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UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, DC 20549

FORM 10-Q

(Mark One)

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

For the quarterly period ended September 30, 2021
OR

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

Commission file number: 001-36014

AGIOS PHARMACEUTICALS, INC.
(Exact Name of Registrant as Specified in Its Charter)

Delaware	**26-0662915**
(State or Other Jurisdiction of Incorporation or Organization)	**(I.R.S. Employer Identification No.)**
88 Sidney Street, Cambridge, Massachusetts	**02139**
(Address of Principal Executive Offices)	**(Zip Code)**

(617) 649-8600
(Registrant's Telephone Number, Including Area Code)

(Former Name, Former Address and Former Fiscal Year, if Changed Since Last Report)

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

Title of each class	Trading symbol(s)	Name of each exchange on which registered
Common Stock, Par Value $0.001 per share	**AGIO**	**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 ☒

Number of shares of the registrant's Common Stock, $0.001 par value, outstanding on October 29, 2021: 54,308,474

AGIOS PHARMACEUTICALS, INC.

FORM 10-Q

FOR THE THREE AND NINE MONTHS ENDED SEPTEMBER 30, 2021

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PART I. FINANCIAL INFORMATION

Item 1. Financial Statements (Unaudited)

AGIOS PHARMACEUTICALS, INC.

Condensed Consolidated Balance Sheets
(Unaudited)

(In thousands, except share and per share data)	September 30, 2021	December 31, 2020
Assets		
Current assets:		
Cash and cash equivalents	$ 400,224	$ 127,436
Marketable securities	865,833	445,493
Other receivable	6,990	—
Prepaid expenses and other current assets	32,238	15,889
Current assets of discontinued operations	—	47,859
Total current assets	1,305,285	636,677
Marketable securities	130,139	97,608
Operating lease assets	77,532	84,661
Property and equipment, net	25,342	30,815
Financing lease assets	300	590
Other non-current assets	2,900	—
Non-current assets of discontinued operations	—	2,601
Total assets	$ 1,541,498	$ 852,952
Liabilities and stockholders' equity		
Current liabilities:		
Accounts payable	$ 10,308	$ 17,724
Accrued expenses	29,234	30,801
Operating lease liabilities	9,883	7,093
Financing lease liabilities	412	317
Taxes payable	8,059	—
Current liabilities of discontinued operations	—	38,459
Total current liabilities	57,896	94,394
Operating lease liabilities, net of current portion	88,840	97,458
Financing lease liabilities, net of current portion	—	331
Non-current liabilities of discontinued operations	—	261,269
Total liabilities	146,736	453,452
Stockholders' equity:		
Preferred stock, $0.001 par value; 25,000,000 shares authorized; no shares issued or outstanding at September 30, 2021 and December 31, 2020	—	—
Common stock, $0.001 par value; 125,000,000 shares authorized; 70,515,336 shares issued and 54,715,184 outstanding at September 30, 2021, and 69,293,920 shares issued and outstanding at December 31, 2020	71	69
Additional paid-in capital	2,322,460	2,242,801
Accumulated other comprehensive (loss) income	(198)	105
Accumulated deficit	(144,133)	(1,843,475)
Treasury stock, at cost (15,800,152 shares at September 30, 2021 and no shares at December 31, 2020)	(783,438)	—
Total stockholders' equity	1,394,762	399,500
Total liabilities and stockholders' equity	$ 1,541,498	$ 852,952

See accompanying Notes to Condensed Consolidated Financial Statements.

AGIOS PHARMACEUTICALS, INC.

Condensed Consolidated Statements of Operations
(Unaudited)

(In thousands, except share and per share data)	Three Months Ended September 30, 2021	Three Months Ended September 30, 2020	Nine Months Ended September 30, 2021	Nine Months Ended September 30, 2020
Cost and expenses:				
Research and development	$ 64,000	$ 51,943	$ 183,674	$ 161,388
Selling, general and administrative	27,152	28,347	89,917	89,196
Total cost and expenses	91,152	80,290	273,591	250,584
Loss from operations	(91,152)	(80,290)	(273,591)	(250,584)
Gain on sale of oncology business	1,996	—	3,996	—
Interest income, net	256	1,115	504	5,820
Other income, net	4,641	—	11,165	—
Net loss from continuing operations	(84,259)	(79,175)	(257,926)	(244,764)
Net (loss) income from discontinued operations, net of tax	(4,507)	(19,804)	1,957,268	15,051
Net (loss) income	$ (88,766)	$ (98,979)	$ 1,699,342	$ (229,713)
Net loss from continuing operations per share - basic and diluted	$ (1.48)	$ (1.15)	$ (4.13)	$ (3.55)
Net (loss) income from discontinued operations per share - basic and diluted	$ (0.08)	$ (0.29)	$ 31.31	$ 0.22
Net (loss) income per share - basic and diluted	$ (1.56)	$ (1.43)	$ 27.19	$ (3.33)
Weighted-average number of common shares used in computing net loss per share from continuing operations, net (loss) income per share from discontinued operations and net (loss) income per share – basic and diluted	57,048,175	69,144,061	62,503,087	68,905,853

See accompanying Notes to Condensed Consolidated Financial Statements.

AGIOS PHARMACEUTICALS, INC.

Condensed Consolidated Statements of Comprehensive (Loss) Income
(Unaudited)

(In thousands)	Three Months Ended September 30,		Nine Months Ended September 30,	
	2021	**2020**	**2021**	**2020**
Net (loss) income	$ (88,766)	$ (98,979)	$ 1,699,342	$ (229,713)
Other comprehensive (loss) income				
Unrealized (loss) gain on available-for-sale securities	(54)	(973)	(303)	461
Comprehensive (loss) income	$ (88,820)	$ (99,952)	$ 1,699,039	$ (229,252)

See accompanying Notes to Condensed Consolidated Financial Statements.

AGIOS PHARMACEUTICALS, INC.

Condensed Consolidated Statements of Stockholders' Equity
(Unaudited)

(in thousands, except share amounts)	Common Stock Shares	Common Stock Amount	Additional Paid-In Capital	Accumulated Other Comprehensive (Loss) Income	Accumulated Deficit	Treasury Stock Shares	Treasury Stock Amount	Total Stockholders' Equity
Balance at December 31, 2020	69,293,920	$ 69	$ 2,242,801	$ 105	$ (1,843,475)	—	$ —	$ 399,500
Common stock issued under stock incentive plan and ESPP	518,285	1	7,346	—	—	—	—	7,347
Stock-based compensation expense	—	—	14,854	—	—	—	—	14,854
Other comprehensive loss	—	—	—	(108)	—	—	—	(108)
Net income	—	—	—	—	1,874,325	—	—	1,874,325
Disposition of oncology business	—	—	712	—	—	—	—	712
Balance at March 31, 2021	69,812,205	$ 70	$ 2,265,713	$ (3)	$ 30,850	—	$ —	$ 2,296,630
Common stock issued under stock incentive plan and ESPP	592,577	$ —	$ 25,673	$ —	$ —	—	$ —	$ 25,673
Stock-based compensation expense	—	—	14,885	—	—	—	—	14,885
Repurchase of common stock	—	—	—	—	—	(10,493,968)	(529,047)	(529,047)
Other comprehensive loss	—	—	—	(141)	—	—	—	(141)
Net loss	—	—	—	—	(86,217)	—	—	(86,217)
Disposition of oncology business	—	—	33	—	—	—	—	33
Balance at June 30, 2021	70,404,782	$ 70	$ 2,306,304	$ (144)	$ (55,367)	(10,493,968)	$ (529,047)	$ 1,721,816
Common stock issued under stock incentive plan and ESPP	110,554	$ 1	$ 4,008	$ —	$ —	—	$ —	$ 4,009
Stock-based compensation expense	—	—	12,148	—	—	—	—	12,148
Repurchase of common stock	—	—	—	—	—	(5,306,184)	(254,391)	(254,391)
Other comprehensive loss	—	—	—	(54)	—	—	—	(54)
Net loss	—	—	—	—	(88,766)	—	—	(88,766)
Balance at September 30, 2021	70,515,336	$ 71	$ 2,322,460	$ (198)	$ (144,133)	(15,800,152)	$ (783,438)	$ 1,394,762

See accompanying Notes to Condensed Consolidated Financial Statements.

AGIOS PHARMACEUTICALS, INC.

Condensed Consolidated Statements of Stockholders' Equity
(Unaudited)

(in thousands, except share amounts)	Common Stock Shares	Common Stock Amount	Additional Paid-In Capital	Accumulated Other Comprehensive (Loss) Income	Accumulated Deficit	Total Stockholders' Equity
Balance at December 31, 2019	68,401,105	$ 68	$ 2,156,363	$ 202	$ (1,516,105)	$ 640,528
Common stock issued under stock incentive plan and ESPP	388,820	1	5,464	—	—	5,465
Stock-based compensation expense	—	—	15,670	—	—	15,670
Other comprehensive loss	—	—	—	(128)	—	(128)
Net loss	—	—	—	—	(40,256)	(40,256)
Disposition of oncology business	—	—	4,020	—	—	4,020
Balance at March 31, 2020	68,789,925	$ 69	$ 2,181,517	$ 74	$ (1,556,361)	$ 625,299
Common stock issued under stock incentive plan and ESPP	268,771	$ —	$ 1,652	$ —	$ —	$ 1,652
Stock-based compensation expense	—	—	17,614	—	—	17,614
Other comprehensive income	—	—	—	1,562	—	1,562
Net loss	—	—	—	—	(90,478)	(90,478)
Disposition of oncology business	—	—	2,816	—	—	2,816
Balance at June 30, 2020	69,058,696	$ 69	$ 2,203,599	$ 1,636	$ (1,646,839)	$ 558,465
Common stock issued under stock incentive plan and ESPP	139,367	$ —	$ 3,532	$ —	$ —	$ 3,532
Stock-based compensation expense	—	—	14,977	—	—	14,977
Other comprehensive loss	—	—	—	(973)	—	(973)
Net loss	—	—	—	—	(98,979)	(98,979)
Disposition of oncology business	—	$ —	$ 3,430	$ —	$ —	$ 3,430
Balance at September 30, 2020	69,198,063	$ 69	$ 2,225,538	$ 663	$ (1,745,818)	$ 480,452

See accompanying Notes to Condensed Consolidated Financial Statements.

AGIOS PHARMACEUTICALS, INC.

Condensed Consolidated Statements of Cash Flows
(Unaudited)

(In thousands)	Nine Months Ended September 30, 2021	2020
Operating activities		
Net income (loss)	$ 1,699,342	$ (229,713)
Less: Net Income from discontinued operations	1,957,268	15,051
Net loss from continuing operations	(257,926)	(244,764)
Adjustments to reconcile net loss from continuing operations to net cash used in operating activities:		
Depreciation and amortization	7,038	7,202
Stock-based compensation expense	41,887	48,261
Net amortization of premium (accretion of discount) on marketable securities	5,326	1,521
Loss on disposal of property and equipment	9	—
Non-cash operating lease expense	7,129	6,691
Changes in operating assets and liabilities:		
Other receivables	(6,990)	—
Prepaid expenses and other current and non-current assets	(19,249)	(1,231)
Accounts payable	(3,337)	(3,056)
Accrued expenses and other current liabilities	(2,667)	(1,317)
Operating lease liabilities	(5,315)	(6,112)
Net cash used in operating activities - continuing operations	(234,095)	(192,805)
Net cash used in operating activities - discontinued operations	(89,132)	(48,557)
Net cash used in operating activities	(323,227)	(241,362)
Investing activities		
Purchases of marketable securities	(951,411)	(430,624)
Proceeds from maturities and sales of marketable securities	492,911	448,866
Purchases of property and equipment	(1,239)	(13,544)
Net cash (used in) provided by investing activities - continuing operations	(459,739)	4,698
Net cash provided by (used in) investing activities - discontinued operations	1,802,936	(348)
Net cash provided by investing activities	1,343,197	4,350
Financing activities		
Payments on financing lease obligations	(773)	(250)
Purchase of treasury stock	(783,438)	—
Net proceeds from stock option exercises and employee stock purchase plan	37,029	10,649
Net cash (used in) provided by financing activities - continuing operations	(747,182)	10,399
Net cash provided by financing activities - discontinued operations	—	250,537
Net cash (used in) provided by financing activities	(747,182)	260,936
Net change in cash and cash equivalents	272,788	23,924
Cash and cash equivalents at beginning of the period	127,436	80,931
Cash and cash equivalents at end of the period	$ 400,224	$ 104,855
Supplemental disclosure of non-cash investing and financing transactions		
Additions to property and equipment in accounts payable and accrued expenses	$ 486	$ 185
Operating lease liabilities arising from obtaining operating lease assets	$ —	$ —
Financing lease liabilities arising from obtaining financing lease assets	$ 511	$ —

See accompanying Notes to Condensed Consolidated Financial Statements.

