adequate system of internal accounting controls. The FCPA is enforced by the DOJ and the SEC.

Compliance with the FCPA is expensive and difficult, particularly in countries in which corruption is a recognized problem. In addition, the FCPA presents particular challenges in the pharmaceutical industry, because, in many countries, hospitals, clinics, universities and similar institutions are operated by the government, and doctors and other healthcare professionals are considered foreign officials. Certain payments to healthcare professionals in connection with clinical trials, regulatory approvals, sales and marketing, and other work have been deemed to be improper payments to government officials and have led to FCPA enforcement actions. Because the FCPA applies to indirect payments, the use of third parties and other collaborators can increase potential FCPA risk, as we could be held liable for the acts of third parties that do not comply with the FCPA's requirements.

The failure to comply with laws governing international business practices may result in substantial penalties, including suspension or debarment from government contracting. Violation of the FCPA can result in significant civil and criminal penalties. Indictment alone under the FCPA can lead to suspension of the right to do business with the U.S. government until the pending claims are resolved. Conviction of a violation of the FCPA can result in long-term disqualification as a government contractor. The termination of a government contract or relationship as a result of our failure to satisfy any of our obligations under laws governing international business practices would have a negative impact on our operations and harm our reputation and ability to procure government contracts. The SEC also may suspend or bar issuers from trading securities on U.S. exchanges for violations of the FCPA's accounting provisions.

Like the FCPA, the UK Bribery Act and other anti-corruption laws throughout the world similarly prohibit offers and payments made to obtain improper business advantages, including offers or payments to healthcare professionals and other government and non-government officials. These other anti-corruption laws also can result in substantial financial penalties and other collateral consequences.

Various laws, regulations and executive orders also restrict the use and dissemination outside of the U.S., or the sharing with certain non-U.S. nationals, of information classified for national security purposes, as well as certain products and technical data relating to those products. Our expansion outside of the U.S., has required, and will continue to require, us to dedicate additional resources to comply with these laws, and these laws may preclude us from developing, manufacturing, or selling certain drugs and product candidates outside of the U.S., which could limit our growth potential and increase our development costs.

With the passage of the CREATES Act, we are exposed to possible litigation and damages by competitors who may claim that we are not providing sufficient quantities of our approved products on commercially reasonable, market-based terms for testing in support of their ANDAs and 505(b)(2) applications.

In December 2019, former President Trump signed legislation intended to facilitate the development of generic and biosimilar products. The bill, previously known as the CREATES Act, authorizes sponsors of abbreviated new drug applications ("ANDAs") and 505(b)(2) applications to file lawsuits against companies holding NDAs that decline to provide sufficient quantities of an approved reference drug on commercially reasonable, market-based terms. Drug products on FDA's drug shortage list are exempt from these new provisions unless the product has been on the list for more than six continuous months or the FDA determines that the supply of the product will help alleviate or prevent a shortage.

To bring an action under the statute, an ANDA or 505(b)(2) applicant must take certain steps to request the reference product, which, in the case of products covered by a Risk Evaluation and Mitigation Strategy with elements to assure safe use, include obtaining authorization from the FDA for the acquisition of the reference product. If the applicant does bring an action for failure to provide a reference product, there are certain affirmative defenses available to the NDA holder, which must be shown by a preponderance of evidence. If the applicant prevails in litigation, it is entitled to a court order directing the NDA holder to provide, without delay, sufficient quantities of the applicable product on commercially reasonable, market-based terms, plus reasonable attorney fees and costs.

Additionally, the new statutory provisions authorize a federal court to award the product developer an amount "sufficient to deter" the NDA holder from refusing to provide sufficient product quantities on commercially reasonable, market-based terms if the court finds, by a preponderance of the evidence, that the NDA holder did not have a legitimate business justification to delay providing the product or failed to comply with the court's order. For the purposes of the statute, the term "commercially reasonable, market-based terms" is defined as (1) the nondiscriminatory price at or below the most recent wholesale acquisition cost for the product, (2) a delivery schedule that meets the statutorily defined timetable, and (3) no additional conditions on the sale.

Although we intend to comply fully with the terms of these new statutory provisions, we are still exposed to potential litigation and damages by competitors who may claim that we are not providing sufficient quantities of our approved products on commercially reasonable, market-based terms for testing in support of ANDAs and 505(b)(2) applications. Such litigation would subject us to additional litigation costs, damages and reputational harm, which could lead to lower revenues. The CREATES Act may enable generic competition with XPOVIO and any of our product candidates, if approved, which could impact our ability to maximize product revenue.

We are subject to governmental export and import controls that could impair our or our collaborators' ability to compete in international markets due to licensing requirements and subject us or them to liability if we or they are not in compliance with applicable laws.

Our products are subject to export control and import laws and regulations, including the U.S. Export Administration Regulations, U.S. Customs regulations, and various economic and trade sanctions regulations administered by the U.S. Treasury Department's Office of Foreign Assets Controls. Exports of our products outside of the U.S. must be made in compliance with these laws and regulations. If we or our collaborators fail to comply with these laws and regulations, we or they and certain of our or their employees could be subject to substantial civil or criminal penalties, including the possible loss of export or import privileges; fines, which may be imposed on us or our collaborators and the respective responsible employees or managers; and, in extreme cases, the incarceration of responsible employees or managers.

In addition, changes in our products or changes in applicable export or import laws and regulations may create delays in the introduction, provision, or sale of our products in international markets, prevent customers from using our products or, in some cases, prevent the export or import of our products to certain countries, governments or persons altogether. Any limitation on our ability to export, provide, or sell our products could adversely affect our business, financial condition and results of operations.

Risks Related to Our Financial Position and Capital Requirements

We have incurred significant losses since inception, expect to continue to incur significant losses, and may never achieve or maintain profitability.

Since inception, we have incurred significant operating losses. Our net loss was $41.4 million for the quarter ended March 31, 2022. As of March 31, 2022, we had an accumulated deficit of $1.2 billion. Although we received our first FDA-approval for XPOVIO in July 2019, we may never attain profitability or positive cash flows from operations. We have historically financed our operations principally through product sales, private placements of our preferred stock, proceeds from our initial public offering and follow-on offerings of common stock, proceeds from the issuance of convertible debt, proceeds from a revenue interest financing agreement, proceeds from sales of common stock under our Open Market Sale Agreement and cash generated from our business development activities. Substantially all of our operating losses have resulted from costs incurred in connection with our research and development programs, the pursuit of regulatory approvals within and outside of the U.S., and the commercialization of XPOVIO. We expect to continue to incur significant expenses and operating losses as we continue to commercialize XPOVIO in the U.S. and engage in activities to prepare for the potential approval and commercialization of additional indications for selinexor and eltanexor as well as our other product candidates. The net losses we incur may fluctuate significantly from quarter to quarter.

While we began to generate revenue from the sales of XPOVIO in July 2019 and have received revenue from our license arrangements, such as the partnership we have with Antengene Therapeutics Limited ("Antengene") for our programs across most of the Asia-Pacific region, and most recently with Menarini for our programs in Europe, Latin America and other key countries, there can be no assurance as to the amount or timing of future product or license and other revenues, and we may not achieve profitability for several years, if at all. Our ability to become and remain profitable depends significantly on our success in many areas, including:

- effectively commercializing XPOVIO or any future products either on our own or with a collaborator, including by maintaining a full commercial organization required to market, sell and distribute our products, and achieving an adequate level of market acceptance;
- the impact of current or future competing products on product sales of XPOVIO or any of our future products;
- obtaining sufficient pricing, coverage and reimbursement for XPOVIO and any of our other approved products from private and government payers and the impact of any pricing changes;

- initiating and successfully completing clinical trials required to file for, obtain and maintain marketing approval for our product candidates;
- obtaining and maintaining regulatory approvals, either by us or our collaborators, and the timing of such approvals;
- manufacturing at commercial scale;
- establishing and managing any collaborations for the development, marketing and/or commercialization of our products and product candidates, including the level of success of our collaborators' efforts and the timing and amount of any milestone or royalty payments we may receive;
- obtaining, maintaining and protecting our intellectual property rights; and
- navigating the negative impacts resulting from the ongoing COVID-19 pandemic to the healthcare systems, the ability of our clinical trial sites to conduct current or future trials and the regulatory review process.

We anticipate that our operating and capital expenses will increase as we continue to:

- commercialize XPOVIO in the U.S., including maintaining or growing our commercial infrastructure;
- obtain and/or maintain regulatory approval for XPOVIO and our product candidates, including completing any required post-marketing requirements to the satisfaction of the FDA or other regulatory agencies;
- expand our research and development programs, identify additional product candidates and initiate and conduct clinical trials, including clinical trials required by the FDA or other regulatory agencies in addition to those that have been or are currently expected to be conducted;
- maintain, expand and protect our intellectual property portfolio;
- manufacture XPOVIO and our product candidates;
- acquire or in-license other products, product candidates or technologies;
- add operational, financial and management information systems and personnel, including clinical, quality control, scientific, commercial and management personnel, to support our development and commercialization efforts and other operations required as a public company; and
- increase our insurance coverage as we grow our commercialization efforts.

Because of the numerous risks and uncertainties associated with pharmaceutical product development and commercialization, we are unable to accurately predict the timing or amount of our revenue and expenses or when, or if, we will be able to achieve profitability. We cannot be certain that our revenue from sales of XPOVIO alone, in the currently approved indications, will be sufficient for us to become profitable for several years, if at all. We may never generate revenues that are significant or large enough to achieve profitability. Even if we do achieve profitability, we may not be able to sustain or increase profitability on a quarterly or annual basis. Our failure to become and remain profitable would decrease the value of our company and could impair our ability to raise capital, maintain our research and development and commercialization efforts, expand our business and/or continue our operations. A decline in the value of our company could also cause our stockholders to lose all or part of their investment.

We will need additional funding to achieve our business objectives. If we are unable to raise capital when needed or on acceptable terms, we would be forced to delay, reduce or eliminate our research and development programs and/or commercialization efforts.

Discovering, developing and commercializing products involve time-consuming, expensive and uncertain processes that take years to complete. We have used substantial funds to develop XPOVIO and expect our operating expenses to continue to increase as we continue to commercialize XPOVIO or any future approved product, conduct further research and development of our product candidates, seek marketing approval and prepare for commercialization of selinexor in additional indications or for our other product candidates, if approved, to the extent that such functions are not the responsibility of a collaborator. Furthermore, we will continue to incur additional costs associated with operating as a public company, hiring additional personnel and expanding our geographical reach. Although currently XPOVIO is commercially available in three indications, we do not anticipate that our revenue from product sales of XPOVIO or any funds we may receive from our collaborators will be sufficient for us to become profitable for several years, if at all. Accordingly, we will need to continue to rely on additional financing to achieve our business objectives.

As of March 31, 2022, we believe that our existing cash, cash equivalents and investments will enable us to fund our current operating and capital expenditure plans for at least twelve months from the date of issuance of the financial statements contained in

this Quarterly Report on Form 10-Q. The amount and timing of our future capital requirements will depend on many factors, including, but not limited to:

- the scope, progress, results, timing and costs of our current and planned development efforts and regulatory review of our product candidates;
- the amount and timing of revenues from sales of XPOVIO, or any product candidate that we develop or acquire;
- the cost of, and our ability to expand and maintain, the commercial infrastructure required to support the commercialization of XPOVIO and any other product for which we receive marketing approval, including medical affairs, manufacturing, marketing and distribution functions;
- our ability to establish and maintain collaboration, partnership, licensing, marketing, distribution or other arrangements on favorable terms and the level and timing of success of these arrangements;
- the extent to which we acquire or in-license other products, product candidates and technologies; and
- the costs and timing of preparing, filing and prosecuting patent applications, maintaining and enforcing our intellectual property rights and defending intellectual property-related claims.

In addition, the terms of any financing may adversely affect the holdings or the rights of our stockholders. If we raise additional funds by issuing equity securities, dilution to our existing stockholders will result. In addition, as a condition to providing additional funding to us, future investors may demand, and may be granted, rights superior to those of existing stockholders. Moreover, any debt financing, if available, may involve restrictive covenants that could limit our flexibility in conducting future business activities and, in the event of insolvency, would be paid before holders of equity securities received any distribution of corporate assets. Our ability to satisfy and meet any future debt service obligations will depend upon our future performance, which will be subject to financial, business and other factors affecting our operations, many of which are beyond our control.

Even if we believe we have sufficient funds for our current or future operating plans, we may seek additional capital due to favorable market conditions or strategic considerations. Any future fundraising efforts could divert our management's attention away from their day-to-day activities. Further, adequate additional financing may not be available to us on acceptable terms, or at all. In addition, raising funds in the current economic environment may present additional challenges. For example, any sustained disruption in the capital markets from the COVID-19 pandemic could negatively impact our ability to raise capital and we cannot predict the extent or duration of the macro-economic disruption stemming from the COVID-19 pandemic. If adequate funds are not available to us on a timely basis or on attractive terms, we may be required to delay, reduce or eliminate our research and development programs or any current or future commercialization efforts for one or more of our products or product candidates, any of which could have a material adverse effect on our business, operating results and prospects.

Our Revenue Interest Agreement with HCR, as amended, contains various covenants and other provisions, which, if violated, could result in the acceleration of payments due under such agreement or the foreclosure on the pledged collateral, including all of our present and future assets relating to selinexor.