AGIOS PHARMACEUTICALS, INC.

Notes to Condensed Consolidated Financial Statements
(Unaudited)

1. Overview and Basis of Presentation

References to Agios

Throughout this Quarterly Report on Form 10-Q, "we," "us," and "our," and similar expressions, except where the context requires otherwise, refer to Agios Pharmaceuticals, Inc. and its consolidated subsidiaries, and "our Board of Directors" refers to the board of directors of Agios Pharmaceuticals, Inc.

Overview

We are a biopharmaceutical company committed to transforming patients' lives through scientific leadership in the field of cellular metabolism and adjacent areas of biology, with the goal of creating differentiated, small molecule medicines for genetically defined diseases, or GDDs. To address our focus areas, we take a systems biology approach to deeply understand disease states, drive the discovery and validation of novel therapeutic targets, and define patient selection strategies, thereby increasing the probability that our experimental medicines will have the desired therapeutic effect. We are located in Cambridge, Massachusetts.

Sale of our Oncology Business to Servier

On March 31, 2021, we completed the sale of our oncology business to Servier Pharmaceuticals LLC, or Servier. The transaction included the sale of our oncology business, including TIBSOVO®, our clinical-stage product candidates vorasidenib, AG-270 and AG-636, and our oncology research programs for a payment of approximately $1.8 billion in cash at the closing, subject to certain adjustments, and a payment of $200 million in cash, if, prior to January 1, 2027, vorasidenib is granted new drug application, or NDA, approval from the U.S. Food and Drug Administration, or FDA, with an approved label that permits vorasidenib's use as a single agent for the adjuvant treatment of patients with Grade 2 glioma that have an isocitrate dehydrogenase 1 or 2 mutation (and, to the extent required by such approval, the vorasidenib companion diagnostic test is granted an FDA premarket approval), as well as a royalty of 5% of U.S. net sales of TIBSOVO® from the close of the transaction through loss of exclusivity, and a royalty of 15% of U.S. net sales of vorasidenib from the first commercial sale of vorasidenib through loss of exclusivity. Servier also acquired our co-commercialization rights for Bristol Myers Squibb's IDHIFA® and the right to receive a $25.0 million potential milestone payment under our prior collaboration agreement with Celgene Corporation, and following the sale Servier will conduct certain clinical development activities within the IDHIFA® development program.

We recorded income from royalties of approximately $2.0 million and $4.0 million on U.S. net sales of TIBSOVO® by Servier in the gain on sale of oncology business line item within the condensed consolidated statements of operations, for the three and nine months ended September 30, 2021, respectively.

Basis of presentation

The condensed consolidated balance sheet as of September 30, 2021, the condensed consolidated statements of operations, comprehensive (loss) income and stockholders' equity for the three and nine months ended September 30, 2021 and 2020, and the condensed consolidated statements of cash flows for the nine months ended September 30, 2021 and 2020 are unaudited. The unaudited condensed consolidated financial statements have been prepared on the same basis as the annual financial statements and, in the opinion of our management, reflect all adjustments, which include only normal recurring adjustments, necessary to fairly state our financial position as of September 30, 2021, our results of operations and stockholders' equity for the three and nine months ended September 30, 2021 and 2020, and cash flows for the nine months ended September 30, 2021 and 2020. The financial data and the other financial information disclosed in these notes to the condensed consolidated financial statements related to the three and nine-month periods are also unaudited. The results of operations for the three and nine months ended September 30, 2021 are not necessarily indicative of the results to be expected for the year ending December 31, 2021 or for any other future annual or interim period. The condensed consolidated balance sheet data as of December 31, 2020 was derived from our audited financial statements, but does not include all disclosures required by U.S. generally accepted accounting principles, or U.S. GAAP. The condensed consolidated interim financial statements should be read in conjunction with the audited consolidated financial statements and notes thereto included in our Annual Report on Form 10-K for the year ended December 31, 2020 that was filed with the Securities and Exchange Commission, or the SEC, on February 25, 2021.

In late March 2021, our oncology business met all the conditions to be classified as held for sale and, because we consider the disposal of the oncology business to be a strategic shift that had a major effect on our operations and financial results, represented a discontinued operation. All assets and liabilities associated with our oncology business were therefore classified

as assets and liabilities of discontinued operations in our condensed consolidated balance sheets for the periods presented. Further, all historical operating results for our oncology business are reflected within discontinued operations in the condensed consolidated statements of operations for all periods presented. For additional information, see Note 3, *Discontinued Operations.*

Our condensed consolidated financial statements include our accounts and the accounts of our wholly owned subsidiaries. All intercompany transactions have been eliminated in consolidation. The condensed consolidated financial statements have been prepared in conformity with U.S. GAAP.

Reclassifications

Certain amounts in prior periods have been reclassified to reflect the impact of the discontinued operations treatment of the oncology business in order to conform to the current period presentation.

Use of estimates

The preparation of our condensed consolidated financial statements requires us to make estimates, judgments and assumptions that may affect the reported amounts of assets, liabilities, equity, revenues and expenses and related disclosure of contingent assets and liabilities. On an ongoing basis we evaluate our estimates, judgments and methodologies. We base our estimates on historical experience and on various other assumptions that we believe are reasonable, the results of which form the basis for making judgments about the carrying values of assets, liabilities and equity and the amount of revenues and expenses. The full extent to which the COVID-19 pandemic will directly or indirectly impact our business, results of operations and financial condition, including expenses, reserves and allowances, clinical trials, research and development costs and employee-related amounts, will depend on future developments that are highly uncertain, including as a result of new information that may emerge concerning COVID-19 and any variant strains of the virus and the actions taken to contain the pandemic or treat COVID-19, as well as the economic impact on local, regional, national and international customers and markets. We have made estimates of the impact of COVID-19 within our financial statements and there may be changes to those estimates in future periods. Actual results may differ from these estimates.

Liquidity

On March 31, 2021, we completed the sale of our oncology business to Servier, and received approximately $1.8 billion in cash at closing. In connection with the sale, on March 25, 2021, we announced that our board of directors authorized the repurchase of up to $1.2 billion of our outstanding shares of common stock, or the Repurchase Program, using the proceeds from the sale of our oncology business to Servier. On March 31, 2021, in connection with the Repurchase Program, we entered into a definitive share repurchase agreement with Bristol-Myers Squibb Company, or BMS, to repurchase 7,121,658 shares of our common stock held by certain subsidiaries of BMS for an aggregate purchase price of $344.5 million, or $48.3785 per share. This repurchase was completed on April 5, 2021. Further, on April 2, 2021, in connection with the Repurchase Program, we entered into a Rule 10b5-1 repurchase plan pursuant to which we may repurchase up to $600 million of shares of our common stock. As of September 30, 2021, we have repurchased approximately 8.7 million shares for $438.9 million, or $50.57 per share, under the plan. In total, as of September 30, 2021, we have repurchased 15.8 million shares of common stock for $783.4 million, or $49.58 per share, under the Repurchase Program.

As of September 30, 2021, we had cash, cash equivalents and marketable securities of $1.4 billion. Although we have incurred recurring losses and expect to continue to incur losses for the foreseeable future, we expect our cash, cash equivalents and marketable securities will be sufficient to fund current operations for at least the next twelve months from the issuance date of these financial statements.

2. Summary of Significant Accounting Policies

Discontinued Operations

We accounted for the sale of our oncology business in accordance with Accounting Standards Codification, ASC, 205 *Discontinued Operations* and Accounting Standards Update, ASU, No. 2014-08, *Reporting of Discontinued Operations and Disclosures of Disposals of Components of an Entity*. We followed the held-for-sale criteria as defined in ASC 360 and ASC 205. ASC 205 requires that a component of an entity that has been disposed of or is classified as held for sale and has operations and cash flows that can be clearly distinguished from the rest of the entity be reported as assets held for sale and discontinued operations. In the period a component of an entity has been disposed of or classified as held for sale, the results of operations for the periods presented are reclassified into separate line items in the unaudited condensed consolidated statements of operations. Assets and liabilities are also reclassified into separate line items on the related condensed consolidated balance sheets for the periods presented. The statements of cash flows for the periods presented are also reclassified to reflect the results of discontinued operations as separate line items. ASU 2014-08 requires that only a disposal of a component of an entity, or a group of components of an entity, that represents a strategic shift that has, or will have, a major effect on the reporting entity’s

operations and financial results be reported in the financial statements as discontinued operations. ASU 2014-08 also provides guidance on the financial statement presentations and disclosures of discontinued operations.

Due to the sale of the oncology business during the first quarter of 2021, in accordance with ASC 205, *Discontinued Operations*, we have classified the results of the oncology business as discontinued operations in our unaudited condensed consolidated statements of operations and cash flows for all periods presented, see Note 3, Discontinued Operations. All assets and liabilities associated with our oncology business were therefore classified as assets and liabilities of discontinued operations in our condensed consolidated balance sheets for the periods presented. All amounts included in the notes to the unaudited condensed consolidated financial statements relate to continuing operations unless otherwise noted.

Treasury Stock

Treasury stock purchases are accounted for under the cost method whereby the entire cost of the acquired stock is recorded as treasury stock.

There have been no other material changes to the significant accounting policies previously disclosed in our Annual Report on Form 10-K for the year ended December 31, 2020.

Recent accounting pronouncements

Other accounting standards that have been issued by the Financial Accounting Standards Board or other standards-setting bodies that do not require adoption until a future date are not expected to have a material impact on our financial statements upon adoption.

3. Discontinued Operations

On March 31, 2021, we completed the sale of our oncology business to Servier. We have determined the sale of the oncology business represents a strategic shift that had a major effect on our business and therefore met the criteria for classification as discontinued operations at March 31, 2021. Accordingly, the oncology business is reported as discontinued operations in accordance with ASC 205-20, *Discontinued Operations*. The related assets and liabilities of the oncology business are classified as assets and liabilities of discontinued operations in the condensed consolidated balance sheets and the results of operations from the oncology business as discontinued operations in the condensed consolidated statements of operations. Applicable amounts in prior years have been recast to conform to this discontinued operations presentation. We recognized a gain on the sale of the oncology business upon closing.

The following table presents the assets and liabilities of the discontinued operations as of December 31, 2020:

(in thousands)		December 31, 2020
Assets		
Current assets:		
Accounts receivable, net	$	21,328
Collaboration receivable – related party		2,123
Collaboration receivable – other		1,948
Inventory		14,698
Prepaid expenses and other current assets		7,762
Total current assets of discontinued operations		47,859
Other non-current assets		2,601
Total assets of discontinued operations	$	50,460
Liabilities		
Current liabilities:		
Accounts payable	$	9,120
Accrued expenses		29,339
Total current liabilities of discontinued operations		38,459
Liability related to the sale of future revenue, net of debt issuance costs		261,269
Total liabilities of discontinued operations	$	299,728

The following table presents the net liabilities transferred for the sale oncology business for the quarter ended March 31, 2021:

(in thousands)	March 31, 2021
Assets	
Current assets:	
Accounts receivable, net	$ 25,386
Collaboration receivable – related party	2,253
Collaboration receivable – other	2,438
Inventory	16,190
Prepaid expenses and other current assets	7,125
Total current assets of discontinued operations	53,392
Other non-current assets	2,234
Total assets of discontinued operations	$ 55,626
Liabilities	
Current liabilities:	
Accounts payable	$ 4,245
Accrued expenses	30,288
Total current liabilities of discontinued operations	34,533
Liability related to the sale of future revenue, net of debt issuance costs	264,281
Total liabilities of discontinued operations	298,814
Net liabilities distributed to Servier	$ (243,188)

The following table presents the gain on the sale for the nine months ended September 30, 2021:

(in thousands)	September 30, 2021
Cash proceeds	$ 1,802,936
Less: transaction and insurance costs	(53,573)
Less: net liabilities distributed	(239,770)
Gain on sale, pre-tax	1,989,133
Income tax expense	(16,756)
Gain on sale, net of tax	$ 1,972,377

As of September 30, 2021, there were no assets or liabilities classified as discontinued operations.

The following table presents the financial results of the discontinued operations:

(in thousands)	Three Months Ended September 30, 2021	Three Months Ended September 30, 2020	Nine Months Ended September 30, 2021	Nine Months Ended September 30, 2020
Revenues:				
Product revenue, net	$ —	$ 31,716	$ 36,909	$ 81,971
Collaboration revenue – related party	—	1,206	1,350	67,038
Collaboration revenue – other	—	1,101	491	2,786
Royalty revenue – related party	—	683	2,659	7,356
Total revenue	—	34,706	41,409	159,151
Cost and expenses:				
Cost of sales	—	638	706	1,846
Research and development	—	37,612	41,564	110,340
Selling, general and administrative	—	6,493	8,551	20,096
Total cost and expenses	—	44,743	50,821	132,282
(Loss) income from discontinued operations	—	(10,037)	(9,412)	26,869
Non-cash interest expense for the sale of future revenue	—	(9,767)	(5,697)	(11,818)
(Loss) gain on the sale of the oncology business	(618)	—	1,989,133	—
(Loss) income from discontinued operations, pre-tax	(618)	(19,804)	1,974,024	15,051
Income tax expense	(3,889)	—	(16,756)	—
Net (loss) income from discontinued operations	$ (4,507)	$ (19,804)	$ 1,957,268	$ 15,051

In accordance with ASC 205-20, only expenses specifically identifiable and related to a business to be disposed may be presented in discontinued operations. As such, the research and development, marketing, selling and general and administrative expenses in discontinued operations include corporate costs incurred directly to solely support our oncology business.

We have also entered into a Transition Services Agreement with Servier, through which we will provide transitional services related to discovery, clinical development, technical operations, commercial and general and administrative related activities for periods ranging from one month to approximately one year after March 31, 2021.

The milestone payment for approval of vorasidenib and royalty payments related to vorasidenib and TIBSOVO® represent contingent consideration. Contingent consideration has been accounted for as a gain contingency in accordance with ASC 450, *Contingencies*, and will be recognized in earnings in the period when realizable.

4. Fair Value Measurements

We record cash equivalents and marketable securities at fair value. ASC 820, *Fair Value Measurements and Disclosures*, establishes a fair value hierarchy for those instruments measured at fair value that distinguishes between assumptions based on market data (observable inputs) and our own assumptions (unobservable inputs). The hierarchy consists of three levels:

Level 1 – Unadjusted quoted prices in active markets for identical assets or liabilities.

Level 2 – Quoted prices for similar assets and liabilities in active markets, quoted prices in markets that are not active, or inputs which are observable, directly or indirectly, for substantially the full term of the asset or liability.

Level 3 – Unobservable inputs that reflect our own assumptions about the assumptions market participants would use in pricing the asset or liability in which there is little, if any, market activity for the asset or liability at the measurement date.

The following table summarizes our cash equivalents and marketable securities measured at fair value on a recurring basis as of September 30, 2021:

(In thousands)	Level 1	Level 2	Level 3	Total
Cash equivalents	$ 93,843	$ 261,986	$ —	$ 355,829
Total cash equivalents	93,843	261,986	—	355,829
Marketable securities:				
U.S. Treasuries	—	319,861	—	319,861
Government securities	—	73,545	—	73,545
Corporate debt securities	—	602,566	—	602,566
Total marketable securities	—	995,972	—	995,972
Total cash equivalents and marketable securities	$ 93,843	$ 1,257,958	$ —	$ 1,351,801

Cash equivalents and marketable securities have been initially valued at the transaction price and subsequently, at the end of each reporting period, valued utilizing third-party pricing services or other observable market data. The pricing services utilize industry standard valuation models, including both income and market-based approaches, and observable market inputs to determine value. After completing our validation procedures, we did not adjust or override any fair value measurements provided by the pricing services as of September 30, 2021.

There have been no changes to the valuation methods during the nine months ended September 30, 2021. We have no financial assets or liabilities that were classified as Level 3 at any point during the nine months ended September 30, 2021.

5. Marketable Securities

Our marketable securities are classified as available-for-sale pursuant to ASC 320, *Investments – Debt and Equity Securities*, and are recorded at fair value. Unrealized gains are included as a component of accumulated other comprehensive (loss) income in the condensed consolidated balance sheets and statements of stockholders' equity and a component of total comprehensive (loss) income in the condensed consolidated statements of comprehensive (loss) income, until realized. Unrealized losses are evaluated for impairment under ASC 326, *Financial Instruments - Credit Losses*, to determine if the impairment is credit-related or noncredit-related. Credit-related impairment is recognized as an allowance on the balance sheet with a corresponding adjustment to earnings, and noncredit-related impairment is recognized in other comprehensive (loss) income, net of taxes. Realized gains and losses are included in investment income on a specific-identification basis. There were no material realized gains or losses on marketable securities for the three and nine months ended September 30, 2021 or 2020.

Marketable securities at September 30, 2021 consisted of the following:

(In thousands)	Amortized Cost	Unrealized Gains	Unrealized Losses	Fair Value
Current:				
U.S. Treasuries	$ 299,856	$ 3	$ (7)	$ 299,852
Government securities	38,560	6	—	38,566
Corporate debt securities	527,504	23	(112)	527,415
Total Current	865,920	32	(119)	865,833
Non-current:				
U.S. Treasuries	20,016	—	(7)	20,009
Government securities	34,996	—	(17)	34,979
Corporate debt securities	75,230	—	(79)	75,151
Total Non-current	130,242	—	(103)	130,139
Total marketable securities	$ 996,162	$ 32	$ (222)	$ 995,972

Marketable securities at December 31, 2020 consisted of the following:

(In thousands)	Amortized Cost	Unrealized Gains	Unrealized Losses	Fair Value
Current:				
U.S. Treasuries	$ 113,559	$ 134	$ (21)	$ 113,672
Government securities	108,263	37	(8)	108,292
Corporate debt securities	223,461	140	(72)	223,529
Total Current	445,283	311	(101)	445,493
Non-current:				
U.S. Treasuries	15,147	—	(10)	15,137
Government securities	26,831	8	—	26,839
Corporate debt securities	55,735	2	(105)	55,632
Total Non-current	97,713	10	(115)	97,608
Total marketable securities	$ 542,996	$ 321	$ (216)	$ 543,101

As of September 30, 2021 and December 31, 2020, we held both current and non-current investments. Investments classified as current have maturities of less than one year. Investments classified as non-current are those that: (i) have a maturity of greater than one year, and (ii) we do not intend to liquidate within the next twelve months, although these funds are available for use and, therefore, are classified as available-for-sale.

As of September 30, 2021 and December 31, 2020, we held 116 and 87 debt securities, respectively, that were in an unrealized loss position for less than one year. We did not record an allowance for credit losses as of September 30, 2021 and December 31, 2020 related to these securities. The aggregate fair value of debt securities in an unrealized loss position at September 30, 2021 and December 31, 2020 was $692.5 million and $299.0 million, respectively. There were no individual securities that were in a significant unrealized loss position as of September 30, 2021 and December 31, 2020. We regularly review the securities in an unrealized loss position and evaluate the current expected credit loss by considering factors such as historical experience, market data, issuer-specific factors, and current economic conditions. We do not consider these marketable securities to be impaired as of September 30, 2021 and December 31, 2020.

6. Leases

Our building leases are comprised of office and laboratory space under non-cancelable operating leases. These lease agreements have remaining lease terms of six years and contain various clauses for renewal at our option. The renewal options were not included in the calculation of the operating lease assets and the operating lease liabilities as the renewal options are not reasonably certain of being exercised. The lease agreements do not contain residual value guarantees.

The components of lease expense and other information related to leases were as follows:

(In millions)	Three Months Ended September 30, 2021	Three Months Ended September 30, 2020	Nine Months Ended September 30, 2021	Nine Months Ended September 30, 2020
Operating lease costs	$ 3.8	$ 3.8	$ 11.4	$ 11.4
Cash paid for amounts included in the measurement of operating lease liabilities	$ 3.6	$ 3.5	$ 10.8	$ 10.9

We have not entered into any material short-term leases or financing leases as of September 30, 2021.

As of September 30, 2021, undiscounted minimum rental commitments under non-cancelable leases, for each of the next five years and total thereafter were as follows:

(In thousands)	
Remaining 2021	$ 2,425
2022	16,773
2023	18,126
2024	18,660
2025	19,507
Thereafter	44,385
Undiscounted minimum rental commitments	$ 119,876
Interest	(21,153)
Operating lease liabilities	$ 98,723

In arriving at the operating lease liabilities as of September 30, 2021 and December 31, 2020, we applied the weighted-average incremental borrowing rate of 5.7% for both periods over a weighted-average remaining lease term of 6.4 years and 7.2 years, respectively.

In August 2021, we entered into a long-term sublease agreement for 12,995 square feet of the office space at 38 Sidney Street Cambridge, Massachusetts. The term of the lease runs until December 2024. We recorded operating sublease income of $0.1 million for both the three and nine months ended September 30, 2021 in other income, net in the condensed consolidated statements of operations.

As of September 30, 2021, the future minimum lease payments to be received under the long-term sublease agreement were as follows:

(In thousands)	
Remaining 2021	$ 276
2022	1,118
2023	1,152
2024	1,186
Total	$ 3,732

7. Accrued Expenses

Accrued expenses consist of the following:

(In thousands)	September 30, 2021	December 31, 2020
Accrued compensation	$ 13,599	$ 20,345
Accrued research and development costs	7,435	5,444
Accrued professional fees	3,246	2,897
Accrued other	4,954	2,115
Total accrued expenses	$ 29,234	$ 30,801

8. Share-Based Payments

2013 Stock Incentive Plan

In June 2013, our Board of Directors adopted and, in July 2013 our stockholders approved, the 2013 Stock Incentive Plan, or the 2013 Plan. The 2013 Plan became effective upon the closing of our initial public offering and provides for the grant of incentive stock options, non-qualified stock options, stock appreciation rights, restricted stock awards, restricted stock units, or RSUs, performance-based share units, or PSUs, and other stock-based awards to employees, non-employees and non-employee directors. Following the adoption of the 2013 Plan, we granted no further stock options or other awards under the 2007 Stock Incentive Plan, or the 2007 Plan. Any options or awards outstanding under the 2007 Plan at the time of adoption of the 2013 Plan remain outstanding and effective. As of September 30, 2021, the total number of shares reserved under the 2007 Plan and the 2013 Plan was 11,457,704, and we had 5,058,266 shares available for future issuance under the 2013 Plan.

Stock options

The following table presents stock option activity for the nine months ended September 30, 2021:

	Number of Stock Options	Weighted-Average Exercise Price
Outstanding at December 31, 2020	6,143,046	$ 58.46
Granted	1,036,439	55.95
Exercised	(744,663)	45.22
Forfeited/Expired	(1,402,231)	62.20
Outstanding at September 30, 2021	5,032,591	$ 58.86
Exercisable at September 30, 2021	3,392,192	$ 61.02
Vested and expected to vest at September 30, 2021	5,032,591	$ 58.86

At September 30, 2021, there was approximately $49.1 million of total unrecognized compensation expense related to unvested stock option awards, which we expect to recognize over a weighted-average period of approximately 2.4 years.