In September 2019, we entered into the Revenue Interest Financing Agreement (the "Revenue Interest Agreement") with HealthCare Royalty Partners III, L.P. and HealthCare Royalty Partners IV, L.P. ("HCR") and which was amended in June 2021 (the "Amended Revenue Interest Agreement"). Pursuant to the Amended Revenue Interest Agreement, we are required to comply with various covenants relating to the conduct of our business and the commercialization of XPOVIO, including obligations to use commercially reasonable efforts to commercialize our products. In addition, the Amended Revenue Interest Agreement limits our ability to incur or prepay indebtedness, create or incur liens, pay dividends on or repurchase outstanding shares of our capital stock or dispose of assets. The Amended Revenue Interest Agreement also includes customary events of default upon the occurrence of enumerated events, including non-payment of revenue interests, failure to perform certain covenants and the occurrence of insolvency proceedings, specified judgments, specified cross-defaults or specified revocations, or withdrawals or cancellations of regulatory approval for XPOVIO. Upon the occurrence of an event of default and in the event of a change of control, HCR may accelerate payments due under the Amended Revenue Interest Agreement up to $249.8 million, less the aggregate of all of the payments previously paid to HCR. Upon the occurrence of specified material adverse events or the material breach of specified representations and warranties, which will not be considered events of default, HCR may elect to terminate the Amended Revenue Interest Agreement and require us to make payments necessary for HCR to receive $135.0 million, less the aggregate of all of the payments made to date, plus a specified annual rate of return. In the event that we are unable to make such payment, HCR may be able to foreclose on the collateral that was pledged to HCR, which consists of all of our present and future assets relating to selinexor. Any such foreclosure remedy would significantly and adversely affect us and could result in us losing our interest in such assets, which would have an adverse material impact on our business.

Our indebtedness could limit cash flow available for our operations, expose us to risks that could adversely affect our business, financial condition and results of operations and impair our ability to satisfy our obligations under the Convertible Senior Notes due 2025 (the "Notes").

We incurred $172.5 million of indebtedness as a result of the sale of the Notes, $75.0 million as a result of the initial closing pursuant to the Revenue Interest Agreement and $60.0 million following the closing of the Amended Revenue Interest Agreement. We may also incur additional indebtedness to meet future financing needs. Our indebtedness could have significant negative consequences for our security holders and our business, results of operations and financial condition by, among other things:

- increasing our vulnerability to adverse economic and industry conditions;
- limiting our ability to obtain additional financing;
- requiring the dedication of a substantial portion of our cash flow from operations to service our indebtedness, which would reduce the amount of cash available for other purposes;
- limiting our flexibility to plan for, or react to, changes in our business;
- diluting the interests of our existing stockholders as a result of issuing shares of our common stock upon conversion of the Notes; and
- placing us at a possible competitive disadvantage with competitors that are less leveraged than us or have better access to capital.

Our ability to pay the principal of or interest on the Notes or to make cash payments in connection with any conversion of the Notes depends on our future performance, which is subject to economic, financial, competitive and other factors beyond our control. Our business may not generate cash flow from operations in the future sufficient to service the Notes or other future indebtedness and make necessary capital expenditures. In addition, if the impact of the COVID-19 pandemic to our results of operations and business prospects is more severe and prolonged than we currently anticipate, our ability to repay the Notes could be impaired.

We may not have the ability to raise the funds necessary to settle conversions of the Notes in cash, to repurchase the Notes for cash upon a fundamental change, to pay the redemption price for any Notes we redeem or to refinance the Notes, and any future debt we incur may contain limitations on our ability to pay cash upon conversion or repurchase of the Notes.

Holders may require us to repurchase their Notes following a fundamental change at a cash repurchase price generally equal to the principal amount of the Notes to be repurchased, plus accrued and unpaid interest. In addition, upon conversion, unless we elect to deliver solely shares of our common stock to settle conversions (other than paying cash in lieu of delivering any fractional share), we must satisfy the conversion in cash. If we do not have enough available cash at the time we are required to repurchase the Notes, pay cash amounts due upon conversion or redemption of the Notes or refinance the Notes, we may be required to adopt one or more alternatives, such as selling assets, restructuring indebtedness or obtaining additional debt financing or equity capital on terms that may be onerous or highly dilutive. Our ability to refinance the Notes or other future indebtedness will depend on the capital markets, our financial condition at such time and our obligations under any other existing indebtedness in effect at such time. We may not be able to engage in any of these activities on desirable terms, or at all, which could result in a default on our debt obligations, including the Notes. In addition, our ability to repurchase the Notes, to pay cash upon conversion or redemption of the Notes or to refinance the Notes may be limited by law, regulatory authority or agreements governing any future indebtedness that we may incur. Our failure to repurchase the Notes at a time when the repurchase is required by the indenture governing the Notes or to pay cash upon conversion of the Notes as required by the indenture would constitute a default under the indenture. A default under the indenture or the fundamental change itself could also lead to a default under agreements governing our future indebtedness, if any. Moreover, the occurrence of a fundamental change under the indenture could constitute an event of default under any such agreements. If the repayment of the related indebtedness were to be accelerated after any applicable notice or grace periods, we may not have sufficient funds to repay the indebtedness and repurchase the Notes or to pay cash upon conversion of the Notes.

The conditional conversion feature of the Notes, if triggered, may adversely affect our financial condition and operating results.

In the event the conditional conversion feature of the Notes is triggered, holders of Notes will be entitled to convert the Notes at any time during specified periods at their option. If one or more holders elect to convert their Notes, unless we elect to satisfy our conversion obligation by delivering solely shares of our common stock (other than paying cash in lieu of delivering any fractional share), we would be required to settle a portion or all of our conversion obligation in cash, which could adversely affect our liquidity. In addition, even if holders do not elect to convert their Notes, we could be required under applicable accounting rules to reclassify all or a portion of the outstanding principal amount of the Notes as a current rather than long-term liability, which would result in a material reduction of our net working capital.

The accounting method for convertible debt securities that may be settled in cash, such as the Notes, could have a material effect on our reported financial results.

Convertible debt instruments (such as the Notes) that may be settled entirely or partly in cash are currently eligible to be accounted for utilizing the treasury stock method, the effect of which is that the shares issuable upon conversion of the Notes are not included in the calculation of diluted earnings per share except to the extent that the conversion value of the Notes exceeds their principal amount. Under the treasury stock method, for diluted earnings per share purposes, the transaction is accounted for as if the number of shares of common stock that would be necessary to settle such excess, if we elected to settle such excess in shares, are issued. We cannot be sure that the accounting standards in the future will continue to permit the use of the treasury stock method. If we are unable to use the treasury stock method in accounting for the shares issuable upon conversion of the Notes, then our diluted earnings per share would be adversely affected.

Raising additional capital may cause dilution to our stockholders, restrict our operations or require us to relinquish rights to our product candidates.

Until such time, if ever, as we can generate substantial revenues from the sale of our products, we expect to finance our cash needs through a combination of equity offerings, debt financings, collaborations, strategic alliances and/or licensing arrangements. We do not have any committed external source of funds. To the extent that we raise additional capital through the sale of equity or convertible debt securities, the ownership interests of stockholders will be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect the rights of common stockholders. Debt financing, if available, may involve agreements that include covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, making capital expenditures or declaring dividends. For example, during the term of the Amended Revenue Interest Agreement, we cannot make any voluntary or optional cash payment or prepayment on our existing convertible debt and cannot enter into any new debt without the consent of HCR.

If we raise additional funds through further collaborations, strategic alliances or licensing arrangements with third parties, we may have to relinquish valuable rights to our future revenue streams, research programs or product candidates or to grant licenses on terms that may not be favorable to us. If we are unable to raise additional funds through equity or debt financings when needed, we may be required to delay, limit, reduce or terminate our research and drug development or current or future commercialization efforts or grant rights to develop and market product candidates that we would otherwise prefer to develop and market ourselves.

Unstable market and economic conditions may have serious adverse consequences on our business, financial condition and stock price.

Global credit and financial markets have experienced extreme disruptions over the past several years. Such disruptions have resulted, and could in the future result, in diminished liquidity and credit availability, declines in consumer confidence, declines in economic growth, increases in unemployment rates and uncertainty about economic stability. For example, the COVID-19 pandemic has resulted in businesses suspending or terminating global operations and travel, self-imposed or government-mandated quarantines, and an overall slowdown of economic activity in many areas. In addition, U.S. and global markets are experiencing volatility and disruption following the escalation of geopolitical tensions and the start of the military conflict between Russia and Ukraine, and the adoption of comprehensive sanctions in response thereto by, among others, the EU, the U.S., and the UK, which sanctions restrict a wide range of trade and financial dealings with Russia and Russian persons, as well as certain regions in Ukraine. Our general business strategy may be compromised by economic downturns, a volatile business environment and unpredictable and unstable market conditions, such as the current global situation resulting from the COVID-19 pandemic and the ongoing conflict between Russia and Ukraine. If the equity and credit markets deteriorate, it may make any necessary equity or debt financing more difficult to secure, more costly or more dilutive. Failure to secure any necessary financing in a timely manner and on favorable terms could harm our growth strategy, financial performance and stock price and could require us to delay or abandon plans with respect to our business, including clinical development plans. In addition, there is a risk that one or more of our current service providers, manufacturers or other third parties with which we conduct business may not survive difficult economic times, including the current global situation resulting from the COVID-19 pandemic and the ongoing conflict between Russia and Ukraine, which could directly affect our ability to attain our operating goals on schedule and on budget.

Risks Related to Our Dependence on Third Parties

We depend on collaborations with third parties for certain aspects of the development, marketing and/or commercialization of XPOVIO and/or our product candidates. If those collaborations are not successful, or if we are not able to maintain our existing collaborations or establish additional collaborations, we may have to alter our development and commercialization plans and may not be able to capitalize on the market potential of XPOVIO or our product candidates.

Our drug development programs and the commercialization of our products and product candidates, if approved, require local expertise and substantial additional cash to fund expenses. We expect to maintain our existing collaborations and collaborate with additional pharmaceutical and biotechnology companies for certain aspects of the development, marketing and/or commercialization

of our products and product candidates. For example, we are parties to license arrangements with Antengene and Menarini and distribution agreements with Promedico Ltd. and FORUS Therapeutics Inc. for the development, marketing and/or commercialization of selinexor in certain geographies outside of the U.S. and we expect to rely on additional partners to develop and commercialize our products outside of the U.S. In addition, we intend to seek one or more collaborators to aid in the further development, marketing and/or commercialization of selinexor and our other compounds for indications both within and outside of oncology. All of the risks relating to product development, regulatory approval and commercialization described in this Quarterly Report on Form 10-Q also apply to the activities of our collaborators.

Potential collaborators include large and mid-size pharmaceutical companies, regional and national pharmaceutical companies and biotechnology companies and we face significant competition in seeking appropriate collaborators, including as a result of a significant number of recent business combinations among large pharmaceutical companies that have reduced the number of potential collaborators. Whether we reach a definitive agreement for a collaboration will depend, among other things, upon the assessment of the collaborator's expertise, its current and expected resources and competing priorities, the terms and conditions of the proposed collaboration and the proposed collaborator's evaluation of a number of factors. Those factors may include the design or results of clinical trials, the likelihood of approval by the FDA or foreign regulatory authorities, the potential market for the product or product candidate, the costs and complexities of manufacturing and delivering such product or product candidate to patients, the potential of competing products, the existence of uncertainty with respect to our ownership of intellectual property, which can exist if there is a challenge to such ownership without regard to the merits of the challenge, and industry and market conditions generally. The collaborator may also consider alternative product candidates or technologies for similar indications that may be available to collaborate on and whether such a collaboration could be more attractive than the one with us.

Collaborations are complex and time-consuming to negotiate, document and manage. We may not be able to negotiate collaborations on a timely basis, on acceptable terms, or at all, or we may be restricted under then-existing collaboration agreements from entering into future agreements on certain terms with potential collaborators. If we are unable to maintain our current collaboration agreements or enter into new collaboration agreements, we may have to curtail, reduce or delay the development or commercialization programs for our products or product candidates, or increase our expenditures and undertake development or commercialization activities at our own expense. If we elect to increase our expenditures to fund and undertake development or commercialization activities on our own, we may need to obtain additional expertise and additional capital, which may not be available to us on acceptable terms, or at all. If we do not have sufficient funds or expertise to undertake the necessary development and commercialization activities, we may not be able to further develop our product candidates or bring them to market and generate product revenue.

Our ability to generate revenues from these arrangements will depend on our collaborators' abilities to successfully perform the functions assigned to them in these arrangements, and our collaboration agreements may not lead to the development or commercialization of our products or product candidates in the most efficient manner, or at all, and may result in lower product revenues or profitability to us than if we were to market and sell these products ourselves. In connection with any such arrangements with third parties, we will likely have limited control over the amount and timing of resources that our collaborators dedicate to the development, marketing and/or commercialization of our products or product candidates. Further, if our collaborations do not result in the successful development and commercialization of our products or product candidates or if one of our collaborators terminates its agreement with us, we may not receive any future milestone or royalty payments under the collaboration. If we do not receive the funding we expect under these agreements, the development and commercialization of our products or product candidates could be delayed and we may need additional resources to develop product candidates.

Further, our ability to enter into new collaboration arrangements and the successful execution of our current arrangements by our collaborators has been and could continue to be negatively impacted by the COVID-19 pandemic, including as a result of supply chain disruptions, businesses suspending or terminating global operations and travel, self-imposed or government-mandated quarantines, and a prolonged economic downturn. If our or our third-party collaborators are so affected, our business prospects and results of operations could be severely adversely impacted.

Collaborations involving our products and product candidates pose the following risks to us:

- collaborators have significant discretion in determining the efforts and resources that they will apply to these collaborations;
- collaborators may not perform their obligations as expected or in compliance with applicable local and national laws and regulatory requirements;
- collaborators may not pursue development, marketing and/or commercialization of our products or product candidates or may elect not to continue or renew development, marketing or commercialization programs based on clinical trial results, changes in the collaborator's strategic focus or available funding or external factors such as an acquisition that diverts resources or creates competing priorities;

- collaborators may delay clinical trials, provide insufficient funding for a clinical trial program, stop a clinical trial or abandon a product candidate, repeat or conduct new clinical trials or require a new formulation of a product candidate for clinical testing;
- collaborators could independently develop, or develop with third parties, products that compete directly or indirectly with our products or product candidates if the collaborators believe that competitive products are more likely to be successfully developed or can be commercialized under terms that are more economically attractive than ours;
- a collaborator with marketing and distribution rights to one or more products or product candidates may not commit sufficient resources to the marketing and distribution of our products or product candidates;
- disagreements with collaborators, including disagreements over proprietary rights, contract interpretation or the preferred course of development or commercialization, might cause delays or termination of the research, development or commercialization of products or product candidates, might lead to additional responsibilities for us with respect to our products or product candidates, or might result in litigation or arbitration, any of which would be time-consuming and expensive;
- collaborators may not properly maintain or defend our intellectual property rights or may use our proprietary information in such a way as to invite litigation that could jeopardize or invalidate our intellectual property or proprietary information or expose us to potential litigation;
- collaborators may infringe the intellectual property rights of third parties, which may expose us to litigation and potential liability;
- we may lose certain valuable rights under circumstances identified in any collaboration arrangement that we enter into, such as if we undergo a change of control;
- collaborations may be terminated and, if terminated, may result in a need for additional capital to pursue further development, marketing and/or commercialization of the applicable products or product candidates or to enter into new collaboration agreements;
- collaborators may learn about our discoveries and use this knowledge to compete with us in the future; and
- the number and type of our collaborations could adversely affect our attractiveness to other collaborators or acquirers.