Restricted stock units

The following table presents RSU activity for the nine months ended September 30, 2021:

	Number of Stock Units	Weighted-Average Grant Date Fair Value
Unvested shares at December 31, 2020	1,284,378	$ 50.78
Granted	813,902	55.76
Vested	(381,865)	57.71
Forfeited	(634,933)	51.65
Unvested shares at September 30, 2021	1,081,482	$ 51.57

As of September 30, 2021, there was approximately $37.5 million of total unrecognized compensation expense related to RSUs, which we expect to recognize over a weighted-average period of approximately 1.9 years.

Performance-based stock units

The following table presents PSU activity for the nine months ended September 30, 2021:

	Number of Stock Units	Weighted-Average Grant Date Fair Value
Unvested shares at December 31, 2020	142,229	$ 54.28
Granted	131,000	55.85
Vested	—	—
Forfeited	(30,559)	51.02
Unvested shares at September 30, 2021	242,670	$ 55.54

Stock-based compensation expense associated with these PSUs is recognized when the underlying performance condition is considered probable of achievement using our management's best estimates.

As of September 30, 2021, there was no unrecognized compensation expense related to PSUs with performance-based vesting criteria that are considered probable of achievement, and $13.5 million of total unrecognized compensation expense related to PSUs with performance-based vesting criteria that are considered not probable of achievement.

Market-based stock units

The following table presents market-based stock unit, or MSU, activity for the nine months ended September 30, 2021:

	Number of Stock Units	Weighted-Average Grant Date Fair Value
Unvested shares at December 31, 2020	42,695	$ 41.50
Granted	—	—
Unvested shares at September 30, 2021	42,695	$ 41.50

The fair value of MSUs are estimated using a Monte Carlo simulation model. Assumptions and estimates utilized in the model include the risk-free interest rate, dividend yield, expected stock volatility and the estimated period to achievement of the market condition. As of September 30, 2021, there was no remaining unrecognized compensation expense related to MSUs.

2013 Employee Stock Purchase Plan

In June 2013, our Board of Directors adopted, and in July 2013 our stockholders approved, the 2013 Employee Stock Purchase Plan, or the 2013 ESPP. We issued and sold 94,888 and 120,293 shares of common stock during the nine months ended September 30, 2021 and 2020, respectively, under the 2013 ESPP. The 2013 ESPP provides participating employees with the opportunity to purchase up to an aggregate of 1,345,454 shares of our common stock. As of September 30, 2021, we had 885,556 shares of common stock available for future issuance under the 2013 ESPP.

Stock-based compensation expense

Stock-based compensation expense by award type included within the condensed consolidated statements of operations is as follows:

	Three Months Ended September 30,		Nine Months Ended September 30,	
(In thousands)	2021	2020	2021	2020
Stock options	$ 7,214	$ 9,472	$ 24,399	$ 28,924
Restricted stock units	4,735	4,925	16,724	15,761
Performance-based stock units	—	—	—	1,760
Employee stock purchase plan	199	339	764	1,035
Other stock awards	—	241	—	781
Total stock-based compensation expense	$ 12,148	$ 14,977	$ 41,887	$ 48,261

Expenses related to stock options and stock-based awards were allocated as follows in the condensed consolidated statements of operations:

	Three Months Ended September 30,		Nine Months Ended September 30,	
(In thousands)	2021	2020	2021	2020
Research and development expense	$ 5,607	$ 6,238	$ 19,002	$ 20,831
Selling, general and administrative expense	6,541	8,739	22,885	27,430
Total stock-based compensation expense	$ 12,148	$ 14,977	$ 41,887	$ 48,261

9. Loss per Share

Basic net loss per share is calculated by dividing net loss by the weighted-average shares outstanding during the period, without consideration for common stock equivalents. Diluted net loss per share is calculated by adjusting the weighted average shares outstanding for the dilutive effect of common stock equivalents outstanding for the period, determined using the treasury stock method. For purposes of the dilutive net loss per share calculation, stock options, RSUs, PSUs and MSUs for which the performance and market vesting conditions, respectively, have been deemed probable, and 2013 ESPP shares are considered to be common stock equivalents, while PSUs and MSUs with performance and market vesting conditions, respectively, that were not deemed probable as of September 30, 2021 are not considered to be common stock equivalents.

We utilize the control number concept in the computation of diluted earnings per share to determine whether potential common stock equivalents are dilutive. The control number used is loss from continuing operations. The control number concept requires that the same number of potentially dilutive securities applied in computing diluted earnings per share from continuing operations be applied to all other categories of income or loss, regardless of their anti-dilutive effect on such categories. Since we had a net loss for continuing operations for all periods presented, no dilutive effect has been recognized in the calculation of income from discontinued operations per share. Basic and diluted net loss per share was the same for all periods presented.

The following common stock equivalents were excluded from the calculation of diluted net loss per share applicable to common stockholders for the periods indicated because including them would have had an anti-dilutive effect:

	Three and Nine Months Ended September 30,	
	2021	2020
Stock options	5,032,591	6,370,245
Restricted stock units	1,081,482	1,205,478
Employee stock purchase plan shares	7,470	13,201
Total common stock equivalents	6,121,543	7,588,924

10. Income Taxes

We recorded a provision for income taxes of $3.9 million and $16.8 million for the three and nine months ended September 30, 2021, respectively. No income tax provision was recorded for the three and nine months ended September 30, 2020. The tax

provision has been recorded within discontinued operations as it relates to the income tax impact on the sale of our oncology business to Servier. There is no income tax expense recorded in continuing operations for the three and nine months ended September 30, 2021 and 2020, respectively. Cash taxes paid were $8.9 million for the nine months ended September 30, 2021. No cash taxes were paid during the nine months ended September 30, 2020.

11. Share Repurchase Program

On March 25, 2021, we announced that our board of directors authorized the Repurchase Program for the repurchase of up to $1.2 billion of our outstanding shares of common stock. On March 31, 2021, in connection with the Repurchase Program, we entered into a definitive share repurchase agreement with BMS to repurchase 7,121,658 shares of our common stock held by certain subsidiaries of BMS for an aggregate purchase price of $344.5 million, or $48.3785 per share. This repurchase was completed on April 5, 2021.

Further, on April 2, 2021, in connection with the Repurchase Program, we entered into a Rule 10b5-1 repurchase plan to which we may repurchase up to $600 million of shares of our common stock. As of September 30, 2021, we have repurchased approximately 8.7 million shares of common stock for $438.9 million, or $50.57 per share, under the plan. In total, as of September 30, 2021, we have repurchased 15.8 million shares of common stock for $783.4 million, or $49.58 per share, under the Repurchase Program.

Repurchased shares are held as treasury stock until they are retired or re-issued. Treasury stock purchases are accounted for under the cost method whereby the entire cost of the acquired stock is recorded as treasury stock. Repurchases of our common stock are accounted for as of the settlement date. There were no retirements or re-issuances of treasury stock during the three or nine months ended September 30, 2021.

12. Subsequent Events

On October 5, 2021, we terminated our Rule 10b5-1 share repurchase program and on October 13, 2021 entered into a Rule 10b-18 repurchase plan that allows us to conduct open market repurchases over time up to our remaining authorization under the Repurchase Program.

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

Forward-looking Information

The following discussion of our financial condition and results of operations should be read with our unaudited condensed consolidated financial statements as of September 30, 2021 and for the three and nine months ended September 30, 2021 and 2020, and related notes included in Part I, Item 1 of this Quarterly Report on Form 10-Q, as well as the audited consolidated financial statements and notes and Management's Discussion and Analysis of Financial Condition and Results of Operations, included in our Annual Report on Form 10-K for the year ended December 31, 2020 filed with the SEC on February 25, 2021. This Management's Discussion and Analysis of Financial Condition and Results of Operations contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. These forward-looking statements are based on current expectations, estimates, forecasts and projections, and the beliefs and assumptions of our management, and include, without limitation, statements with respect to our expectations regarding our research, development and commercialization plans and prospects, results of operations, selling, general and administrative expenses, research and development expenses, the sufficiency of our cash for future operations and business activity disruption due to the COVID-19 pandemic. Words such as "anticipate," "believe," "estimate," "expect," "goal," "intend," "may," "plan," "predict," "project," "strategy," "target," "potential," "will," "would," "could," "should," "continue," "vision" and similar statements or variation of these terms or the negative of those terms and similar expressions are intended to identify these forward-looking statements. Readers are cautioned that these forward-looking statements are predictions and are subject to risks, uncertainties and assumptions that are difficult to predict. Therefore, actual results may differ materially and adversely from those expressed in any forward-looking statements. Among the important factors that could cause actual results to differ materially from those indicated by our forward-looking statements are those discussed under the heading "Risk Factors" in Part II, Item 1A and elsewhere in this report, and in our Annual Report on Form 10-K for the year ended December 31, 2020. We undertake no obligation to revise the forward-looking statements contained herein to reflect events or circumstances after the date hereof or to reflect the occurrence of unanticipated events, except as required by law.

Overview

We are a biopharmaceutical company committed to transforming patients' lives through scientific leadership in the field of cellular metabolism and adjacent areas of biology, with the goal of creating differentiated, small molecule medicines for genetically defined diseases, or GDDs. To address our focus areas, we take a systems biology approach to deeply understand disease states, drive the discovery and validation of novel therapeutic targets, and define patient selection strategies, thereby increasing the probability that our experimental medicines will have the desired therapeutic effect.

Sale of our Oncology Business to Servier

On March 31, 2021, we completed the sale of our oncology business to Servier Pharmaceuticals LLC, or Servier. The transaction included the sale of our oncology business, including TIBSOVO®, our clinical-stage product candidates vorasidenib, AG-270 and AG-636, and our oncology research programs for a payment of approximately $1.8 billion in cash at the closing, subject to certain adjustments, and a payment of $200 million in cash, if, prior to January 1, 2027, vorasidenib is granted new drug application, or NDA, approval from the U.S. Food and Drug Administration, or FDA, with an approved label that permits vorasidenib's use as a single agent for the adjuvant treatment of patients with Grade 2 glioma that have an isocitrate dehydrogenase 1 or 2 mutation (and, to the extent required by such approval, the vorasidenib companion diagnostic test is granted an FDA premarket approval), as well as a royalty of 5% of U.S. net sales of TIBSOVO® from the close of the transaction through loss of exclusivity, and a royalty of 15% of U.S. net sales of vorasidenib from the first commercial sale of vorasidenib through loss of exclusivity. Servier also acquired our co-commercialization rights for Bristol Myers Squibb's IDHIFA® and the right to receive a $25.0 million potential milestone payment under our prior collaboration agreement with Celgene Corporation, and following the sale Servier will conduct certain clinical development activities within the IDHIFA® development program.

The oncology business met the criteria within Accounting Standards Codification 205-20 to be reported as discontinued operations because the transaction was a strategic shift in business that had a major effect on our operations and financial results. Therefore, we have reported the historical results of the oncology business including the results of operations and cash flows as discontinued operations, and related assets and liabilities were retrospectively reclassified as assets and liabilities of discontinued operations for all periods presented herein. Unless otherwise noted, applicable amounts in the prior year have been recast to conform to this discontinued operations presentation. Refer to Note 3 of our condensed consolidated financial statements included in this Quarterly Report on Form 10-Q for additional information. Unless otherwise indicated, the following information relates to our continuing operations following the sale to Servier. A more complete description of our business prior to the consummation of the transaction is included in Item 1. "Business", in Part I of the Annual Report on Form 10-K for the year ended December 31, 2020 that was previously filed with the Securities and Exchange Commission, or SEC, on February 25, 2021.

GDDs

Our primary focus in the GDD area relates to therapeutic categories where we believe we have differentiated expertise and demonstrated capabilities (e.g., -enzyme stabilizers, pyruvate kinase, phenylalanine hydroxylase). As a result, we expect the new therapies that we plan to advance through the discovery, development and commercialization stages to be in the areas of non-malignant hematology and inborn errors of metabolism, though our future efforts may not be limited to these categories.