If any of these events occurs, the market potential of our products and product candidates could be reduced, and our business could be materially harmed.

If we are unable to establish and maintain our agreements with third parties to distribute XPOVIO to patients, our results of operations and business could be adversely affected.

We rely on third parties to commercially distribute XPOVIO to patients. For example, we have contracted with a limited number of specialty pharmacies, which sell XPOVIO directly to patients, and specialty distributors, which sell XPOVIO to healthcare entities who then resell XPOVIO to patients. While we have entered into agreements with each of these pharmacies and distributors to distribute XPOVIO in the U.S., they may not perform as agreed or they may terminate their agreements with us. We may also need to enter into agreements with additional pharmacies or distributors, and there is no guarantee that we will be able to do so on a timely basis, at commercially reasonable terms, or at all. If we are unable to maintain and, if needed, expand, our network of specialty pharmacies and specialty distributors, we would be exposed to substantial distribution risk.

The use of specialty pharmacies and specialty distributors involves certain risks, including, but not limited to, risks that these organizations will:

- not provide us accurate or timely information regarding their inventories, the number of patients who are using XPOVIO or serious adverse reactions, events and/or product complaints regarding XPOVIO;
- not effectively sell or support XPOVIO or communicate publicly concerning XPOVIO in a manner that is contrary to FDA rules and regulations;
- reduce their efforts or discontinue to sell or support, or otherwise not effectively sell or support, XPOVIO;
- not devote the resources necessary to sell XPOVIO in the volumes and within the time frames that we expect;
- be unable to satisfy financial obligations to us or others; or
- cease operations.

Any such events may result in decreased product sales, which would harm our results of operations and business.

We rely on third parties as we conduct our clinical trials and some aspects of our research and preclinical studies, and those third parties may not perform satisfactorily, including failing to meet deadlines for the completion of such trials, research or testing.

We rely on third parties, such as CROs, clinical data management organizations, medical institutions and clinical investigators, as we conduct our clinical trials. We currently rely and expect to continue to rely on third parties to conduct some aspects of our research and preclinical studies. Any of these third parties may terminate their engagements with us at any time. If we need to enter into alternative arrangements, it would delay our drug development activities.

Our reliance on these third parties for research and development activities reduces our control over these activities but does not relieve us of our responsibilities. For example, we remain responsible for ensuring that each of our clinical trials is conducted in accordance with the general investigational plan and protocols for the trial. Moreover, the FDA requires us to comply with GCP standards when conducting, recording and reporting the results of clinical trials to assure that data and reported results are credible and accurate and that the rights, integrity and confidentiality of trial participants are protected. The EMA also requires us to comply with comparable standards. Regulatory authorities ensure compliance with these requirements through periodic inspections of trial sponsors, principal investigators and trial sites. If we or any of the third parties that we rely on in connection with our clinical trials fail to comply with applicable requirements, the clinical data generated in our clinical trials may be deemed unreliable and the FDA, EMA or other comparable foreign regulatory authorities may require us to perform additional clinical trials before approving our marketing applications. We cannot assure you that upon inspection by a given regulatory authority, such regulatory authority will determine that any of our clinical trials comply with such requirements. For example, in late 2021, as part of the review process of the Type II variation, the EMA conducted a preapproval GCP inspection at one of the clinical trial sites that participated in the BOSTON Study. There can be no assurances that the response by the clinical site to the questions and findings included in the inspection report will be acceptable to the EMA. We also are required to register ongoing clinical trials and post the results of completed clinical trials on a government-sponsored database, ClinicalTrials.gov, within certain timeframes. Failure to do so can result in fines, adverse publicity and civil and criminal sanctions.

Furthermore, these third parties may also have relationships with other entities, some of which may be our competitors. If these third parties do not successfully carry out their contractual duties, meet expected deadlines or conduct our clinical trials in accordance with regulatory requirements or our stated protocols, we will not be able to obtain, or may be delayed in obtaining, marketing approvals for our product candidates and will not be able to, or may be delayed in our efforts to, successfully commercialize our products. In such an event, our financial results and the commercial prospects for our products or product candidates, if approved, could be harmed, our costs could increase and our ability to generate revenues could be delayed, impaired or foreclosed.

We also expect to rely on other third parties to store and distribute drug supplies for our clinical trials. Any performance failure on the part of such third parties could delay clinical development or marketing approval of our product candidates or commercialization of our products, producing additional losses and depriving us of potential product revenue.

In addition, as discussed above, the third-parties upon whom we rely to conduct our clinical trials could be negatively impacted as a result of disruptions caused by the COVID-19 pandemic, including difficulties in initiating clinical sites or enrolling participants, diversion of healthcare resources away from clinical trials, travel or quarantine policies, and other factors. If these third parties are so affected, our business prospects and results of operations could be severely adversely impacted.

We rely on third parties to conduct investigator-sponsored clinical trials of selinexor and our product candidates. Any failure by a third party to meet its obligations with respect to the clinical development of our product candidates may delay or impair our ability to obtain regulatory approval for selinexor and our product candidates.

We rely on academic and private non-academic institutions to conduct and sponsor clinical trials relating to selinexor and our product candidates. We do not control the design or conduct of the investigator-sponsored trials, and it is possible that the FDA or foreign regulatory authorities will not view these investigator-sponsored trials as providing adequate support for future clinical trials, whether controlled by us or third parties, for any one or more reasons, including elements of the design, execution of the trials, safety concerns or other trial results.

Such arrangements will provide us certain information rights with respect to the investigator-sponsored trials, including access to and the ability to use and reference the data, including for our own regulatory filings, resulting from the investigator-sponsored trials. However, we do not have control over the timing and reporting of the data from investigator-sponsored trials, nor do we own the data from the investigator-sponsored trials. If we are unable to confirm or replicate the results from the investigator-sponsored trials or if negative results are obtained, we would likely be further delayed or prevented from advancing clinical development of our product candidates. Further, if investigators or institutions breach their obligations with respect to the clinical development of our product candidates, or if the data proves to be inadequate compared to the first-hand knowledge we might have gained had the investigator-sponsored trials been sponsored and conducted by us, then our ability to design and conduct any future clinical trials ourselves may be adversely affected.

Additionally, the FDA or foreign regulatory authorities may disagree with the sufficiency of our right to reference the preclinical, manufacturing or clinical data generated by these investigator-sponsored trials, or our interpretation of preclinical, manufacturing or clinical data from these investigator-sponsored trials. If so, the FDA or foreign regulatory authorities may require us to obtain and submit additional preclinical, manufacturing, or clinical data before we may initiate our planned trials and/or may not accept such additional data as adequate to initiate our planned trials.

We are completely dependent on third parties for the manufacture of our products and product candidates and any difficulties, disruptions, delays or unexpected costs, or the need to find alternative sources, could adversely affect our results of operations, profitability and future business prospects.

We do not own or operate, and currently have no plans to establish, any manufacturing facilities for our products or product candidates. We currently rely, and expect to continue to rely, on third-party contract manufacturers to manufacture our products and product candidates for our commercial and clinical use.

Facilities used by our third-party manufacturers may be inspected by the FDA after we submit an NDA and before potential approval of the product candidate and are also subject to ongoing periodic unannounced inspections by the FDA for compliance with cGMP and other regulatory requirements following approval. Similar regulations apply to manufacturers of our product candidates for use or sale in foreign countries. We do not control the manufacturing processes of, and are completely dependent on, our third-party manufacturers for compliance with the applicable regulatory requirements for the manufacture of our products and product candidates. Third-party manufacturers may not be able to comply with cGMP regulations or similar regulatory requirements outside of the U.S. If our manufacturers cannot successfully manufacture material that conforms to our specifications and the strict regulatory requirements of the FDA and any applicable foreign regulatory authority, they will not be able to secure and/or maintain regulatory approval for their manufacturing facilities. If these facilities are not approved for commercial manufacture or are not able to maintain approval, we may need to find alternative manufacturing facilities, which could significantly impact our ability to develop, obtain regulatory approval for or market our products or product candidates as alternative qualified manufacturing facilities may not be available on a timely or cost-efficient basis, or at all. Failure by any of our manufacturers to comply with applicable cGMP regulations or other regulatory requirements could result in sanctions being imposed on us or the contract manufacturer, including fines, injunctions, civil penalties, delays, suspensions or withdrawals of approvals, operating restrictions, interruptions in supply and criminal prosecutions, any of which could significantly and adversely affect supplies of our products or product candidates and have a material adverse impact on our business, financial condition and results of operations.

We currently have long-term supply agreements with our third-party contract manufacturers to manufacture the clinical and commercial supplies of the drug product for XPOVIO. Our ability to have our products manufactured in sufficient quantities and at acceptable costs to meet our commercial demand and clinical development needs is dependent on the uninterrupted and efficient operation of our third-party contract manufacturers' facilities. Reliance on third-party manufacturers entails risks, including:

- reliance on the third party for regulatory compliance and quality assurance;
- the possible breach, termination or nonrenewal of a manufacturing agreement by the third party, including at a time that is costly or inconvenient to us;
- the possible failure of the third party to manufacture our products or product candidates according to our schedule, or at all, including if the third-party manufacturer gives greater priority to the supply of other products over our products and product candidates, or otherwise does not satisfactorily perform according to the terms of the manufacturing agreement;
- equipment malfunctions, power outages or other general disruptions experienced by our third-party manufacturers to their respective operations and other general problems with a multi-step manufacturing process; and
- the possible misappropriation or disclosure by the third party or others of our proprietary information, including our trade secrets and know-how.

We currently rely on a single source supplier for our active pharmaceutical ingredient and our drug product manufacturing requirements. Any performance failure on the part of our existing or future manufacturers could delay clinical development, marketing approval or commercialization of our products or product candidates. For example, as a result of the COVID-19 pandemic, our suppliers and contract manufacturers could be disrupted by worker absenteeism, quarantines, or other travel or health-related restrictions or could incur increased costs associated with ensuring the safety and health of their personnel. If our suppliers or contract manufacturers are so affected, our supply chain could be disrupted, our product shipments could be delayed, our costs could be increased and our business could be adversely affected. If our current contract manufacturers cannot perform as agreed, we may be required to replace those manufacturers. Although we believe that there are several potential alternative manufacturers who could manufacture our products and product candidates, we could incur added costs and delays in identifying and qualifying any such replacement. Consequently, we may not be able to reach agreement with third-party manufacturers on satisfactory terms, which could negatively impact our XPOVIO revenues or delay commercialization of any product candidates that are subsequently approved.

If, because of the factors discussed above, we are unable to have our products manufactured on a timely or sufficient basis, we may not be able to meet clinical development needs or commercial demand for our products or product candidates or we may not be able to manufacture our products in a cost-effective manner. As a result, we may lose sales, fail to generate projected revenues or suffer development or regulatory setbacks, any of which could have an adverse impact on our profitability and future business prospects.

Risks Related to Our Intellectual Property

If we are unable to obtain and maintain patent protection for our products or product candidates and other discoveries, or if the scope of the patent protection obtained is not sufficiently broad, our competitors could develop and commercialize drugs and other discoveries similar or identical to ours, and our ability to successfully commercialize our products or product candidates and other discoveries may be adversely affected.

Our success depends in large part on our ability to obtain and maintain patent protection in the U.S. and other countries with respect to our proprietary products and product candidates and other discoveries. We seek to protect our proprietary position by filing patent applications in the U.S. and abroad related to our novel products and product candidates and other discoveries that are important to our business. As of April 29, 2022, 95 patents were in force that relate to XPO1 inhibitors, including composition of matter patents for selinexor, verdinexor and eltanexor in the U.S., and their use in targeted therapeutics. In addition, 25 patents were in force that relate to our PAK4/NAMPT inhibitors, including three composition of matter patents for KPT-9274 in the U.S. and its use in targeted therapeutics. With respect to our IL-12 Program, as of April 29, 2022, 21 patents were in force, 10 of which are exclusively licensed to Karyopharm by the University of Southern California, that relate to IL-12 compositions and uses of IL-12 in targeted therapeutics. We cannot be certain that any other patents will issue with claims that cover any of our key products, product candidates or other discoveries.

The patent prosecution 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, involves complex legal and factual questions and has in recent years been the subject of much litigation. As a result, the issuance, scope, validity, enforceability and commercial value of our patent rights are highly uncertain. Our pending and future patent applications may not result in patents being issued which protect our product candidates or other discoveries, or which effectively prevent others from commercializing competitive drugs and discoveries. Changes in either the patent laws or interpretation of the patent laws in the U.S. and other countries may diminish the value of our patents or narrow the scope of our patent protection.

The laws of foreign countries may not protect our rights to the same extent as the laws of the U.S. For example, in some foreign jurisdictions, our ability to secure patents based on our filings in the U.S. may depend, in part, on our ability to timely obtain assignment of rights to the invention from the employees and consultants who invented the technology. Publications of discoveries in the scientific literature often lag behind the actual discoveries, and patent applications in the U.S. and other jurisdictions are typically not published until 18 months after filing, or in some cases not at all. Therefore, we cannot be certain that we were the first to make the inventions claimed in our patents or pending patent applications, or that we were the first to file for patent protection of such inventions.

Assuming the other requirements for patentability are met, prior to March 2013, in the U.S., the first to invent the claimed invention was entitled to the patent, while outside of the U.S., the first to file a patent application is entitled to the patent. In March 2013, the U.S. transitioned to a first-inventor-to-file system in which, assuming the other requirements for patentability are met, the first inventor to file a patent application is entitled to the patent. We may be subject to a third-party preissuance submission of prior art to the U.S. Patent and Trademark Office (“USPTO”) or become involved in opposition, derivation, revocation, reexamination, or post-grant or inter partes review or interference proceedings challenging our patent rights or the patent rights of others. An adverse determination in any such submission, proceeding or litigation could reduce the scope of, or invalidate, our patent rights, allow third parties to commercialize our discoveries or drugs and compete directly with us, without payment to us, or result in our inability to manufacture or commercialize drugs without infringing third-party patent rights.

Even if our patent applications issue as patents, they may not issue in a form that will provide us with any meaningful protection, prevent competitors from competing with us or otherwise provide us with any competitive advantage. Our competitors may be able to circumvent our patents by developing similar or alternative discoveries or drugs in a non-infringing manner.

The issuance of a patent is not conclusive as to its inventorship, scope, validity or enforceability, and our patents may be challenged in the courts or patent offices in the U.S. and abroad. Such challenges may result in loss of exclusivity or in patent claims being narrowed, invalidated or held unenforceable, which could limit our ability to stop others from using or commercializing similar or identical discoveries and drugs, or limit the duration of the patent protection of our products, product candidates and discoveries. Given the amount of time required for the development, testing and regulatory review of new product candidates, patents protecting

such candidates might expire before or shortly after such candidates are commercialized. As a result, our patent portfolio may not provide us with sufficient rights to exclude others from commercializing drugs similar or identical to ours.

We may become involved in lawsuits to protect or enforce our patents and other intellectual property rights, which could be expensive, time-consuming and unsuccessful.

Competitors or commercial supply companies or others may infringe our patents and other intellectual property rights. For example, we are aware of third parties selling a version of our lead product candidate for research purposes, which may infringe our intellectual property rights. To counter such infringement, we may advise such companies of our intellectual property rights, including, in some cases, intellectual property rights that provide protection for our lead product candidates, and demand that they stop infringing those rights. Such demand may provide such companies the opportunity to challenge the validity of certain of our intellectual property rights, or the opportunity to seek a finding that their activities do not infringe our intellectual property rights. We may also be required to file infringement actions, which can be expensive and time-consuming. In an infringement proceeding, a defendant may assert and a court may agree with a defendant that a patent of ours is invalid or unenforceable, or may refuse to stop the other party from using the intellectual property at issue. An adverse result in any litigation could put one or more of our patents at risk of being invalidated or interpreted narrowly. 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.

Third parties may initiate legal proceedings alleging that we are infringing their intellectual property rights, the outcome of which would be uncertain and could have a material adverse effect on the success of our business.

Our commercial success depends upon our ability and the ability of any current and future collaborators to develop, manufacture, market and sell XPOVIO and our product candidates and use our proprietary technologies without infringing the proprietary rights of third parties. We may become party to, or threatened with, future adversarial proceedings or litigation regarding intellectual property rights with respect to our products or product candidates and technology, including interference proceedings before the USPTO. Third parties may assert infringement claims against us based on existing patents or patents that may be granted in the future. No litigation asserting such infringement claims is currently pending against us, and we have not been found by a court of competent jurisdiction to have infringed a third party's intellectual property rights. If we are found to infringe or think there is a risk we may be found to infringe, a third party's intellectual property rights, we could be required or choose to obtain a license from such third party to continue developing, marketing and selling our drugs, product candidates and technology. However, we may not be able to obtain any required license on commercially reasonable terms, or at all. Even if we were able to obtain a license, it could be non-exclusive, thereby giving our competitors access to the same intellectual property licensed to us. We could be forced, including by court order, to cease commercializing the infringing intellectual property or drug or to cease using the infringing technology. In addition, we could be found liable for monetary damages. A finding of infringement could prevent us from commercializing our products or product candidates or force us to cease some of our business operations, which could materially harm our business. Claims that we have misappropriated the confidential information or trade secrets of third parties could have a similar negative impact on our business.

We may be subject to claims that our employees have wrongfully used or disclosed alleged trade secrets of their former employers.

Many of our employees 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 do not use the proprietary information or know-how of others in their work for us, we may be subject to claims that we or these employees have used or disclosed intellectual property, including trade secrets or other proprietary information, of any such employee's former employer. Although we have no knowledge of any such claims being alleged to date, if such claims were to arise, litigation may be necessary to defend against any such claims. If we fail in defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights or personnel. Even if we are successful in defending against such claims, litigation could result in substantial costs and be a distraction to management.

Intellectual property litigation could cause us to spend substantial resources and distract our personnel from their normal responsibilities.

Even if resolved in our favor, litigation or other legal proceedings relating to intellectual property claims may cause us to incur significant expenses and could distract our technical and management personnel from their normal responsibilities. In addition, there could be public announcements of the results of hearings, motions or other interim proceedings or developments and 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. Such litigation or proceedings could substantially increase our operating losses and reduce the resources available for development activities or any future sales, marketing or distribution activities. We may not have sufficient financial or other resources to adequately conduct such litigation or proceedings. Some of our competitors may be able to sustain the costs of such litigation or proceedings

more effectively than we can because of their greater financial resources. Uncertainties resulting from the initiation and continuation of patent litigation or other proceedings could have a material adverse effect on our ability to compete in the marketplace.

Obtaining and maintaining our patent protection depends on compliance with various procedural, documentary, fee payment and other requirements imposed by governmental patent agencies, and our patent protection could be reduced or eliminated for non-compliance with these requirements.

Periodic maintenance fees, renewal fees, annuity fees and various other governmental fees on patents and/or applications will be due to the USPTO and various foreign patent offices at various points over the lifetime of the patents and/or applications. We have systems in place to remind us to pay these fees, and we rely on our outside counsel to pay these fees when due. Additionally, the USPTO and various foreign patent offices require compliance with a number of procedural, documentary, fee payment and other similar provisions during the patent application process. We employ reputable law firms and other professionals to help us comply with such provisions, and in many cases, an inadvertent lapse can be cured by payment of a late fee or by other means in accordance with rules applicable to the particular jurisdiction. However, there are situations in which non-compliance can result in abandonment or lapse of the patent or patent application, resulting in partial or complete loss of patent rights in the relevant jurisdiction. If such an event were to occur, it could have a material adverse effect on our business.

If our drug product candidates or any of our future drug product candidates obtain regulatory approval, additional competitors could enter the market with generic versions of such products, which may result in a material decline in sales of our competing products.

Under the Drug Price Competition and Patent Term Restoration Act of 1984 (the "Hatch-Waxman Amendments") to the FDCA, a company may file an ANDA, seeking approval of a generic version of an approved innovator product. Under the Hatch-Waxman Amendments, a company may also submit an NDA under section 505(b)(2) of the FDCA that references the FDA's prior approval of the innovator product or preclinical studies and/or clinical trials that were not conducted by, or for, the applicant and for which the applicant has not obtained a right of reference. A 505(b)(2) NDA product may be for a new or improved version of the original innovator product. The Hatch-Waxman Amendments also provide for certain periods of regulatory exclusivity, which preclude FDA approval (or in some circumstances, FDA filing and review) of an ANDA or 505(b)(2) NDA. 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 FDA publication "Approved Drug Products with Therapeutic Equivalence Evaluations," known as the Orange Book. If there are patents listed in the Orange Book for the applicable, approved innovator product, a generic or 505(b)(2) applicant that seeks to market its product before expiration of the patents must include in their applications what is known as a "Paragraph IV" certification, challenging the validity or enforceability, or claiming non-infringement, of the listed patent or patents. Notice of the certification must be given to the patent owner and NDA holder and if, within 45 days of receiving notice, either the patent owner or NDA holder sues for patent infringement, approval of the ANDA or 505(b)(2) NDA is stayed for up to 30 months.

Accordingly, if any of our product candidates that are regulated as drugs are approved, competitors could file ANDAs for generic versions of these products or 505(b)(2) NDAs that reference our products. If there are patents listed for such drug products 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 which, if any, patents in our current portfolio or patents we may obtain in the future 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.

If we do not successfully extend the term of patents covering our product candidates under the Hatch-Waxman Amendments and similar foreign legislation, our business may be materially harmed.

Depending upon the timing, duration and conditions of FDA marketing approval, if any, of our products or product candidates, one or more of our U.S. patents may be eligible for patent term extension under the Hatch-Waxman Amendments. The Hatch-Waxman Amendments permit a patent term extension of up to five years for one patent covering an approved product as compensation for effective patent term lost during product development and the FDA regulatory review process. However, we may not receive an extension if we fail to apply within applicable deadlines, fail to apply prior to expiration of relevant patents or otherwise fail to satisfy applicable requirements. Moreover, the length of the extension could be less than we request. The total patent term, including the extension period, may not exceed 14 years following FDA approval. Accordingly, the length of the extension, or the ability to even obtain an extension, depends on many factors.

In the U.S., only a single patent can be extended for each qualifying FDA approval, and any patent can be extended only once and only for a single product. Laws governing analogous patent term extensions in foreign jurisdictions vary widely, as do laws governing the ability to obtain multiple patents from a single patent family. Because both selinexor and verdinexor are protected by a single family of patents and applications, we may not be able to secure patent term extensions for both of these product candidates in all jurisdictions where these product candidates are approved.

If we are unable to obtain a patent term extension for a product or product candidate or the term of any such extension is less than we request, the period during which we can enforce our patent rights for that product or product candidate, if any, in that jurisdiction will be shortened and our competitors may obtain approval to market competing products sooner. As a result, our revenue could be materially reduced.

If we are unable to protect the confidentiality of our trade secrets, our business and competitive position would be harmed.

In addition to seeking patents for our products, product candidates and other discoveries, we also rely on trade secrets, including unpatented know-how, technology and other proprietary information, to maintain our competitive position. We seek to protect these trade secrets, in part, by entering into non-disclosure and confidentiality agreements with parties who have access to them, such as our employees, outside scientific collaborators, CROs, contract manufacturers, consultants, advisors and other third parties. We also enter into confidentiality and invention or patent assignment agreements with our employees and consultants. Despite these efforts, any of these parties may breach the agreements and disclose our proprietary information, including our trade secrets, and we may not be able to obtain adequate remedies for such breaches. To the extent that we are unable to timely enter into confidentiality and invention or patent assignment agreements with our employees and consultants, our ability to protect our business through trade secrets and patents may be harmed. Enforcing a claim that a party illegally disclosed or misappropriated a trade secret is difficult, expensive and time-consuming, and the outcome is unpredictable. In addition, some courts inside and outside of the U.S. are less willing or unwilling to protect trade secrets. If any of our trade secrets were to be lawfully obtained or independently developed by a competitor, we would have no right to prevent them from using that technology or information to compete with us. If any of our trade secrets were to be disclosed to or independently developed by a competitor, our competitive position would be harmed. To the extent inventions are made by a third party under an agreement that does not grant us an assignment of their rights in inventions, we may choose or be required to obtain a license.

Not all of our trademarks are registered. Failure to secure those registrations could adversely affect our business.

As of April 29, 2022, we have trademark registrations in the U.S. for KARYOPHARM THERAPEUTICS, our color logo, and a combination of the two, XPOVIO, PORE for our online research portal, and KARYFORWARD and our KARYFORWARD logo for our financial aid and charitable services. We also have pending applications in the U.S. to register KARYOPHARM alone, and our logo in greyscale, for pharmaceuticals. Outside of the U.S., XPOVIO is registered or pending in 46 additional jurisdictions, and is registered in Katakana in Japan, Hangul in South Korea, and Chinese characters in Taiwan. KARYOPHARM, the greyscale logo, KARYOPHARM THERAPEUTICS with the color logo, and the KARYFORWARD logo are each registered or pending in four jurisdictions outside of the U.S. We also have registrations or applications for eight additional possible drug names in numerous foreign jurisdictions. If we do not secure registrations for our trademarks, we may encounter more difficulty in enforcing them against third parties than we otherwise would, which could adversely affect our business. During trademark registration proceedings in the U.S. and foreign jurisdictions, we may receive rejections. We are given an opportunity to respond to those rejections, but we may not be able to overcome such rejections. In addition, in the USPTO and in comparable agencies in many foreign jurisdictions, third parties are given an opportunity to oppose pending trademark applications and to seek to cancel registered trademarks. Opposition or cancellation proceedings may be filed against our trademarks, and our trademarks may not survive such proceedings.

In addition, any proprietary name we propose to use with our key product candidates in the U.S. must be approved by the FDA, regardless of whether we have registered it, or applied to register it, as a trademark. The FDA typically conducts a review of proposed drug names, including an evaluation of potential for confusion with other drug names. If the FDA objects to any of our proposed proprietary drug names for any of our product candidates, if approved, we may be required to expend significant additional resources in an effort to identify a suitable proprietary drug name that would qualify under applicable trademark laws, not infringe the existing rights of third parties and be acceptable to the FDA.

Risks Related to Employee Matters and Managing Growth

Our future success depends on our ability to retain key members of our management team and to attract, retain and motivate qualified personnel.

We are highly dependent on the management, technical and scientific expertise of principal members of our management and scientific teams, including our President and Chief Executive Officer. Although we have entered into formal employment agreements with our executive officers, these agreements do not prevent them from terminating their employment with us at any time. We do not maintain “key person” insurance for any of our executives or other employees. The loss of the services of any of our key employees could impede the achievement of our research, development, commercialization and other business objectives.

Recruiting and retaining qualified scientific, clinical, manufacturing and sales and marketing personnel is critical to our success. We may not be able to attract and retain these personnel on acceptable terms given the competition among numerous pharmaceutical and biotechnology companies for similar personnel. We also experience competition for the hiring of scientific and clinical personnel from universities and research institutions. In addition, we rely on consultants and advisors, including scientific and clinical advisors, to assist us in formulating our research and development and commercialization strategies. Our consultants and advisors may be

employed by employers other than us and may have commitments under consulting or advisory contracts with other entities that may limit their availability to us.

We have expanded and expect to continue to expand our development, regulatory and sales, marketing and distribution capabilities, and as a result, we may encounter difficulties in managing our growth, which could disrupt our operations.