The lead product candidate in our GDD portfolio, mitapivat, targets pyruvate kinase-R, or PKR, for the treatment of pyruvate kinase, or PK, deficiency and other hemolytic anemias including thalassemia and sickle cell disease, or SCD. Mitapivat is an orally available small molecule and a potent activator of the wild-type (normal) and mutated PKR enzymes, which has resulted in restoration of adenosine triphosphate levels and a decrease in 2,3-diphosphoglycerate levels in blood sampled from patients with PK deficiency and treated ex-vivo with mitapivat. PK deficiency is a rare genetic disorder that often results in severe hemolytic anemia, jaundice and lifelong conditions associated with chronic anemia and secondary complications due to inherited mutations in the pyruvate kinase enzyme within red blood cells. We are currently developing mitapivat for the treatment of patients with PK deficiency, thalassemia and SCD in the following ongoing or planned pivotal clinical trials:

Pyruvate Kinase Deficiency:

- ACTIVATE-T, a single arm, global, pivotal trial of mitapivat in regularly-transfused patients with PK deficiency. This trial has completed enrollment and we are conducting an extension study for previously enrolled patients, which is designed to evaluate the long-term safety, tolerability and efficacy of treatment with mitapivat.
- ACTIVATE, a 1:1 randomized, placebo-controlled, global, pivotal trial of mitapivat in patients with PK deficiency who do not receive regular transfusions. This trial has completed enrollment and we are conducting an extension study for previously enrolled patients, which is designed to evaluate the long-term safety, tolerability and efficacy of treatment with mitapivat.
- Pivotal trials of mitapivat in pediatric PK deficiency, which we expect to initiate in 2022.

Thalassemia:

- ENERGIZE and ENERGIZE-T, phase 3 trials of mitapivat in not-regularly-transfused and regularly-transfused adults with thalassemia, have been initiated.

SCD:

- RISE UP, a phase 2/3 trial of mitapivat in patients with SCD, is expected to initiate by the end of 2021.

We have worldwide development and commercial rights to mitapivat and expect to fund the future development and commercialization costs related to this program. The FDA and European Medicines Agency, or EMA, granted orphan drug designations for mitapivat for the treatment of patients with PK deficiency, and the FDA granted orphan drug designation for mitapivat for the treatment of patients with thalassemia and patients with SCD. In June 2021, we submitted an NDA for mitapivat to the FDA for the treatment of adults with PK deficiency in the United States and a marketing authorization application, or MAA, to the EMA for the treatment of adults with PK deficiency the European Union. Our NDA was accepted with priority review and granted a Prescription Drug User Fee Act, or PDUFA, action date of February 17, 2022. The MAA has passed validation, and both regulatory review processes are ongoing. We also expect to continue to grow our U.S. commercial infrastructure and evaluate all options to maximize the patient impact and value of mitapivat globally, including strategic transactions. We are also developing AG-946, a novel activator of both the PKR and PKM2 isoforms of pyruvate kinase, in an ongoing phase 1 trial which is currently enrolling healthy volunteers. PKR activation is specific to red blood cells and hemolytic anemias, while PKM2 activation occurs in other tissues which express this isoform, and is potentially important in a variety of disease indications.

In addition to these development programs, we are seeking to advance a number of early-stage discovery programs for GDDs. Drug candidates for PK activation and other mechanisms, while primarily targeting GDD may also have utility in nongenetically defined disease, or non-GDD indications. Where differentiated, nonclinical proof of concept emerges for these non-GDD indications, appropriate partnership may be used to drive the best patient benefit.

Critical Accounting Policies and Estimates

Our critical accounting policies are those policies which require the most significant judgments and estimates in the preparation of our condensed consolidated financial statements. We have determined that our most critical accounting policies are those relating to accrued research and development expenses and stock-based compensation. Except those that have been disclosed in Note 2, *Summary of Significant Accounting Policies*, of the notes to our condensed consolidated financial statements included in this Quarterly Report on Form 10-Q, there have been no significant changes to our existing critical accounting policies discussed in our Annual Report on Form 10-K for the year ended December 31, 2020.

Financial Operations Overview

Impact of COVID-19 on our Business

As of September 30, 2021, we have not experienced a significant financial or supply chain impact directly related to the COVID-19 pandemic but have experienced some disruptions to clinical operations, including timelines to complete patient enrollment in some of our clinical trials, as further described below. We are continuing to serve third parties while taking precautions to provide a safe work environment for our employees and third parties. Our lab-based employees who need to be onsite to fulfill their job responsibilities have been onsite since late May 2020, and we have opened our Cambridge office to employees who prefer to work onsite. Our field-based employees engage with healthcare providers and other third parties remotely and, where local regulations allow, on a limited in-person basis. We are conducting our return to work program under strict guidelines as required by federal, state, and local authorities. Effective November 8, 2021, we will require all employees, regardless of role or work location, to be fully vaccinated against COVID-19, as defined by the Center of Disease Control and Prevention's guidelines, subject to limited exceptions. We have been monitoring our supply chain network for disruptions due to the COVID-19 pandemic, and our third-party manufacturers remain largely unaffected, with any campaign delays experienced to date being limited to a few days in duration. Although global shipping continues to be disrupted due to the pandemic, we have not experienced a supply impact.

The extent of the pandemic's effect on our operational and financial performance will depend in large part on future developments, which cannot be predicted with confidence at this time. Future developments include changes in the duration, scope and severity of the pandemic, including any variant strains of the COVID-19 virus, the actions taken to contain or mitigate its impact, the impact on governmental programs and budgets, the supply, distribution and efficacy of vaccines, and the resumption of widespread economic activity. Any prolonged material disruption of our employees, suppliers, manufacturing, or third parties could negatively impact our consolidated financial position, consolidated results of operations and consolidated cash flows. As a result, we may have to take further actions that we determine are in the best interests of our employees or as required by federal, state, or local authorities.

General

Since inception, our operations have primarily focused on organizing and staffing our company, business planning, raising capital, assembling our core capabilities in cellular metabolism, identifying potential product candidates, undertaking preclinical studies, conducting clinical trials, establishing a commercial infrastructure and, prior to the sale of our oncology business to Servier on March 31, 2021, marketing our approved products. Through March 31, 2021, we have financed our operations primarily through proceeds from the sale of our royalty rights, commercial sales of TIBSOVO®, funding received from our collaboration agreements, private placements of our preferred stock, our initial public offering of our common stock and concurrent private placement of common stock to an affiliate of Celgene, and our follow-on public offerings. Following the sale of our oncology business to Servier on March 31, 2021, we expect to finance our operations primarily through cash on hand, royalty payments from Servier with respect to U.S. net sales of TIBSOVO®, the potential milestone payment from Servier if vorasidenib is approved by the FDA, and future potential sales of mitapivat if approved for marketing by regulatory authorities and successfully launched by us and, potentially, collaborations, strategic alliances, licensing arrangements and other nondilutive strategic transactions.

We have historically incurred operating losses. Our net income for the nine months ended September 30, 2021 was $1,699.3 million and our net loss for the nine months ended September 30, 2020 was $229.7 million. As of September 30, 2021, we had an accumulated deficit of $144.1 million. The net income we generated in the nine months ended September 30, 2021 was primarily due to the sale of our oncology business to Servier, which was consummated on March 31, 2021. Following the consummation of the sale of our oncology business, we expect to incur significant expenses and net losses until such time we are able to report profitable results. Our net losses may fluctuate significantly from year to year. We expect that we will continue to incur significant expenses as we continue to advance and expand clinical development activities for our lead programs: mitapivat, and AG-946; continue to discover and validate novel targets and drug product candidates; expand and protect our intellectual property portfolio; and hire additional commercial, development and scientific personnel.

Research and development expenses

Research and development activities are central to our business model. Product candidates in later stages of clinical development generally have higher development costs than those in earlier stages of clinical development, primarily due to the increased size and duration of later-stage clinical trials. We expect research and development costs related to our GDD portfolio to increase significantly for the foreseeable future as our product candidate development programs progress. However, the successful development of our product candidates is highly uncertain. As such, at this time, we cannot reasonably estimate or know the nature, timing and estimated costs of the efforts that will be necessary to complete the remainder of the development and to commercialize these product candidates. We are also unable to predict when future net cash inflows will commence from

mitapivat, AG-946 or any of our other product candidates. This is due to the numerous risks and uncertainties associated with developing medicines, including the uncertainty of:

- establishing an appropriate safety profile with an investigational new drug application, or IND, and/or NDA-enabling toxicology and clinical trials;
- the successful enrollment in, and completion of, clinical trials;
- the receipt of marketing approvals from applicable regulatory authorities;
- establishing compliant commercial manufacturing capabilities or making arrangements with third-party manufacturers;
- obtaining and maintaining patent and trade secret protection and regulatory exclusivity for our product candidates;
- launching commercial sales of the products, if and when approved, whether alone or in collaboration with others; and
- maintaining an acceptable safety profile of the products following approval.

A change in the outcome of any of these variables with respect to the development of any of our product candidates would significantly change the costs and timing associated with the development of that product candidate.

Research and development expenses consist primarily of costs incurred for our research activities, including our drug discovery efforts, and the development of our product candidates, which include:

- employee-related expenses, including salaries, benefits and stock-based compensation expense;
- expenses incurred under agreements with third parties, including contract research organizations, or CROs, that conduct research and development and both preclinical and clinical activities on our behalf, and the cost of consultants;
- the cost of lab supplies and acquiring, developing and manufacturing preclinical and clinical study materials; and
- facilities, depreciation, and other expenses, which include direct and allocated expenses for rent and the maintenance of facilities, insurance and other operating costs.

The following summarizes the clinical development activities related to our most advanced programs. The timing of trial and site initiations, enrollment and data readouts may be impacted depending on the duration, scope and severity of the COVID-19 pandemic:

Mitapivat: PK Activator

- DRIVE PK, a global phase 2, first-in-patient, open-label safety and efficacy clinical trial of mitapivat in adult, transfusion-independent patients with PK deficiency. This trial has completed enrollment and we are conducting an extension study for previously enrolled patients, which is designed to evaluate the long-term safety, tolerability and efficacy of treatment with mitapivat.
- ACTIVATE-T, a single arm, global, pivotal trial of mitapivat in regularly-transfused patients with PK deficiency. We reported in June 2021, in a full analysis of updated data, that this trial met its primary endpoint of a statistically significant and clinically meaningful reduction in transfusion burden and that improvements were also observed for certain patient reported outcomes. This trial has completed enrollment and we are conducting an extension study for previously enrolled patients, which is designed to evaluate the long-term safety, tolerability and efficacy of treatment with mitapivat.
- ACTIVATE, a 1:1 randomized, placebo-controlled, global, pivotal trial of mitapivat in patients with PK deficiency who do not receive regular transfusions. We reported in June 2021, in a full analysis of updated data, that this trial met its primary endpoint of a statistically significant, sustained increase in hemoglobin compared to placebo. In addition, data from the trial demonstrated that treatment with mitapivat showed statistically significant improvement in key pre-specified secondary endpoints including patient reported outcomes This trial has completed enrollment and we are conducting an extension study for previously enrolled patients, which is designed to evaluate the long-term safety, tolerability and efficacy of treatment with mitapivat.
- A phase 2, open-label safety and efficacy clinical trial of mitapivat in adult patients with non-transfusion-dependent α- and β-thalassemia. We reported in June 2021 that this trial met its primary endpoint of hemoglobin increase of greater than or equal to 1.0 gram per deciliter from baseline at one or more assessments during weeks 4-12 of the trial. The trial has completed enrollment and we are conducting an extension study for previously enrolled patients, which is designed to evaluate the long-term safety, tolerability and efficacy of treatment with mitapivat.
- In collaboration with the National Institutes of Health, or NIH, we are evaluating mitapivat in a phase 1 trial in patients with SCD pursuant to a cooperative research and development agreement. Enrollment has been completed in the core trial period, and patients are enrolling in an ongoing long-term extension study. In June 2020, clinical proof of concept was established based on a preliminary analysis of the data from this trial.

- In collaboration with UMC Utrecht, or UMC, we are evaluating mitapivat in patients with SCD pursuant to an investigator sponsored trial agreement. The trial is ongoing and enrolling patients, although UMC experienced disruptions related to the COVID-19 pandemic.