We have experienced and expect to continue to experience significant growth in the number of our employees and the scope of our operations, particularly in the areas of drug development, clinical operations, regulatory affairs, sales, marketing and distribution. To manage our current and anticipated future growth, we must continue to implement and improve our managerial, operational and financial systems, expand our facilities and continue to recruit and train additional qualified personnel. Due to our limited financial resources and the limited experience of our management team in managing such growth, we may not be able to effectively manage the expansion of our operations or recruit and train additional qualified personnel. The expansion of our operations may lead to significant costs and may divert our management and business development resources. Any inability to manage growth could delay the execution of our business plans or disrupt our operations.

Our business and operations may be materially adversely affected in the event of information technology system failures or security breaches, and the costs and consequences of implementing data protection measures could be significant.

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, natural disasters, fire, terrorism, war and telecommunication and electrical failures. Such systems are also vulnerable to service interruptions or to security breaches from inadvertent or intentional actions by our employees, third-party vendors and/or business partners, or from cyber incidents by malicious third parties. Cyber incidents are increasing in their frequency, sophistication and intensity, and have become increasingly difficult to detect. Cyber incidents could include the deployment of harmful malware, ransomware, denial-of-service attacks, unauthorized access to or deletion of files, social engineering and other means to affect service reliability and threaten the confidentiality, integrity and availability of information. Cyber incidents also could include phishing attempts or e-mail fraud to cause payments or information to be transmitted to an unintended recipient. We could be subject to risks caused by misappropriation, misuse, leakage, falsification or intentional or accidental release or loss of information maintained in the information systems and networks of our company, including personal data of our employees. In addition, we face other kinds of risks related to our commercial and personal data, including lost or stolen devices or other systems (including paper records) that collect and store our personal and commercial information.

If such an event were to occur and cause interruptions in our operations, it could result in a material disruption of our development and commercialization programs and our business operations, whether due to a loss of our trade secrets or other proprietary information or other similar disruptions. For example, the loss of clinical trial data from completed, 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 were to result in a loss of, or damage to, our data or applications, or inappropriate disclosure of confidential or proprietary information, we could incur liability, our reputation or competitive position could be damaged, and the further development and commercialization of our products or product candidates could be delayed or halted. In addition, we may in certain instances be required to provide notification to individuals or others in connection with the loss of their personal or commercial information.

If a material breach of our security or that of our vendors occurs, our financial or other confidential information could be compromised and could adversely affect our business or result in legal proceedings. In addition, the cost and operational consequences of implementing further data protection measures could be significant. The development and maintenance of these systems, controls and processes is costly and requires ongoing monitoring and updating as technologies change and efforts to overcome security measures become more sophisticated. Moreover, the possibility of these events occurring cannot be eliminated entirely.

Risks Related to Our Common Stock

Provisions in our corporate charter documents and under Delaware law could make an acquisition of us, which may be beneficial to our stockholders, more difficult and may prevent attempts by our stockholders to replace or remove our current management.

Provisions in our corporate charter and our bylaws may discourage, delay or prevent a merger, acquisition or other change in control of us that stockholders may consider favorable, including transactions in which stockholders might otherwise receive a premium for their shares. These provisions could also limit the price that investors might be willing to pay in the future for shares of our common stock, thereby depressing the market price of our common stock. In addition, because our board of directors is responsible for appointing the members of our management team, these provisions may frustrate or prevent any attempts by our stockholders to replace or remove our current management by making it more difficult for stockholders to replace members of our board of directors. Among other things, these provisions:

- establish a classified board of directors such that not all members of the board are elected at one time;
- allow the authorized number of our directors to be changed only by resolution of our board of directors;

- limit the manner in which stockholders can remove directors from the board;
- establish advance notice requirements for stockholder proposals that can be acted on at stockholder meetings and nominations to our board of directors;
- require that stockholder actions must be effected at a duly called stockholder meeting and prohibit actions by our stockholders by written consent;
- limit who may call stockholder meetings;
- authorize our board of directors to issue preferred stock without stockholder approval, which could be used to institute a "poison pill" that would work to dilute the stock ownership of a potential hostile acquirer, effectively preventing acquisitions that have not been approved by our board of directors; and
- require the approval of the holders of at least 75% of the votes that all our stockholders would be entitled to cast to amend or repeal certain provisions of our charter or bylaws.

Moreover, because we are incorporated in Delaware, we are governed by the provisions of Section 203 of the Delaware General Corporation Law, which prohibits a person who owns in excess of 15% of our outstanding voting stock from merging or combining with us for a period of three years after the date of the transaction in which the person acquired in excess of 15% of our outstanding voting stock, unless the merger or combination is approved in a prescribed manner.

The price of our common stock has been and may continue to be volatile and your investment in our stock could decline in value or fluctuate significantly, including as a result of analysts' activities.

Our stock price has been, and may continue to be, volatile and your investment in our stock could decline or fluctuate significantly. Our common stock price has ranged from $4.42 to $14.73 in the 52-week period ended April 29, 2022. On April 29, 2022, the closing sale price of our common stock on the Nasdaq Global Select Market was $6.10 per share. The stock market in general and the market for pharmaceutical and biotechnology companies in particular have experienced extreme volatility that has often been unrelated to the operating performance of particular companies, such as the response to the ongoing COVID-19 pandemic and related world-wide economic disruptions. The market price for our common stock may be influenced by many factors, including:

- our failure to successfully execute on our commercialization strategy for XPOVIO or our product candidates, if approved;
- the level of success of competitive products or technologies;
- results, delays in, or the halting of our clinical trials or those of our competitors, including reports of AEs related to the use of our products;
- announcements by us or our competitors of new products, significant mergers, acquisitions, licenses or joint ventures;
- commencement or termination of collaborations for our development programs and the commercialization of our products;
- adverse regulatory or legal developments in the U.S. and other countries;
- developments or disputes concerning patent applications, issued patents or other proprietary rights;
- additions or departures of key personnel;
- the level of expenses related to the commercialization of XPOVIO and clinical development programs for any of our product candidates;
- the results of our efforts to discover, develop, acquire or in-license additional products or product candidates;
- actual or anticipated changes in estimates of financial results or guidance, development timelines or recommendations by securities analysts;
- actual or anticipated fluctuations in our quarterly or annual financial results;
- changes in healthcare laws affecting pricing, reimbursement or access;
- market conditions in the pharmaceutical and biotechnology sectors, including as the result of uncertainties due to or impacts from the ongoing COVID-19 pandemic;
- general economic, industry and market conditions, such as those caused by the COVID-19 pandemic and the ongoing conflict between Russia and Ukraine;
- our ability to raise additional capital and the terms on which we can raise it;

- sales of large blocks of our common stock, including by our executive officers, directors and significant stockholders; and
- the other risks and uncertainties described in this "*Risk Factors*" section.

The COVID-19 pandemic has caused significant disruptions in the financial markets, and may continue to cause such disruptions, and has also impacted, and may continue to impact, the volatility of our stock price and trading in our stock. In addition, U.S. and global markets are experiencing volatility and disruption following the escalation of geopolitical tensions and the start of the military conflict between Russia and Ukraine. A continuation or worsening of the levels of market disruption and volatility could have an adverse effect on the market price of our common stock. Furthermore, the trading market for our common stock relies, in part, on the research and reports that industry or financial analysts publish about us or our business. Our stock price could decline significantly if we fail to meet or exceed analysts' forecasts and expectations or if one or more of the analysts covering our business downgrade their evaluations of our stock. Further, if one or more of these analysts cease to cover our stock, we could lose visibility in the market for our stock, which in turn could cause our stock price to decline.

Securities or other litigation could result in substantial costs and may divert management's time and attention from our business.

Securities class action litigation is often brought against a company following a decline or periods of volatility in the market price of its securities. This risk is especially relevant for us because pharmaceutical companies have experienced significant stock price volatility in recent years, including as a result of the COVID-19 pandemic, and we are therefore a target of this type of litigation. For example, we are currently subject to a shareholder derivative lawsuit initiated against us and certain of our executive officers and directors and certain other defendants, as described further in Part I, Item 3, "*Legal Proceedings*" in our Annual Report. We may face additional securities class action litigation or other litigation if we fail to successfully commercialize XPOVIO, or if we cannot obtain regulatory approvals for, or if we otherwise fail to successfully commercialize and launch, our product candidates.

The outcome of litigation is necessarily uncertain, and we could be forced to expend significant resources in the defense of such suits, and we may not prevail. Monitoring and defending against legal actions is time-consuming for our management and detracts from our ability to fully focus our internal resources on our business activities. In addition, we may incur substantial legal fees and costs in connection with any such litigation. We have not established any reserves for any potential liability relating to any such potential lawsuits. It is possible that we could, in the future, incur judgments or enter into settlements of claims for monetary damages. We currently maintain insurance coverage for some of these potential liabilities. Other potential liabilities may not be covered by insurance, insurers may dispute coverage or the amount of insurance may not be enough to cover damages awarded. In addition, certain types of damages may not be covered by insurance, and insurance coverage for all or certain forms of liability may become unavailable or prohibitively expensive in the future. A decision adverse to our interests on one or more legal matters or litigation could result in the payment of substantial damages, or possibly fines, and could have a material adverse effect on our reputation, financial condition and results of operations.

We have broad discretion in the use of our cash, cash equivalents and investments and may not use them effectively.

Our management has broad discretion to use our cash, cash equivalents and investments to fund our operations and could spend these funds in ways that do not improve our results of operations or enhance the value of our common stock. The failure by our management to apply these funds effectively could result in financial losses that could have a material adverse effect on our business, cause the price of our common stock to decline and delay the development of our product candidates. Pending their use to fund our operations, we may invest our cash and cash equivalents in a manner that does not produce income or that loses value.

If we identify a material weakness in our internal control over financial reporting, it could have an adverse effect on our business and financial results and our ability to meet our reporting obligations could be negatively affected, each of which could negatively affect the trading price of our common stock.

A material weakness is a deficiency, or a combination of deficiencies, in internal control over financial reporting, such that there is a reasonable possibility that a material misstatement of our annual or interim financial statements will not be prevented or detected on a timely basis. Accordingly, a material weakness increases the risk that the financial information we report contains material errors.

We regularly review and update our internal controls, disclosure controls and procedures, and corporate governance policies. In addition, we are required under the Sarbanes-Oxley Act of 2002 to report annually on our internal control over financial reporting. Any system of internal controls, however well designed and operated, is based in part on certain assumptions and can provide only reasonable, not absolute, assurances that the objectives of the system are met. If we, or our independent registered public accounting firm, determine that our internal control over our financial reporting is not effective, or we discover areas that need improvement in the future, or we experience high turnover of our personnel in our financial reporting functions, these shortcomings could have an adverse effect on our business and financial results, and the price of our common stock could be negatively affected.

If we cannot conclude that we have effective internal control over our financial reporting, or if our independent registered public accounting firm is unable to provide an unqualified opinion regarding the effectiveness of our internal control over financial reporting, investors could lose confidence in the reliability of our financial statements, which could lead to a decline in our stock price. Failure to

comply with reporting requirements could also subject us to sanctions and/or investigations by the SEC, the Nasdaq Stock Market or other regulatory authorities.

If the estimates we make, or the assumptions on which we rely, in preparing our consolidated financial statements, our projected guidance and/or our projected market opportunities prove inaccurate, our actual results may vary from those reflected in our projections and accruals.

Our consolidated financial statements have been prepared in accordance with accounting principles generally accepted in the United States of America ("GAAP"). The preparation of these consolidated financial statements requires us to make estimates and judgments that affect the reported amounts of our assets, liabilities, revenues and expenses, the amounts of charges accrued by us and related disclosure of contingent assets and liabilities. We base our estimates on historical experience and on various other assumptions that we believe to be reasonable under the circumstances.

We cannot assure you, however, that our estimates, or the assumptions underlying them, will be correct. Further, from time to time we issue guidance on our expected financial performance for future periods, such as our expectations regarding our revenue, non-GAAP research and development and selling, general and administrative expenses, and cash, cash equivalents and investments available for operations, which guidance is based on estimates and the judgment of management. If, for any reason, our actual results differ materially from our guidance, we may have to adjust our publicly announced financial guidance. If we fail to meet, or if we are required to change or update any element of, our publicly disclosed financial guidance or other expectations about our business, our stock price could decline.

Further our estimates of the potential market opportunities for XPOVIO and our product candidates include several key assumptions based on our industry knowledge, industry publications, third-party research and other surveys, which may be based on a small sample size and fail to accurately reflect market opportunities. While we believe that our internal assumptions are reasonable, these assumptions involve the exercise of significant judgment on the part of our management, are inherently uncertain and the reasonableness of these assumptions has not been assessed by an independent source. If any of our assumptions or estimates, or these publications, research, surveys or studies prove to be inaccurate, then the actual market for XPOVIO or any other products or product candidates may be smaller than we expect, and as a result our product revenue may be limited and it may be more difficult for us to achieve profitability.

Our ability to use our net operating loss carryforwards and tax credit carryforwards to offset future taxable income may be subject to certain limitations.

Under the provisions of the Internal Revenue Code of 1986, as amended (the "Code"), our net operating loss and tax credit carryforwards are subject to review and possible adjustment by the Internal Revenue Service (and state tax authorities under relevant state tax rules). In addition, as described below in "*Changes in tax laws or in their implementation or interpretation may adversely affect our business and financial condition*," the TCJA, as amended by the CARES Act, includes changes to U.S. federal tax rates and the rules governing net operating loss carryforwards that may significantly impact our ability to utilize our net operating losses to offset taxable income in the future. Furthermore, the use of net operating loss and tax credit carryforwards may become subject to an annual limitation under Sections 382 and 383 of the Code, respectively, and similar state provisions in the event of certain cumulative changes in the ownership interest of significant stockholders in excess of 50 percent over a three-year period. This could limit the amount of tax attributes that can be utilized annually to offset future taxable income or tax liabilities. The amount of the annual limitation is determined based on the value of a company immediately prior to the ownership change. Subsequent ownership changes may further affect the limitation in future years. Our company has completed several financings since its inception which resulted in an ownership change under Sections 382 and 383 of the Code. In addition, future changes in our stock ownership, some of which are outside of our control, could result in ownership changes in the future. For these reasons, we may not be able to use some or all of our net operating loss and tax credit carryforwards, even if we attain profitability.

Changes in tax laws or in their implementation or interpretation may adversely affect our business and financial condition.

Changes in tax law may adversely affect our business or financial condition. The TCJA, as amended by the CARES Act, significantly revises the Code. The TCJA, among other things, contains significant changes to corporate taxation, including reduction of the corporate tax rate from a top marginal rate of 35% to a flat rate of 21%, limitation of the tax deduction for net interest expense to 30% of adjusted taxable income (except for certain small businesses), limitation of the deduction for net operating losses to 80% of current year taxable income and elimination of net operating loss carrybacks, in each case, for losses arising in taxable years beginning after December 31, 2017 (though any such net operating losses may be carried forward indefinitely and such net operating losses arising in taxable years beginning before January 1, 2021 are generally eligible to be carried back up to five years), one time taxation of offshore earnings at reduced rates regardless of whether they are repatriated, elimination of U.S. tax on foreign earnings (subject to certain important exceptions), immediate deductions for certain new investments instead of deductions for depreciation expense over time, and modifying or repealing many business deductions and credits.

In addition to the CARES Act, as part of Congress' response to the COVID-19 pandemic, economic relief legislation has been enacted in 2020 and 2021 containing tax provisions. Regulatory guidance under the TCJA and such additional legislation is and continues to be forthcoming, and such guidance could ultimately increase or lessen their impact on our business and financial condition. Also, as a result of the changes in the U.S. presidential administration and control of the U.S. Senate in 2021, additional tax legislation may be enacted; any such additional legislation could have an impact on us. In addition, it is uncertain if and to what extent various states will conform to the TCJA and additional tax legislation.

Item 6. Exhibits.

Exhibit Number	Description of Exhibit
10.1	Transition Agreement, dated March 28, 2022, between the Registrant and Michael G. Kauffman (incorporated by reference to Exhibit 10.1 to the Registrant's Current Report on Form 8-K (File No. 001-36167) filed with the Commission on March 29, 2022).
10.2	Transition Agreement, dated March 28, 2022, between the Registrant and Sharon Shacham (incorporated by reference to Exhibit 10.2 to the Registrant's Current Report on Form 8-K (File No. 001-36167) filed with the Commission on March 29, 2022).
10.3*	Severance Agreement, dated February 18, 2022, between the Registrant and Jatin Shah.
10.4*	Consulting Agreement, dated March 1, 2022, between the Registrant and Jatin Shah.
10.5*	Amendment #1 to Consulting Agreement, dated March 21, 2022, between the Registrant and Jatin Shah.
10.6	Offer Letter, dated June 7, 2015, between the Registrant and Ran Frenkel (incorporated by reference to Exhibit 10.1 to the Registrant's Current Report on Form 8-K (File No. 001-36167) filed with the Commission on June 10, 2015).
10.7	First Amendment to Letter Agreement, dated October 4, 2016, between the Registrant and Ran Frenkel (incorporated by reference to Exhibit 10.16 to the Registrant's Annual Report on Form 10-K (File No. 001-36167) filed with the Commission on March 16, 2017).
10.8*	Side Letter to Offer Letter, dated October 1, 2020, between the Registrant and Ran Frenkel.
31.1*	Certification of principal executive officer pursuant to Rule 13a-14(a)/15d-14(a) of the Securities Exchange Act of 1934, as amended.
31.2*	Certification of principal financial officer pursuant to Rule 13a-14(a)/15d-14(a) of the Securities Exchange Act of 1934, as amended.
32.1**	Certification of principal executive officer pursuant to 18 U.S.C. §1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.
32.2**	Certification of principal financial officer pursuant to 18 U.S.C. §1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.
101.INS	Inline XBRL Instance Document. The instance document does not appear in the Interactive Data File because its XBRL tags are embedded within the Inline XBRL document.
101.SCH	Inline XBRL Taxonomy Extension Schema Document.
101.CAL	Inline XBRL Taxonomy Extension Calculation Linkbase Document.
101.DEF	Inline XBRL Taxonomy Extension Definition Linkbase Document.
101.LAB	Inline XBRL Taxonomy Extension Label Linkbase Document.
101.PRE	Inline XBRL Taxonomy Extension Presentation Linkbase Document.
104	Cover Page Interactive Data File (formatted as inline XBRL with applicable taxonomy extension information contained in Exhibits 101)

* Filed herewith.
** Furnished herewith.

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.

KARYOPHARM THERAPEUTICS INC.

Date: May 5, 2022

By: /s/ RICHARD PAULSON
Richard Paulson
President and Chief Executive Officer
(Principal executive officer)

Date: May 5, 2022

By: /s/ MICHAEL MASON
Michael Mason
Executive Vice President, Chief Financial Officer and Treasurer
(Principal financial and accounting officer)

Exhibit 10.3

VIA E-MAIL

February 18, 2022

Jatin Shah, M.D.
4402 Dorothy Street
Bellaire, Texas 77401

Dear Jatin:

As we discussed, your employment with Karyopharm Therapeutics Inc. (the "Company") will end effective at the close of business on **February 18, 2022** (the "Separation Date"). As we also discussed, you will be eligible to receive the severance benefits described in paragraph 1 below if you sign and return this letter agreement to me by **March 14, 2022 (but no earlier than February 18, 2022)** and do not revoke your agreement (as described below). By signing and returning this letter agreement and not revoking your acceptance, you will be entering into a binding agreement with the Company and will be agreeing to the terms and conditions set forth in the numbered paragraphs below, including the release of claims set forth in paragraph 2. Therefore, you are advised to consult with an attorney before signing this letter agreement and you have been given at least twenty-one (21) days to do so. If you sign this letter agreement, you may change your mind and revoke your agreement during the seven (7) day period after you have signed it (the "Revocation Period") by notifying me in writing. If you do not so revoke this letter agreement will become a binding agreement between you and the Company upon the expiration of the Revocation Period.

Although your receipt of the severance benefits is expressly conditioned on your entering into this letter agreement, the following will apply regardless of whether or not you timely sign and return this letter agreement:

- As of the Separation Date, all salary payments from the Company will cease and any benefits you had as of the Separation Date under Company-provided benefit plans, programs, or practices will terminate, except as required by federal or state law.
- You will receive on or before the Separation Date payment for your final wages and any unused vacation time accrued through the Separation Date.
- You may, if eligible and at your own cost (unless otherwise stated in paragraph 1 below), elect to continue receiving group medical insurance pursuant to the "COBRA" law. Please consult the COBRA materials to be provided under separate cover for details regarding these benefits.
- You are obligated to keep confidential and not to use or disclose any and all non-public information concerning the Company that you acquired during the course of your employment with the Company, including any non-public information concerning the Company's business affairs, business prospects, and financial condition, except to the extent permitted by law and as otherwise permitted by

paragraph 9 below. Further, you remain subject to your continuing confidentiality, non-competition, and non-solicitation obligations to the Company as set forth in the Non-Disclosure, Inventions Assignment, Non-Competition**,** and Non-Solicitation Agreement you previously executed for the benefit of the Company, which remain in full force and effect.

- You must return to the Company on the Separation Date all Company property.
- You will have three (3) months following the Separation Date to exercise any stock options that were vested as of the Separation Date. After that three (3) month period, your stock options will expire and you will no longer have any rights with respect thereto. You have been provided with a report showing your vested stock options.

If you elect to timely sign and return this letter agreement and do not revoke your acceptance within the Revocation Period, the following terms and conditions will also apply:

1. **Severance Benefits** – The Company will provide you with the following severance benefits (the "severance benefits"):

a. **Severance Pay**. The Company will pay to you **twenty-four (24)** semi-monthly payments of **$19,082.50**, less all applicable taxes and withholdings, as severance pay (an amount equivalent to **twelve (12)** months of your current base salary). This severance pay will be paid in installments in accordance with the Company's regular payroll practices, but in no event shall payments begin earlier than the Company's first payroll date following expiration of the Revocation Period.

b. **COBRA Benefits**. Should you timely elect and be eligible to continue receiving group health insurance pursuant to the "COBRA" law, the Company will, until the earlier of (x) **February 18, 2023**, and (y) the date on which you obtain alternative coverage (as applicable, the "COBRA Contribution Period"), pay the premiums for such coverage. You agree that, should you obtain alternative coverage prior to **February 18, 2023**, you will so inform the Company in writing within five (5) business days of obtaining such coverage.

You will not be eligible for, nor shall you have a right to receive, any payments or benefits from the Company following the Separation Date other than as set forth in this paragraph.

2. **Release of Claims** – In consideration of the severance benefits, which you acknowledge you would not otherwise be entitled to receive, you hereby fully, forever, irrevocably and unconditionally release, remise and discharge the Company, its affiliates, subsidiaries, parent companies, predecessors, and successors, and all of their respective past and present officers, directors, stockholders, partners, members, employees, agents, representatives, plan administrators, attorneys, insurers and fiduciaries (each in their individual and corporate capacities) (collectively, the "Released Parties") from any and all claims, charges, complaints, demands, actions, causes of action, suits, rights, debts, sums of money, costs, accounts, reckonings, covenants, contracts, agreements, promises, doings, omissions, damages, executions, obligations, liabilities, and expenses (including attorneys' fees and costs), of every kind and nature that you ever had or now have against any or all of the Released Parties, whether known or unknown, including, but not limited to, any and all claims arising out of or relating to your employment with and/or separation from the Company,

including, but not limited to, all claims under Title VII of the Civil Rights Act of 1964, 42 U.S.C. § 2000e et seq., the Americans With Disabilities Act of 1990, 42 U.S.C. § 12101 et seq., the Age Discrimination in Employment Act, 29 U.S.C. § 621 et seq., the Genetic Information Nondiscrimination Act of 2008, 42 U.S.C. § 2000ff et seq., the Family and Medical Leave Act, 29 U.S.C. § 2601 et seq., the Worker Adjustment and Retraining Notification Act ("WARN"), 29 U.S.C. § 2101 et seq., the Rehabilitation Act of 1973, 29 U.S.C. § 701 et seq., Executive Order 11246, Executive Order 11141, the Fair Credit Reporting Act, 15 U.S.C. § 1681 et seq., and the Employee Retirement Income Security Act of 1974 ("ERISA"), 29 U.S.C. § 1001 et seq., all as amended; all claims arising out of the: Massachusetts Fair Employment Practices Act, Mass. Gen. Laws ch. 151B, § 1 et seq., the Massachusetts Wage Act, Mass. Gen. Laws ch. 149, § 148 et seq. (Massachusetts law regarding payment of wages and overtime), the Massachusetts Civil Rights Act, Mass. Gen. Laws ch. 12, §§ 11H and 11I, the Massachusetts Equal Rights Act, Mass. Gen. Laws. ch. 93, § 102, Mass. Gen. Laws ch. 214, § 1C (Massachusetts right to be free from sexual harassment law), the Massachusetts Labor and Industries Act, Mass. Gen. Laws ch. 149, § 1 et seq., Mass. Gen. Laws ch. 214, § 1B (Massachusetts right of privacy law), the Massachusetts Maternity Leave Act, Mass. Gen. Laws ch. 149, § 105D, and the Massachusetts Small Necessities Leave Act, Mass. Gen. Laws ch. 149, § 52D, all as amended; all claims arising out of the Texas Commission on Human Rights Act, Tex. Lab. Code Ann. § 21.001 et seq., Tex. Lab. Code Ann. § 21.401 et seq. (Texas genetic testing law), Tex. Lab. Code Ann. § 61.011 et seq. (Texas wage payment law), Tex. Lab. Code Ann. § 52.001 et seq. (Texas religious accommodation law), Tex. Lab. Code Ann. § 21.055 et seq. (Texas whistleblower protection law), and Tex. Health & Safety Code Ann. § 165.002 (Texas breastfeeding law), all as amended; all common law claims including, but not limited to, actions in defamation, intentional infliction of emotional distress, misrepresentation, fraud, wrongful discharge, and breach of contract; all claims to any non-vested ownership interest in the Company, contractual or otherwise; all state and federal whistleblower claims to the maximum extent permitted by law; and any claim or damage arising out of your employment with and/or separation from the Company (including a claim for retaliation) under any common law theory or any federal, state or local statute or ordinance not expressly referenced above; *provided, however, that this release of claims does not prevent you from filing a charge with, cooperating with, or participating in any investigation or proceeding before, the Equal Employment Opportunity Commission or a state fair employment practices agency (except that you acknowledge that you may not recover any monetary benefits in connection with any such charge, investigation, or proceeding, and you further waive any rights or claims to any payment, benefit, attorneys' fees or other remedial relief in connection with any such charge, investigation or proceeding).*

3. **Continuing Obligations** – You acknowledge and reaffirm your confidentiality and non-disclosure obligations discussed on page 1 of this letter agreement, as well as the obligations set forth in the Non-Disclosure, Inventions Assignment, Non-Competition, and Non-Solicitation Agreement you entered into with the Company on May 16, 2017, which survives your separation from employment with the Company. For purposes of Section 5 of the Non-Disclosure, Inventions Assignment, Non-Competition, and Non-Solicitation Agreement you acknowledge that your separation from the Company is not a termination by the Company other than for Cause (as defined in your Non-Disclosure, Inventions Assignment, Non-Competition, and Non-Solicitation Agreement).

4. **Non-Disparagement** – You understand and agree that, to the extent permitted by law and except as otherwise permitted by paragraph 9 below, you will not, in public or private, make any false, disparaging, derogatory or defamatory statements, online (including, without limitation, on any social media, networking, or employer review site) or otherwise, to any person or entity, including, but not limited to, any media outlet, industry group, financial institution or current or former employee, board member, consultant, client or customer of the Company, regarding the Company or any of the other Released Parties, or regarding the Company's business affairs, business prospects, or financial condition.