In the third quarter of 2021, we initiated two phase 3 trials of mitapivat, ENERGIZE and ENERGIZE-T, in not regularly transfused and regularly transfused adults with thalassemia. We expect to initiate RISE UP, a phase 2/3 trial of mitapivat in patients with SCD, by the end of 2021. We expect to initiate pivotal trials of mitapivat in pediatric PK deficiency in 2022.

AG-946: Novel PK Activator

- A phase 1 trial of AG-946 in healthy volunteers and in patients with SCD. The trial is currently enrolling healthy volunteers.

Other research and platform programs

Other research and platform programs include activities related to exploratory efforts, target validation and lead optimization for our discovery and follow-on programs, and our proprietary metabolomics platform.

Selling, general and administrative expenses

Selling, general and administrative expenses consist primarily of salaries and other related costs, including stock-based compensation, for personnel in executive, finance, business development, commercial, legal and human resources functions. Other significant costs include facility-related costs not otherwise included in research and development expenses, legal fees relating to patent and corporate matters, and fees for accounting and consulting services.

We anticipate that our selling, general and administrative expenses will increase in the future to support continued research and development activities and future commercialization activities related to our GDD portfolio, including the potential commercialization of our product candidates. These increases will likely include increased costs related to the hiring of additional personnel and fees to outside consultants, lawyers and accountants, among other expenses.

Results of Operations

Certain amounts in prior periods have been reclassified to reflect the impact of the discontinued operations treatment of the oncology business in order to conform to the current period presentation.

Comparison of the three and nine months ended September 30, 2021 and 2020

Total Operating Expenses

	Three Months Ended September 30,		Nine Months Ended September 30,	
(In thousands)	2021	2020	2021	2020
Cost and expenses:				
Research and development	$ 64,000	$ 51,943	$ 183,674	$ 161,388
Selling, general and administrative	27,152	28,347	89,917	89,196
Total Operating Expenses	$ 91,152	$ 80,290	$ 273,591	$ 250,584

Total Operating Expenses - Three Months ended September 30, 2021 vs. Three Months ended September 30, 2020 - The increase in total operating expenses of $10.9 million for the three months ended September 30, 2021 compared to the three months ended September 30, 2020 was primarily due to an increase in research and development expenses of $12.1 million which is described below under Research and Development Expenses. Included in selling, general and administrative expenses is approximately $1.3 million of reimbursable transition related services we provided to Servier related to the sale of the oncology business.

Total Operating Expenses - Nine Months ended September 30, 2021 vs. Nine Months ended September 30, 2020 - The increase in total operating expenses of $23.0 million for the nine months ended September 30, 2021 compared to the nine months ended September 30, 2020 was primarily due to an increase in research and development expenses of $22.3 million which is described below under Research and Development Expenses. Included in selling, general and administrative expenses is approximately $3.4 million of reimbursable transition related services we provided to Servier related to the sale of the oncology business.

Research and Development Expenses

Our research and development expenses, by major program, are outlined in the table below:

(In thousands)	Three Months Ended September 30, 2021	Three Months Ended September 30, 2020	Nine Months Ended September 30, 2021	Nine Months Ended September 30, 2020
Mitapivat (PKR activator)	$ 20,130	$ 10,634	$ 49,543	$ 31,410
AG-946 (Novel PK activator)	2,820	2,357	6,849	7,195
Other research and platform programs	6,109	3,522	14,684	9,478
Total direct research and development expenses	29,059	16,513	71,076	48,083
Compensation and related expenses	21,816	23,153	70,965	76,124
Facilities and IT related expenses & other	9,883	12,277	33,987	37,181
Other expenses - transition services	3,242	—	7,646	—
Total indirect research and development expenses	34,941	35,430	112,598	113,305
Total research and development expense	$ 64,000	$ 51,943	$ 183,674	$ 161,388

Total Research and Development Expenses - Three Months ended September 30, 2021 vs. Three Months ended September 30, 2020 - The increase in total research and development expenses of $12.1 million for the three months ended September 30, 2021 compared to the three months ended September 30, 2020 was primarily due to a $9.5 million increase in mitapivat costs due to start up costs for the initiated phase 3 trials of mitapivat, ENERGIZE and ENERGIZE-T, and the planned phase 2/3 trial of mitapivat in patients with SCD, RISE UP, and launch preparation activities. The increase in other research and platform programs of $2.6 million was primarily driven by planned increased activity on various exploratory and discovery activities. Included in total indirect research and development expenses was $3.2 million of reimbursable transition related services we provided to Servier related to the sale of the oncology business for discovery, clinical development, technical operations, and commercial related activities which will continue for periods ranging from one month to approximately one year after March 31, 2021.

Total Research and Development Expenses - Nine Months ended September 30, 2021 vs. Nine Months ended September 30, 2020 - The increase in total research and development expenses of $22.3 million for the nine months ended September 30, 2021 compared to the nine months ended September 30, 2020 was primarily due to a $18.1 million increase in mitapivat costs due to start up costs for the initiated phase 3 trials of mitapivat, ENERGIZE and ENERGIZE-T, the planned phase 2/3 trial of mitapivat in patients with SCD, RISE UP, and filing and launch preparation activities which includes $0.5 million in filing fees. The increase in other research and platform programs of $5.2 million was primarily driven by planned increased activity on various exploratory and discovery activities. Included in total indirect research and development expenses was $7.6 million of reimbursable transition related services we provided to Servier related to the sale of the oncology business related to discovery, clinical development, technical operations, and commercial related activities which will continue for periods ranging from one month to approximately one year after March 31, 2021.

Other Income and Expense

(In thousands)	Three Months Ended September 30, 2021	Three Months Ended September 30, 2020	Nine Months Ended September 30, 2021	Nine Months Ended September 30, 2020
Gain on sale of oncology business	$ 1,996	$ —	$ 3,996	$ —
Interest income, net	256	1,115	504	5,820
Other income, net	4,641	—	11,165	—

Other Income and Expense- Three Months ended September 30, 2021 vs. Three Months ended September 30, 2020 - The increase in other income, net primarily relates to approximately $4.5 million of reimbursable transition related services for the sale of the oncology business for the three months ended September 30, 2021. The increase in gain on sale of oncology business primarily relates to income from royalties on U.S. net sales of TIBSOVO® by Servier of approximately $2.0 million in the third quarter of 2021. The decrease in interest income, net is primarily attributable to a decrease in interest rates.

Other Income and Expense- Nine Months ended September 30, 2021 vs. Nine Months ended September 30, 2020 - The increase in other income, net primarily relates to approximately $11.0 million of reimbursable transition related services and fees for the sale of the oncology business for the nine months ended September 30, 2021. The increase in gain on sale of oncology business

primarily relates to income from royalties on U.S. net sales of TIBSOVO® by Servier of approximately $4.0 million for the nine months ended September 30, 2021. The decrease in interest income, net is primarily attributable to a decrease in interest rates.

Loss from Operations and Net (Loss) Income

	Three Months Ended September 30,		Nine Months Ended September 30,	
(In thousands)	2021	2020	2021	2020
Net loss from continuing operations	$ (84,259)	$ (79,175)	$ (257,926)	$ (244,764)
Net (loss) income from discontinued operations	(4,507)	(19,804)	1,957,268	15,051
Net (loss) income	(88,766)	(98,979)	1,699,342	(229,713)

Loss from Operations and Net (Loss) Income – Three Months ended September 30, 2021 vs. Three Months ended September 30, 2020 – The increase in net loss from continuing operations for the three months ended September 30, 2021 compared to the three months ended September 30, 2020 was primarily driven by the higher research and development expenses discussed above under Research and Development Expenses, partially offset by $4.5 million of reimbursable transition related services related to the sale of the oncology business and a $2.0 million gain on sale of oncology business related to income from royalties on U.S. net sales of TIBSOVO® by Servier, both occurring in the third quarter of 2021. The change in net loss from discontinued operations for the three months ended September 30, 2021 compared to the three months ended September 30, 2020 was primarily driven by the sale of our oncology business to Servier in the first quarter of 2021, which significantly reduced revenues and expenses related to our oncology programs. The decrease in net (loss) income for the three months ended September 30, 2021 compared to the three months ended September 30, 2020 was primarily driven by the increase in net loss from continuing operations discussed above, partially offset by a lower net loss from discontinued operations for the three months ended September 30, 2021 on the sale of the oncology business discussed above.

Loss from Operations and Net (Loss) Income – Nine Months ended September 30, 2021 vs. Nine Months ended September 30, 2020 – The increase in loss from continuing operations for the nine months ended September 30, 2021 compared to the nine months ended September 30, 2020 was primarily driven by the higher research and development expenses discussed above under Research and Development Expenses, partially offset by $11.0 million of reimbursable transition related services and fees related to the sale of the oncology business and a $4.0 million gain on sale of oncology business related to income from royalties on U.S. net sales of TIBSOVO® by Servier, both occurring in the nine months ended September 30, 2021. The change in net income from discontinued operations and net (loss) income for the nine months ended September 30, 2021 compared to the nine months ended September 30, 2020 was primarily driven by the sale of our oncology business to Servier for approximately $1.8 billion in cash in the first quarter of 2021, which is included within net income from discontinued operations.

Liquidity and Capital Resources

Sources of liquidity

Since our inception, and through September 30, 2021, we have funded our operations through proceeds from the sale of our oncology business, commercial sales of TIBSOVO®, upfront, milestone, extension, cost reimbursement and royalty payments related to our collaboration agreements, product sales, proceeds from the sale of our royalty rights, proceeds received from our issuance of preferred stock, our initial public offering and concurrent private placement of common stock to an affiliate of Celgene, and our follow-on public offerings.

As of September 30, 2021, we had cash, cash equivalents and marketable securities of $1.4 billion. On March 25, 2021, we announced that our board of directors authorized the repurchase of up to $1.2 billion of our outstanding shares of common stock, or the Repurchase Program, using the proceeds from the sale of our oncology business to Servier. On March 31, 2021, in connection with the Repurchase Program, we entered into a definitive share repurchase agreement with Bristol-Myers Squibb Company, or BMS, to repurchase 7,121,658 shares of our common stock held by certain subsidiaries of BMS for an aggregate purchase price of $344.5 million, or $48.3785 per share. This repurchase was completed on April 5, 2021. Further, on April 2, 2021, in connection with the Repurchase Program, we entered into a Rule 10b5-1 repurchase plan pursuant to which we may repurchase up to $600 million of shares of our common stock. As of September 30, 2021, we have repurchased approximately 8.7 million shares of common stock for $438.9 million, or $50.57 per share, under the plan. On October 5, 2021, we terminated our Rule 10b5-1 share repurchase program and on October 13, 2021 entered into a Rule 10b-18 repurchase plan that allows us to conduct open market repurchases over time up to our remaining authorization under the Repurchase Program. We have paused our share repurchases and for the foreseeable future, we expect that our capital allocation will be prioritized towards

opportunities to accelerate programs in our development pipeline and/or pursue potential complementary business development opportunities.

In addition to our existing cash, cash equivalents and marketable securities, under the purchase agreement we are eligible to receive a $200 million milestone payment upon regulatory approval of vorasidenib, and royalty payments with respect to U.S. net sales of TIBSOVO® and, if approved, vorasidenib. Our right to such payments from Servier is our only committed potential external source of funds. Whether the regulatory approval milestone for vorasidenib will be achieved is subject to various risks and uncertainties, many of which are outside our control, including adverse clinical developments with respect to vorasidenib. Furthermore, we cannot predict what success, if any, Servier may have in the United States with respect to sales of TIBSOVO® and, if approved, vorasidenib, and consequently we cannot estimate the amount of royalty payments that we can expect to receive from Servier under the purchase agreement prior to the loss of exclusivity of these products.