5. **Company Affiliation** – You agree that, following the Separation Date, you will not hold yourself out as an officer, employee, or otherwise as a representative of the Company, and you agree to update any directory information that indicates you are currently affiliated with the Company. Without limiting the foregoing, you confirm that, within five (5) days following the Separation Date, you will update any and all social media accounts (including, without limitation, LinkedIn, Facebook, Twitter and Four Square) to reflect that you are no longer employed by or associated with the Company.

6. **Return of Company Property** – You confirm that you have returned to the Company all keys, files, records (and copies thereof), equipment (including, but not limited to, computer hardware, software, printers, flash drives and other storage devices, wireless handheld devices, cellular phones, tablets, etc.), Company identification, and any other Company owned property in your possession or control, and that you have left intact all, and have otherwise not destroyed, deleted, or made inaccessible to the Company any electronic Company documents, including, but not limited to, those that you developed or helped to develop during your employment, and that you have not (a) retained any copies in any form or media; (b) maintained access to any copies in any form, media, or location; (c) stored any copies in any physical or electronic locations that are not readily accessible or not known to the Company or that remain accessible to you; or (d) sent, given, or made accessible any copies to any persons or entities that the Company has not authorized to receive such electronic or hard copies. You further confirm that you have cancelled all accounts for your benefit, if any, in the Company's name, including but not limited to, credit cards, telephone charge cards, cellular phone accounts, and computer accounts.

7. **Business Expenses and Final Compensation** – You acknowledge that you have been reimbursed by the Company for all business expenses incurred in conjunction with the performance of your employment and that no other reimbursements are owed to you. You further acknowledge that you have received payment in full for all services rendered in conjunction with your employment by the Company, including payment for all wages, bonuses, commissions, and accrued, unused vacation time, and that no other compensation is owed to you except as provided herein.

8. **Confidentiality** – You understand and agree that, to the extent permitted by law and except as otherwise permitted by paragraph 9 below, the terms and contents of this letter agreement, and the contents of the negotiations and discussions resulting in this letter agreement, shall be maintained as confidential by you and your agents and representatives and shall not be disclosed except as otherwise agreed to in writing by the Company.

9. **Scope of Disclosure Restrictions** – Nothing in this letter agreement prohibits you from communicating with government agencies about possible violations of federal, state, or local laws or otherwise providing information to government agencies, filing a complaint with government

agencies, or participating in government agency investigations or proceedings. You are not required to notify the Company of any such communications; provided, however, that nothing herein authorizes the disclosure of information you obtained through a communication that was subject to the attorney-client privilege. Further, notwithstanding your confidentiality and nondisclosure obligations, you are hereby advised as follows pursuant to the Defend Trade Secrets Act: "An individual shall not be held criminally or civilly liable under any Federal or State trade secret law for the disclosure of a trade secret that (A) is made (i) in confidence to a Federal, State, or local government official, either directly or indirectly, or to an attorney; and (ii) solely for the purpose of reporting or investigating a suspected violation of law; or (B) is made in a complaint or other document filed in a lawsuit or other proceeding, if such filing is made under seal. An individual who files a lawsuit for retaliation by an employer for reporting a suspected violation of law may disclose the trade secret to the attorney of the individual and use the trade secret information in the court proceeding, if the individual (A) files any document containing the trade secret under seal; and (B) does not disclose the trade secret, except pursuant to court order."

10. **Cooperation** – You agree that, to the extent permitted by law, you shall cooperate fully with the Company in the investigation, defense or prosecution of any claims or actions which already have been brought, are currently pending, or which may be brought in the future against the Company by a third party or by or on behalf of the Company against any third party, whether before a state or federal court, any state or federal government agency, or a mediator or arbitrator. Your full cooperation in connection with such claims or actions shall include, but not be limited to, being available to meet with the Company's counsel, at reasonable times and locations designated by the Company, to investigate or prepare the Company's claims or defenses, to prepare for trial or discovery or an administrative hearing, mediation, arbitration or other proceeding and to act as a witness when requested by the Company. You further agree that, to the extent permitted by law, you will notify the Company promptly in the event that you are served with a subpoena (other than a subpoena issued by a government agency), or in the event that you are asked to provide a third party (other than a government agency) with information concerning any actual or potential complaint or claim against the Company.

11. **Amendment and Waiver** – This letter agreement shall be binding upon the parties and may not be modified in any manner, except by an instrument in writing of concurrent or subsequent date signed by duly authorized representatives of the parties hereto. This letter agreement is binding upon and shall inure to the benefit of the parties and their respective agents, assigns, heirs, executors, successors and administrators. No delay or omission by the Company in exercising any right under this letter agreement shall operate as a waiver of that or any other right. A waiver or consent given by the Company on any one occasion shall be effective only in that instance and shall not be construed as a bar to or waiver of any right on any other occasion.

12. **Validity** – Should any provision of this letter agreement be declared or be determined by any court of competent jurisdiction to be illegal or invalid, the validity of the remaining parts, terms or provisions shall not be affected thereby and said illegal or invalid part, term or provision shall be deemed not to be a part of this letter agreement.

13. **Nature of Agreement –** You understand and agree that this letter agreement is a severance agreement and does not constitute an admission of liability or wrongdoing on the part of the Company.

14. **Acknowledgments –** You acknowledge that you have been given at least twenty-one (21) days to consider this letter agreement, and that the Company is hereby advising you to consult with an attorney of your own choosing prior to signing this letter agreement. You understand that you may revoke this letter agreement for a period of seven (7) days after you sign this letter agreement by notifying me in writing, and the letter agreement shall not be effective or enforceable until the expiration of this seven (7) day revocation period. You understand and agree that by entering into this letter agreement, you are waiving any and all rights or claims you might have under the Age Discrimination in Employment Act, as amended by the Older Workers Benefit Protection Act, and that you have received consideration beyond that to which you were previously entitled.

15. **Voluntary Assent –** You affirm that no other promises or agreements of any kind have been made to or with you by any person or entity whatsoever to cause you to sign this letter agreement, and that you fully understand the meaning and intent of this letter agreement. You further state and represent that you have carefully read this letter agreement, understand the contents herein, freely and voluntarily assent to all of the terms and conditions hereof, and sign your name of your own free act.

16. **Applicable Law** – This letter agreement shall be interpreted and construed by the laws of the Commonwealth of Massachusetts, without regard to conflict of laws provisions. You hereby irrevocably submit to and acknowledge and recognize the jurisdiction of the courts of the Commonwealth of Massachusetts, or if appropriate, a federal court located in the Commonwealth of Massachusetts (which courts, for purposes of this letter agreement, are the only courts of competent jurisdiction), over any suit, action or other proceeding arising out of, under or in connection with this letter agreement or the subject matter hereof.

17. **Entire Agreement** – This letter agreement contains and constitutes the entire understanding and agreement between the parties hereto with respect to your severance benefits and the settlement of claims against the Company and cancels all previous oral and written negotiations, agreements, and commitments in connection therewith.

18. **Tax Acknowledgement** – In connection with the severance benefits provided to you pursuant to this letter agreement, the Company shall withhold and remit to the tax authorities the amounts required under applicable law, and you shall be responsible for all applicable taxes with respect to such severance benefits under applicable law. You acknowledge that you are not relying upon the advice or representation of the Company with respect to the tax treatment of any of the severance benefits set forth in paragraph 1 of this letter agreement.

If you have any questions about the matters covered in this letter agreement, please call me at (857) 297-2328 x253 or by email at steven.rotman@karyopharm.com.

Very truly yours,

By: /s/ Steven Rotman_____
Steven Rotman
Chief People & Corporate Engagement Officer

I hereby agree to the terms and conditions set forth above. I have been given at least twenty-one (21) days to consider this letter agreement, and I have chosen to execute this on the date below. I intend that this letter agreement will become a binding agreement between me and the Company if I do not revoke my acceptance in seven (7) days.

/s/ Jatin Shah **Jatin Shah, M.D.**	March 2, 2022 Date

To be returned in a timely manner as set forth on the first page of this letter agreement.

Exhibit 10.4

CONSULTING AGREEMENT

This Consulting Agreement (the "Agreement"), effective as of the Effective Date (as defined herein), is entered into between Karyopharm Therapeutics Inc. (the "Company") and Jatin Shah, M.D. (the "Consultant"). The Consultant and the Company are referred to in this Agreement individually as a "Party" and collectively as the "Parties".

WHEREAS, the Company wishes to engage the Consultant to provide certain advisory and other consulting services to the Company, and the Consultant wishes to provide such services to the Company, in each case subject to the terms and conditions of this Agreement.

NOW, THEREFORE, in consideration of the foregoing, and of the mutual covenants set forth in this Agreement, the Parties agree as follows:

1. Engagement and Performance of Services. The Company hereby engages the Consultant to perform the consulting services as described under the heading Services in Exhibit A (the "Services"). The Consultant shall perform the Services remotely unless the
circumstances specifically require that the Consultant be present at the Company's facilities, or at other locations as mutually agreed upon by the Parties. The Services may be provided by telephone or video conference or as otherwise agreed by the Parties. In performing the Services, the Consultant shall comply with all applicable laws and regulations and shall perform Services in a manner that is consistent with relevant industry and professional standards.

2. Consideration. In full consideration of the Services performed and rights granted by the Consultant under this Agreement, and for so long as the Consultant provides Services to the Company pursuant to this Agreement, any and all outstanding and unvested equity awards granted to the Consultant by the Company will continue to vest and be exercisable in accordance with the applicable equity plans and award agreement. In addition, the Company shall reimburse the Consultant for all reasonable and necessary expenses incurred or paid by the Consultant, at the Company's request and with the Company's prior written approval, in connection with the Consultant's performance of the Services, subject, however, to any applicable Company expense policy provided to the Consultant. In addition, the Company shall pay to the Consultant a consulting fee of $500 per hour worked (as requested by the Company), after the eighth hour worked in any one month period, payable in arrears on the last day of each month. For clarity, hours worked includes time spent actively in transit as required for the Consultant to perform the services requested by the Company.

3. Relationship of Parties. The Consultant shall perform the Services as an "independent contractor" and not as an employee or agent of the Company. The Consultant is not authorized to assume or create any obligation or responsibility, express or implied, on behalf of, or in the name of, the Company or to bind the Company in any manner. The Consultant shall not be entitled to any benefits, coverage or privileges, including, without limitation, social security, unemployment, medical or pension payments, made available to employees of the Company. The Consultant will be fully responsible for all taxes, contributions and insurance coverage applicable to the Consultant.

4. Non-Disclosure, Inventions Assignment, Non-Competition, and Non-Solicitation Obligations.

(a) The Consultant acknowledges and reaffirms the obligations set forth in the May 16, 2017 Non-Disclosure, Inventions Assignment, Non-Competition, and Non-Solicitation Agreement by and between the Consultant and the Company (the "Restrictive Covenant Agreement. For purposes of the Restrictive Covenants Agreement, the Parties acknowledge and agree that the Business Relationship between the Parties will continue for the term of this Agreement and the
Consultant's obligations pursuant to the Restrictive Covenants Agreement will continue for the duration of such Business Relationship, and as applicable, for twelve (12) months thereafter.

(b) Scope of Disclosure Restrictions. Nothing in this Agreement or elsewhere prohibits either Party from communicating with government agencies about possible violations of federal, state, or local laws or otherwise providing information to government agencies or participating in government agency investigations or proceedings. Neither Party is required to notify the other Party of any such communications; provided, however, that nothing herein authorizes the disclosure of information one Party obtained through a communication that was subject to the attorney-client privilege. Further, notwithstanding the Consultant's confidentiality and nondisclosure obligations, the Consultant is hereby advised as follows pursuant to the Defend Trade Secrets Act: "An individual shall not be held criminally or civilly liable under any Federal or State trade secret law for the disclosure of a trade secret that (A) is made (i) in confidence to a Federal, State, or local government official, either directly or indirectly, or to an attorney; and (ii) solely for the purpose of reporting or investigating a suspected violation of law; or (B) is made in a complaint or other document filed in a lawsuit or other proceeding, if such filing is made under seal. An individual who files a lawsuit for retaliation by an employer for reporting a suspected violation of law may disclose the trade secret to the attorney of the individual and use the trade secret information in the court proceeding, if the individual (A) files any document containing the trade secret under seal; and (B) does not disclose the trade secret, except pursuant to court order."

5. Use of Third Party Facilities or Property. Except as the Company may otherwise consent in writing, the Consultant agrees not to make any use of any funds, space, personnel, facilities, equipment, employees or other resources of a third party, in performing the Services, nor to take any other action that would result in a third party owning or having a right in the results of the Services or the Inventions. Without limiting the foregoing, the Consultant agrees that it will not utilize in the performance of any Services or incorporate into any deliverables or materials provided to the Company: (i) any confidential information of the Consultant or any third party; or (ii) any technology, materials, know- how or inventions, covered by proprietary rights of the Consultant or any third party, except as the Consultant is freely permitted to do without further compensation by the Company to the Consultant or any third party. In the event the Consultant incorporates

any proprietary know-how, materials, inventions or technology of the Consultant into any Inventions or deliverables or other results of Services, the Consultant hereby grants to the Company a perpetual, irrevocable, non-exclusive, worldwide, royalty-free, fully paid-up
license (with a right to grant sublicenses) under the Consultant's intellectual property rights in such know-how, materials, inventions or technology solely to the extent necessary for the Company to utilize the Inventions or deliverables or other results of Services for any purpose.

6. Record Retention and Storage. In no event shall the Consultant dispose of any records or files generated by the Consultant in the course of providing the Services (the "Records") without first giving the Company sixty (60) days' prior written notice of the Consultant's intent to do so and an opportunity to have the Records transferred to the Company. Notwithstanding anything in this Section 6 to the contrary, the Consultant may retain copies of the Records to the extent necessary for compliance with applicable law or regulatory requirements, subject to the Consultant's continuing obligations of confidentiality and restrictions on use under this Agreement, and the Company's right to access such retained Records, and have copies made upon reasonable notice to the Consultant.