Cash flows

The following table provides information regarding our cash flows for the nine months ended September 30, 2021 and 2020:

	Nine Months Ended September 30,	
(In thousands)	**2021**	**2020**
Net cash used in operating activities	$ (323,227)	$ (241,362)
Net cash provided by investing activities	1,343,197	4,350
Net cash (used in) provided by financing activities	(747,182)	260,936
Net change in cash and cash equivalents	$ 272,788	$ 23,924

Net cash used in operating activities. Cash used in operating activities of $323.2 million during the nine months ended September 30, 2021, of which $234.1 million was used by continuing operations and $89.1 million was used by discontinued operations, was primarily driven by research and development costs described above under Research and Development Expenses, offset by cash received of $39.5 million from sales of TIBSOVO®, and $1.2 million in cost reimbursements related to our collaboration agreements with Celgene.

Cash used in operating activities of $241.4 million during the nine months ended September 30, 2020, of which $192.8 million was used by continuing operations and $48.6 million was used by discontinued operations, was primarily due to operating expenses driven by research and development costs described above in Research and Development Expenses and increased staffing needs due to our expanding operations, offset by cash received of $83.3 million from sales of TIBSOVO®, $12.6 million in royalty payments and cost reimbursements under our collaboration agreements with Celgene, $6.1 million in interest received, and $2.7 million in cost reimbursement related to our collaboration agreement with CStone Pharmaceuticals.

Net cash provided by investing activities. Cash provided by investing activities of $1.3 billion for the nine months ended September 30, 2021, of which $459.7 million was used by continuing operations and $1.8 billion was provided by discontinued operations, was primarily due to the approximately $1.8 billion in cash proceeds received from the sale of our oncology business to Servier that was completed on March 31, 2021, partially offset by lower proceeds from maturities and sales of marketable securities than purchases of marketable securities. Cash provided by investing activities of $4.4 million for nine months ended September 30, 2020, of which approximately all was provided by continuing operations and $348.0 thousand was used by discontinued operations, was primarily the result of higher proceeds from maturities and sales of marketable securities than purchases of marketable securities, offset by $13.9 million in purchases of property and equipment.

Net cash (used in) provided by financing activities. Cash used in financing activities of $747.2 million for the nine months ended September 30, 2021, of which all was provided by continuing operations and none was used by discontinued operations, was primarily the result of $783.4 million in common stock repurchases in the nine months ended September 30, 2021 under our Repurchase Program, partially offset by the $37.0 million of proceeds received from stock option exercises and purchases made pursuant to our 2013 ESPP. Cash provided by financing activities of $260.9 million for the nine months ended September 30, 2020, of which $10.4 million was provided by continuing operations and $250.5 million was provided by discontinued operations, was primarily the result of net proceeds of $250.5 million from the sale of our tiered, sales-based royalty rights on worldwide net sales of IDHIFA® (enasidenib) and our ex-US regulatory milestones to Royalty Pharma in June 2020 and $10.6 million of proceeds received from stock option exercises and purchases made pursuant to our 2013 ESPP.

Funding requirements

Although we expect our expenses to decrease following the completion of the sale of our oncology business to Servier on March 31, 2021, we anticipate that this decrease will be offset as we transition our operations to focus solely on GDDs, particularly as we continue the research, development and clinical trials of, seek marketing approvals for, and commercialize our product candidates. If we obtain marketing approval for any of our product candidates, we expect to incur significant commercialization expenses related to product sales, marketing, manufacturing and distribution.

We expect that our existing cash, cash equivalents and marketable securities as of September 30, 2021, will enable us to execute our operating plan through major catalysts and to cash-flow positivity without the need to raise additional equity. Our future capital requirements will depend on many factors, including:

- the amount of contingent consideration we ultimately receive in connection with the sale of our oncology business to Servier;
- the scope, progress, results and costs of drug discovery, preclinical development, laboratory testing and clinical trials for our product candidates;
- the costs, timing and outcome of regulatory review of our product candidates;
- the costs of preparing, filing and prosecuting patent applications, maintaining and enforcing our intellectual property rights and defending intellectual property-related claims;
- the costs and timing of future commercialization activities, including product manufacturing, sales, marketing and distribution, for any of our product candidates for which we may receive marketing approval;
- the amount and timing of revenue, if any, received from commercial sales of our product candidates for which we receive marketing approval;
- our ability to establish and maintain collaborations on favorable terms, if at all;
- our ability to successfully execute on our strategic plans;
- operational delays due to the ongoing COVID-19 pandemic; and
- the extent to which we acquire or in-license, or monitor or out-license, other medicines and technologies.

Until such time, if ever, as we can generate substantial product revenue, we expect to finance our cash needs primarily through cash on hand, royalty payments from Servier with respect to U.S. net sales of TIBSOVO®, a potential milestone payment from Servier if vorasidenib is approved by the FDA and, potentially, collaborations, strategic alliances, licensing arrangements and other nondilutive strategic transactions. In addition, in connection with potential future strategic transactions, we may pursue opportunistic debt offerings, and equity or equity-linked offerings. We do not have any committed external source of funds other than the potential milestone and royalty payments that we are eligible to receive under our purchase agreement with Servier. To the extent that we raise additional capital through the sale of equity or convertible debt securities, the ownership interest of our stockholders will be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect the rights of our 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.

If we raise funds through collaborations, strategic alliances or licensing arrangements with third parties, we may have to relinquish valuable rights to our technologies, future revenue streams, research programs or product candidates, or 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 or on attractive terms, we may be required to delay, limit, reduce or terminate our product development or future commercialization efforts, or grant rights to develop and market product candidates that we would otherwise prefer to develop and market ourselves.

Off-Balance Sheet Arrangements

We did not have, during the periods presented, and we do not currently have, any off-balance sheet arrangements, as defined under applicable SEC rules.

Contractual Obligations

We have entered into agreements in the normal course of business with CROs for clinical trials and contract manufacturing organizations for supply manufacturing and with vendors for preclinical research studies and other services and products for operating purposes. These contractual obligations are cancelable at any time by us, generally upon prior written notice to the vendor.

During the three and nine months ended September 30, 2021, there were no significant changes to our contractual obligations and commitments described under Management’s Discussion and Analysis of Financial Condition and Results of Operations in our Annual Report on Form 10-K for the year ended December 31, 2020.

Item 3. Quantitative and Qualitative Disclosures about Market Risk

We are exposed to market risk related to changes in interest rates. As of September 30, 2021 and December 31, 2020, we had cash, cash equivalents and marketable securities of $1.4 billion and $670.5 million, respectively. Our marketable securities

consist primarily of investments in U.S. Treasuries, government securities and corporate debt securities. 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 primarily in short-term marketable securities. Our marketable securities are subject to interest rate risk and could fall in value if market interest rates increase. Due to the short-term duration of our investment portfolio and the low risk profile of our investments, we do not believe an immediate and uniform 100 basis point change in interest rates would have a material effect on the fair market value of our investment portfolio.

We are also exposed to market risk related to changes in foreign currency exchange rates. We have contracts with CROs located in Asia and Europe that are denominated in foreign currencies, and 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. As of September 30, 2021 and December 31, 2020, liabilities denominated in foreign currencies were immaterial.

Item 4. Controls and Procedures

Disclosure Controls and Procedures

Our management, with the participation of our principal executive officer and principal financial officer, evaluated, as of the end of the period covered by this Quarterly Report on Form 10-Q, the effectiveness of our disclosure controls and procedures. Based on that evaluation of our disclosure controls and procedures as of September 30, 2021, our principal executive officer and principal financial officer concluded that our disclosure controls and procedures as of such date are effective at the reasonable assurance level. The term “disclosure controls and procedures,” as defined in Rules 13a-15(e) and 15d-15(e) under 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 it files or submits under the Exchange Act is accumulated and communicated to its management, including its principal executive officer and principal financial officer, or persons performing similar functions, as appropriate to allow timely decisions regarding required disclosure. Our management recognizes that any controls and procedures, no matter how well designed and operated, can provide only reasonable assurance of achieving their objectives, and our management necessarily applies its judgment in evaluating the cost-benefit relationship of possible controls and procedures.

Changes in Internal Control Over Financial Reporting

There were no changes in our internal control over financial reporting, as defined in Rules 13a-15(f) and 15d-15(f) under the Exchange Act, that occurred during the fiscal quarter ended September 30, 2021 that have materially affected, or are reasonably likely to materially affect, our internal control over financial reporting.

PART II. OTHER INFORMATION

Item 1A. Risk Factors

This Quarterly Report on Form 10-Q contains forward-looking statements that involve substantial risks and uncertainties. All statements, other than statements of historical facts, contained herein, including statements regarding our strategy, future operations, future financial position, future revenue, projected costs, prospects, plans and objectives of our management are forward-looking statements. These statements involve known and unknown risks, uncertainties and other important factors that may cause our actual results, performance or achievements to be materially different from any future results, performance or achievements expressed or implied by the forward-looking statements. The words “anticipate,” “believe,” “estimate,” “expect,” “goal,” “intend,” “may,” “plan,” “predict,” “project,” “strategy,” “target,” “potential,” “will,” “would,” “could,” “should,” “continue,” “vision” and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. We may not actually achieve the plans, intentions or expectations disclosed in our forward-looking statements, and you should not place undue reliance on our forward-looking statements. Actual results or events could differ materially from the plans, intentions and expectations disclosed in the forward-looking statements we make. You should read this Quarterly Report on Form 10-Q completely and with the understanding that our actual future results may be materially different from what we expect. The risks described are not the only risks facing our company. Additional risks and uncertainties not currently known to us or that we currently deem to be immaterial also may materially adversely affect our business, financial condition and/or operating results. 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. These risk factors restate and supersede the risk factors set forth under the heading “Risk Factors” in our Annual Report on Form 10-K for the year ended December 31, 2020.

Summary Risk Factors

Our business is subject to a number of risks that if realized could materially affect our business, financial condition, results of operations, cash flows and access to liquidity. These risks are discussed more fully below. Our principal risks include the following:

- We may not be able to realize the anticipated benefits of the recent sale of our oncology business to Servier, including deploying the proceeds to expand our GDD business, and we may face new challenges as a smaller, less diversified company.
- If our existing capital is insufficient to execute our operating plan through major catalysts and to cash-flow positivity, we will need to raise capital, and if we are unable to raise capital when needed, we would be forced to delay, reduce or eliminate our product development programs or commercialization efforts.
- We have historically incurred operating losses. We expect to incur losses in the future and may never achieve or maintain profitability. Our net income for the nine months ended September 30, 2021 was $1,699.3 million and our net loss for the nine months ended September 30, 2020 was $229.7 million. The net income we generated in the nine months ended September 30, 2021 was primarily due to the sale of our oncology business to Servier, which was consummated on March 31, 2021. As of September 30, 2021, we had an accumulated deficit of $144.1 million.
- The amount of contingent consideration we will receive from the sale of our oncology business to Servier is subject to various risks and uncertainties.
- We depend heavily on the success of our clinical product candidates, including our lead product candidate mitapivat. Clinical trials of our product candidates may not be successful for a number of important reasons. If we or our collaborators are unable to commercialize our product candidates or experience significant delays in doing so, our business will be materially harmed.
- The COVID-19 pandemic has and may continue to affect our ability to initiate or continue our planned, ongoing and future clinical trials, disrupt regulatory activities, or have other adverse effects on our business and operations.
- We may not be successful in our efforts to identify or discover potential product candidates or to develop medicines of commercial value and we may not achieve our goals included in our strategic vision.
- Even if any of our product candidates receives marketing approval, we or others may later discover that the product is less effective than previously believed or causes undesirable side effects that were not previously identified, which could compromise our ability, or that of any collaborators, to market the product.
- Even if any of our product candidates receive marketing approval, they may fail to achieve the degree of market acceptance by physicians, patients, healthcare payors and others in the medical community necessary for commercial success.
- We face substantial competition, which may result in others discovering, developing or commercializing products before or more successfully than we do. There are a number of large pharmaceutical and biotechnology companies that

currently market and sell products or are pursuing the development of products for the treatment of the disease indications for which we are developing our product candidates.