7. Representation, Warranties and Covenants.

(a) No Conflict. The Consultant represents that, except as the Consultant has disclosed in writing to the Company, the Consultant is not bound by the terms of any agreement with any employer or other party which are inconsistent with the provisions of this Agreement. The Consultant further represents that the Consultant's performance of the Services, and the grant of rights specified in this Agreement, do not and will not conflict with, or breach any, agreement with any prior or existing employer or other entity (including without limitation any nondisclosure or non-competition agreement), and that the Consultant will not disclose to the Company or induce the Company to use any confidential or proprietary information or material belonging to any employer or others unless the Consultant has a license to use such information and materials and to allow the Company to use such information and materials.

(b) No Debarment. The Consultant has not been, and is not under consideration to be, excluded, suspended, debarred or otherwise declared ineligible to participate in federal healthcare programs, federal procurement or non-procurement programs, or from any other activities or programs related to the Services contemplated by this Agreement, including debarment under the provisions of the Generic Drug Enforcement Act of 1992, as amended from time to time.

(c) No Use of Name. Unless the Company otherwise consents in writing, the Consultant shall not disclose to a third party the contents of the negotiations and discussions resulting in this Agreement; provided, however, Consultant may provide the Consulting Agreement and the Restrictive Covenants Agreement to a prospective future employer. Neither Party may use the other Party's name in any

form of advertising or promotion, including press releases, without the prior written consent of the other Party, except the Company may disclose that it has engaged the Services of the Consultant and may describe the nature of the Services. The provisions of this Section 7(c) shall not restrict a Party's ability to use the other Party's name in filings with the Securities and Exchange Commission, the United States Food and Drug Administration, or other governmental agencies, when required by applicable law or regulation to do so.

(d) Not Employment Contract. The Consultant acknowledges that the Consultant is not an employee of the Company, that this Agreement does not constitute a contract of employment and does not imply that the Company will continue this Agreement in effect for any period of time beyond its terms.

8. Consultation Period; Termination.

(a) Consultation Period. The term of this Agreement shall commence on the date following the Consultant's separation from employment with the Company (such that there shall be no gap in the Consultant's business relationship with the Company) (the "Effective Date") and shall continue in effect until February 28, 2023, unless earlier terminated (x) at any time upon the mutual written consent of the parties hereto or (y) by either Party as set forth in Section 8(b) below (the "Consultation Period").

(b) Termination. Either party may terminate this Agreement upon thirty (30) days' prior written notice to the other Party. In addition, either Party may terminate this Agreement upon fifteen (15) days' prior written notice to the other Party if such other Party has materially breached this Agreement and fails to cure the breach within sixty (60) days of notice being effectively given pursuant to Section 9 hereof. In the event of termination by either Party as permitted under this Agreement, the Company shall direct the Consultant as to whether the Consultant shall stop performing the Services immediately or shall continue such performance for all or part of the applicable notice period.

(c) Survival. The termination or expiration of this Agreement shall not affect the rights or obligations which have accrued prior to the effective date of such termination or expiration. Sections 4, 6, 7(c), 8, and 12 of this Agreement shall survive any termination or expiration of this Agreement.

9. Notice. All notices required or permitted under this Agreement will be in writing. Notices shall be given by: (a) delivery in person; (b) by first class mail with confirmation of delivery, or overnight courier with confirmation of delivery, to, in the case of Consultant, to the address on file for the Company, and in the case of the Company, to 85 Wells Ave, Newton, MA 02459, or for either Party, at such other address as the recipient may specify in writing under this procedure; or (c) by email with confirmation of read receipt. Notices will be deemed to have been given (i) three (3) business days after deposit in the U.S. mail with proper postage for first class registered or certified mail

prepaid, return receipt requested; (ii) one (1) business day after being sent by a nationally recognized courier service for next day delivery; or (iii) confirmation of read receipt of email. In case of email Notice, if confirmation of read receipt is not returned, notices must be sent by overnight courier. Notices to the Company must be marked "Attention: Chief Executive Officer" with a copy to the Chief People & Corporate Engagement Officer.

10. Assignment; No Subcontracting. This Agreement shall be binding upon and inure to the benefit of the Parties and their respective successors and permitted assigns. The Consultant may not assign, subcontract or delegate any of the Consultant's rights or obligations under this Agreement without the prior written consent of the Company. The Company may assign this Agreement to any of its affiliates or to any successor by law or by merger, acquisition or sale of assets, provided that any such assignee shall assume all obligations of the Company under this Agreement.

11. Severability. Each and every provision set forth in this Agreement is independent and severable from the others, and no provision will be rendered unenforceable by virtue of the fact that, for any reason, any other provision may be invalid or unenforceable in whole or in part. If any provision of this Agreement is invalid or unenforceable for any reason whatsoever, that provision will be appropriately limited and reformed to the maximum extent provided by applicable law. If the scope of any restriction contained herein is too broad to permit enforcement to its full extent, then such restriction will be enforced to the maximum extent permitted by law so as to be judged reasonable and enforceable. If, as a result of the unenforceability of a provision or any limitation on enforceability, the intent of the parties in entering into this Agreement is materially affected, the parties will negotiate in good faith to amend this Agreement to as close as possible implement the original intent of the parties.

12. Governing Law. This Agreement shall be construed in accordance with and governed by the laws of the Commonwealth of Massachusetts, without reference to the state's conflict-of-laws principles.

13. Entire Agreement. This Agreement constitutes the entire agreement between the Parties pertaining to its subject matter; provided, however, that this Agreement does not supersede any obligation by any individual who was formerly employed by the Company. For clarification, but not limitation, this means that if there is a conflict between Sections 4, 5, or 6 of this Agreement, on the one hand, and any agreement regarding confidentiality, inventions assignment, non-solicitation, and/or non- competition obligations for a former employee of the Company, including, without limitation, the Restricted Covenant Agreement, such conflict will be resolved in the manner most protective of the Company.

14. Waivers. No delay or omission by a Party in exercising any right under this Agreement will operate as a waiver of that or any other right. A waiver or consent given by a Party will be effective only if contained in a written document signed by such Party. A waiver

or consent given by a Party on any one occasion is effective only in that instance and will not be construed as a bar to or waiver of any right on any other occasion.

15. Amendments. No amendment of this Agreement shall be binding unless executed in writing by both Parties.

[Signature Page Follows]

IN WITNESS WHEREOF, the Company and the Consultant have caused this Agreement to be executed by their duly authorized representatives as of the Effective Date.

KARYOPHARM THERAPEUTICS INC.:	CONSULTANT:
By: /s/ Steven Rotman Name: Steven Rotman Title: Chief People & Corporate Engagement Officer	By: /s/ Jatin Shah Name: Jatin Shah, M.D.

Exhibit A

I. DESCRIPTION OF SERVICES

The Consultant shall provide assistance to the Company, as from time to time reasonably requested by the Chief Executive Officer or his designees in any area, including but not limited to, external affairs and clinical development matters of the Company and its subsidiaries.

The Consultant shall devote up to 40 hours per month to providing Services.

AMENDMENT #1 TO
CONSULTING AGREEMENT BETWEEN
KARYOPHARM THERAPEUTICS INC.
AND JATIN SHAH, M.D.

THIS AMENDMENT #1 ("Amendment") amends the Consulting Agreement between Karyopharm Therapeutics Inc. ("Karyopharm") and Jatin Shah, M.D. ("Consultant") with an Effective Date of the 1st day of March 2022, (the "Agreement"). This Amendment shall be effective as of March 21, 2022 (the "Amendment 1 Effective Date").

WHEREAS, the Consultant and the Company agree to amend the description of services provided by the Consultant; and

WHEREAS, the Parties wish to amend the hours of services to be provided by Consultant.

NOW THEREFORE, for good and valuable consideration, the sufficiency of which is hereby acknowledged, the Parties hereby agree as follows:

1. Amendments.

   Exhibits. Exhibit A is hereby deleted in its entirety, and replaced with A-1, attached hereto, which shall be effective as of the Amendment 1 Effective Date.

2. Miscellaneous. Except as specifically amended by this Amendment, the terms and conditions of the Agreement shall remain in full force and effect. Capitalized terms in this Amendment have the same meaning as set forth in the Agreement. This Amendment may be executed in any number of counterparts and electronically, each of which will be deemed to be an original and all of which together will constitute one and the same instrument.

IN WITNESS WHEREOF, this Amendment is effective as of the Amendment #1 Effective Date.

KARYOPHARM THERAPEUTICS INC.	**JATIN SHAH, M.D.**
/s/ Steven Rotman	/s/ Jatin Sha
By: Steven Rotman	By:
Title: Chief People & Corporate Engagement Officer	Title:

Exhibit A-1

DESCRIPTION OF SERVICES

The Consultant shall provide assistance to the Company, as from time to time reasonably requested by the Chief Executive Officer or his designees limited to institutional knowledge relating to myeloma specific matters for internal purposes only.

The Consultant shall devote up to 15 hours per month to providing Services.

Exhibit 10.8

October 1, 2020

Ran Frankel

Dear Ran:

You and Karyopharm Therapeutics Inc. (the "Company") are parties to a letter agreement dated June 7, 2015, as amended on October 4, 2016, related to your employment as the Chief Development Operations Officer of the Company (the "Letter Agreement"). This letter is to inform you that, effective August 28, 2020 the Compensation Committee of the Board of Directors of the Company approved certain enhanced severance benefits for you, as described below, in addition to the benefits you may be entitled to under the Letter Agreement. Except as specifically set forth below, the Letter Agreement remains in full force and effect, and no provisions thereof are amended except as set forth below. Capitalized terms used but not defined herein shall have the meaning set forth in the Letter Agreement.

The first paragraph of the "*Severance Compensation*" section of the Letter Agreement shall be replaced with the following:

Severance Compensation. If the Company (which, for the purposes of this paragraph, includes any successor entity) terminates the term of your employment without Cause, or you resign for Good Reason, then provided that you execute a release of any and all claims that you may have against the Company arising from your employment with the Company, reasonably satisfactory to the Company in form and substance, which release becomes effective within 60 days following your termination, the Company (i) will continue to pay you your base compensation at its then-current rate, in accordance with the Company's then-current regular payroll procedures for employees, for twelve (12) months (subject to upward adjustment in the event that standardized severance terms are authorized for all employees of your level and such terms exceed the severance amount provided herein) beginning in the first payroll period following the effectiveness of the release; and (ii) provided you elect to continue your and your eligible dependents' participation in the Company's medical and dental benefit plans pursuant to the Consolidated Omnibus Budget Reconciliation Act of 1986 ("COBRA"), will pay the monthly premium to continue such coverage for the lesser of the twelve (12) full calendar months immediately following the month in which the termination of your employment occurs and the end of the calendar month in which you become eligible to receive group health plan coverage under another employee benefit plan. Notwithstanding the foregoing, if your employment is terminated without Cause, or you resign for Good Reason, in either case within one year following the consummation of a Change in Control (as defined below), then, provided that you execute a release of any and all claims that you may

have against the Company arising from your employment with the Company, reasonably satisfactory to the Company in form and substance, which release becomes effective within 60 days following your termination, the Company (or its successor entity) will (i) continue to pay you your base compensation at its then-current rate, in accordance with the Company's (or successor's) then-current regular payroll procedures for employees, for at least twelve (12) months beginning in the first payroll period following the effectiveness of the release; (ii) pay to you an amount equal to 100% of your target annual bonus for the year in which your termination occurs, which amount shall be payable in a lump sum on the date that the first continued salary payment is made to you under this agreement and (iii) provided you elect to continue your and your eligible dependents' participation in the Company's medical and dental benefit plans pursuant to COBRA, pay the monthly premium to continue such coverage for the lesser of the twelve (12) full calendar months immediately following the month in which the termination of your employment occurs and the end of the calendar month in which you become eligible to receive group health plan coverage under another employee benefit plan.

For the avoidance of doubt, that nothing herein supersedes the Non Disclosure, Inventions Assignment, Non-Competition, and Non-Solicitation Agreement you previously executed with the Company, which remains in effect, unaltered, in all respects.

Thank you for your continued commitment to Karyopharm!

Sincerely,

/s/ Michael Kauffman

Michael Kauffman, M.D., Ph.D.

Exhibit 31.1

CERTIFICATIONS

I, Richard Paulson, certify that:

1. I have reviewed this Quarterly Report on Form 10-Q of Karyopharm Therapeutics Inc.;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

/s/ RICHARD PAULSON
Richard Paulson
President and Chief Executive Officer
(Principal executive officer)

Date: May 5, 2022

Exhibit 31.2

CERTIFICATIONS

I, Michael Mason, certify that:

1. I have reviewed this Quarterly Report on Form 10-Q of Karyopharm Therapeutics Inc.;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

/s/ MICHAEL MASON

Michael Mason

Executive Vice President, Chief Financial Officer and Treasurer

(Principal financial and accounting officer)

Date: May 5, 2022

Exhibit 32.1

CERTIFICATION PURSUANT TO 18 U.S.C. SECTION 1350,
AS ADOPTED PURSUANT TO
SECTION 906 OF THE SARBANES-OXLEY ACT OF 2002

In connection with the Quarterly Report on Form 10-Q of Karyopharm Therapeutics Inc. (the "Company") for the period ended March 31, 2022, as filed with the Securities and Exchange Commission on the date hereof (the "Report"), the undersigned, Richard Paulson, President and Chief Executive Officer of the Company, hereby certifies, pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, that to his knowledge:

(1) the Report fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934; and

(2) the information contained in the Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

/s/ RICHARD PAULSON
Richard Paulson
President and Chief Executive Officer
(Principal executive officer)

Date: May 5, 2022

Exhibit 32.2

CERTIFICATION PURSUANT TO 18 U.S.C. SECTION 1350,
AS ADOPTED PURSUANT TO
SECTION 906 OF THE SARBANES-OXLEY ACT OF 2002

In connection with the Quarterly Report on Form 10-Q of Karyopharm Therapeutics Inc. (the "Company") for the period ended March 31, 2022, as filed with the Securities and Exchange Commission on the date hereof (the "Report"), the undersigned, Michael Mason, Executive Vice President, Chief Financial Officer and Treasurer of the Company, hereby certifies, pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, that to his knowledge:

(1) the Report fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934; and

(2) the information contained in the Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

/s/ MICHAEL MASON
Michael Mason
Executive Vice President, Chief Financial Officer and Treasurer
(Principal financial and accounting officer)

Date: May 5, 2022