- We currently rely, and expect to continue to rely, on third-party manufacturers for the materials and manufacture of our product candidates for preclinical and clinical testing and we expect to rely on third-party manufacturers for commercial supply of any product candidate for which we or our collaborators obtain marketing approval. Any performance failure on the part of our existing or future third-party manufacturers could delay clinical development or marketing approval.
- If we are unable to obtain and maintain patent or trade secret protection for our medicines and technology, or if the scope of the patent protection obtained is not sufficiently broad, our competitors could develop and commercialize medicines and technology similar or identical to ours, and our ability to successfully commercialize our medicines and technology may be adversely affected. If we do not, or are unable to, obtain or maintain any issued patents for any of our lead product candidates, it could have a material adverse effect on our competitive position, business, financial condition, results of operations, and prospects.

Risks Related to Our Financial Position

We may not be able to realize the anticipated benefits of the recent sale of our oncology business to Servier and we may face new challenges as a smaller, less diversified company.

We may not be able to realize the anticipated benefits from the recent sale of our oncology business to Servier, including deploying the proceeds from the transaction to expand our GDD business. Our ability to realize the anticipated benefits of the transaction and the success of the GDD business is subject to various risks and uncertainties, including the possibility of adverse clinical and other developments in respect of mitapivat or other pipeline products of the GDD business, the possibility that we may not be able to successfully develop and commercialize products based on PK activation and cellular metabolism and unanticipated changes in applicable laws and regulations that may adversely affect the GDD business.

We developed most of our initial products and product candidates for the treatment of various types of cancer. The sale of our oncology business to Servier, including all of our approved products, resulted in us being a smaller, less diversified company with a more limited business concentrated on product candidates for the treatment of GDDs. As a result, we may be more susceptible to changing market conditions, including fluctuations and risks particular to the markets for patients with GDDs, than a more diversified company, which could adversely affect our business, financial condition and results of operations. In addition, the diversification of our revenues, costs and cash flows will diminish following the transaction, such that our results of operations, cash flows, working capital and financing requirements may be subject to increased volatility and our ability to fund capital expenditures and investments or satisfy other financial commitments may be diminished.

We may also face new challenges with maintaining employee morale, retaining key management and other employees and attracting new employees and retaining existing business and operational relationships, including with third parties, employees and other counterparties that otherwise prefer to transact with larger companies (or will only transact with smaller companies on less favorable terms).

We have broad discretion as to the use of the proceeds from the sale of our oncology business to Servier, and we may not use the proceeds effectively.

We have broad discretion with respect to the use of proceeds of the sale of our oncology business to Servier. The results and effectiveness of the use of proceeds, including the repurchase of up to $1.2 billion of our outstanding shares of common stock, are uncertain, and we could spend the proceeds in ways that do not improve our remaining business, financial condition or results of operations. Our failure to apply these funds effectively could have an adverse effect on its business, financial condition and results of operations.

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

Until such time, if ever, as we can generate substantial product revenue, we expect to finance our cash needs primarily through cash on hand, royalty payments from Servier with respect to U.S. net sales of TIBSOVO®, a potential milestone payment from Servier if vorasidenib is approved by the FDA and, potentially, collaborations, strategic alliances, licensing arrangements and other nondilutive strategic transactions. In addition, in connection with potential future strategic transactions, we may pursue opportunistic debt offerings, and equity or equity-linked offerings. We do not have any committed potential external source of funds other than the potential milestone and royalty payments that we are eligible to receive under our purchase agreement with Servier. To the extent that we raise additional capital through the sale of equity or convertible debt securities, the ownership interest of our stockholders will be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect the rights of our common stockholders. Debt financing, if available, may require us to enter into agreements that include covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, making capital expenditures or declaring dividends. In addition, securing financing could require a substantial amount of time and

attention from our management and may divert a disproportionate amount of their attention away from day-to-day activities, which may adversely affect our management's ability to oversee the development of our product candidates.

If we raise funds through collaborations, strategic alliances or licensing arrangements with third parties, we may have to relinquish valuable rights to our technologies, future revenue streams, research programs or product candidates or to grant licenses on terms that may not be favorable to us.

If our existing capital is insufficient to execute our operating plan through major catalysts and to cash-flow positivity, we will need to raise capital, and if we are unable to raise capital when needed, we would be forced to delay, reduce or eliminate our product development programs or commercialization efforts.

We expect to incur significant expenses as we continue to advance our ongoing activities. We expect to execute our operating plan through major catalysts and to cash-flow positivity without the need to raise additional equity. Our estimate as to how long we expect our existing cash, cash equivalents, and marketable securities to be available to fund our operating plan is based on assumptions that may prove to be wrong, and we could use our available capital resources sooner than we currently expect. Further, changing circumstances, some of which may be beyond our control, could cause us to consume capital significantly faster than we currently anticipate, and we may need to seek additional funds. Our future capital requirements will depend on many factors, including:

- the amount of contingent consideration we ultimately receive in connection with the sale of our oncology business to Servier;
- the scope, progress, results and costs of drug discovery, preclinical development, laboratory testing and clinical trials for our product candidates;
- the costs, timing and outcome of regulatory review of our product candidates;
- the costs of preparing, filing and prosecuting patent applications, maintaining and enforcing our intellectual property rights and defending intellectual property-related claims;
- the costs and timing of future commercialization activities, including product manufacturing, sales, marketing and distribution, for any of our product candidates for which we may receive marketing approval;
- the amount and timing of revenue, if any, received from commercial sales of our product candidates for which we receive marketing approval;
- our ability to establish and maintain collaborations on favorable terms, if at all;
- our ability to successfully execute on our strategic plans;
- operational delays due to the COVID-19 pandemic; and
- the extent to which we acquire or in-license, or monitor or out-license, other medicines and technologies.

We have historically incurred operating losses. We expect to incur losses in the future and may never achieve or maintain profitability.

We have historically incurred operating losses. Our net income for the nine months ended September 30, 2021 was $1.7 billion and our net loss for the nine months ended September 30, 2020 was $229.7 million. The net income we generated in the nine months ended September 30, 2021 was primarily due to the sale of our oncology business to Servier, which was consummated on March 31, 2021. As of September 30, 2021, we had an accumulated deficit of $144.1 million. Prior to the sale of our oncology business to Servier, we had generated only modest revenue from sales of TIBSOVO® and, prior to our sale to Royalty Pharma, or RPI, of our royalty rights to IDHIFA®, royalties on sales of IDHIFA®. Other than the FDA approvals of TIBSOVO® (for the treatment of IDH1 mutant-positive adult patients with relapsed or refractory acute myeloid leukemia, R/R AML, or newly diagnosed AML who are at least 75 years old or who have comorbidities that preclude use of intensive induction chemotherapy) and IDHIFA® (for the treatment of IDH2 mutant-positive adult patients with R/R AML), the rights to both of which we have sold to Servier, we have not obtained marketing approval for any of our product candidates, all of which are in preclinical or clinical development stages. In June 2021, we submitted an NDA to the FDA for mitapivat for the treatment of adults with PK deficiency, which was accepted with priority review and granted a Prescription Drug User Fee Act, or PDUFA, action date of February 17, 2022, and a MAA, for mitapivat in adults with PK deficiency to the EMA.

We have financed our operations primarily through public offerings of our common stock and our collaboration agreements with Celgene and have devoted substantially all of our efforts to research and development. Following the sale of our oncology business to Servier on March 31, 2021, we expect to finance our operations primarily through cash on hand, royalty payments from Servier with respect to U.S. net sales of TIBSOVO®, a potential milestone payment from Servier if vorasidenib is approved by the FDA, future potential sales of mitapivat, if approved for marketing by regulatory authorities and successfully launched by us and, potentially, collaborations, strategic alliances, licensing arrangements and other nondilutive strategic transactions. We expect to continue to incur significant expenses and net losses until such time as we are able to report

profitable results. The net losses we incur may fluctuate significantly from quarter to quarter. We anticipate that we will incur significant expenses if and as we:

- initiate and continue clinical trials for our product candidates; continue our research and preclinical development of our product candidates and seek to identify additional product candidates;
- seek marketing approvals for our product candidates that successfully complete clinical trials;
- establish and maintain a sales, marketing and distribution infrastructure to commercialize any medicines for which we may obtain marketing approval;
- require the manufacture of larger quantities of product candidates for clinical development and, potentially, commercialization;
- maintain, expand and protect our intellectual property portfolio;
- add additional personnel to support our product research and development and planned future commercialization efforts and our operations;
- add equipment and physical infrastructure to support our research and development; and
- acquire or in-license other medicines and technologies.

To become and remain profitable, we must develop and eventually commercialize one or more medicines with significant market potential. This will require us to be successful in a range of challenging activities, including completing preclinical testing and clinical trials of our product candidates, obtaining marketing approval for these product candidates, manufacturing, marketing and selling those medicines for which we may obtain marketing approval and satisfying any post-marketing requirements. Notwithstanding the extent to which we may succeed in any of these activities, we may never generate revenues that are significant or large enough to achieve profitability. 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 efforts, expand our business 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.

The amount of contingent consideration we will receive from the sale of our oncology business to Servier is subject to various risks and uncertainties.

Upon closing of the sale of our oncology business to Servier, Servier assumed certain liabilities with respect to the oncology business and paid to us: approximately $1.8 billion in cash, net of certain adjustments for the working capital of the oncology business at the time of closing of the transaction and amounts for a representation and warranty insurance policy. In addition, Servier will pay to us:

- $200 million in cash if, prior to January 1, 2027, vorasidenib is granted approval for a new drug application, or NDA, from the FDA with an approved label that permits vorasidenib's use as a single agent for the adjuvant treatment of patients with Grade 2 glioma that have an IDH1 or IDH2 mutation (and, to the extent required by such approval, the vorasidenib companion diagnostic test is granted an FDA premarket approval);
- a royalty payment of 5% of the U.S. net sales (as defined in the purchase agreement with Servier) of TIBSOVO® from the completion of the transaction through loss of exclusivity of TIBSOVO®; and
- a royalty payment of 15% of the U.S. net sales (as defined in the purchase agreement with Servier) of vorasidenib from its first commercial sale through loss of exclusivity of vorasidenib.

The contingent consideration described above is subject to various risks and uncertainties.

Whether the regulatory approval milestone will be achieved prior to January 1, 2027 is subject to various risks and uncertainties, many of which are outside of the control of the parties, including adverse clinical developments with respect to vorasidenib.

In addition, we cannot predict what success, if any, Servier may have in the United States with respect to sales of TIBSOVO® and vorasidenib, if approved, and, therefore, the amount of royalty payments that we can expect to receive from Servier under the terms of the purchase agreement prior to the loss of exclusivity of these products. The royalty payments are also subject to deductions and other adjustments under the terms of the purchase agreement, the amounts of which are uncertain as of the date of this Quarterly Report on Form 10-Q.

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. On December 22, 2017, the U.S. government enacted the Tax Cuts and Jobs Act, or the Tax Act, which significantly reformed the U.S. Internal Revenue Code of 1986, as amended, or the Code. The Tax Act, among other things, contained significant changes to corporate taxation.

As part of Congress' response to the COVID-19 pandemic, the Families First Coronavirus Response Act, or FFCR Act, was enacted on March 18, 2020, the Coronavirus Aid, Relief, and Economic Security Act, or CARES Act, was enacted on March 27, 2020, and COVID-19 relief provisions were included in the Consolidated Appropriations Act, 2021, or CAA, which was enacted on December 27, 2020. All contain numerous tax provisions. Regulatory guidance under the Tax Act, the FFCR Act, the CARES Act, and the CAA is and continues to be forthcoming, and such guidance could ultimately increase or lessen impact of these laws on our business and financial condition. It is also possible that Congress will enact additional legislation in connection with the COVID-19 pandemic, some of which could have an impact on our company. In addition, it is uncertain if and to what extent various states will conform to the Tax Act, the FFCR Act, the CARES Act, or the CAA.

Risks Related to the Discovery, Development, and Commercialization of our Product Candidates

We depend heavily on the success of our clinical product candidates, including our lead product candidate mitapivat. Clinical trials of our product candidates may not be successful for a number of important reasons. If we or our collaborators are unable to commercialize our product candidates or experience significant delays in doing so, our business will be materially harmed.

Our ability to generate product revenue will depend heavily on the successful clinical development and eventual commercialization of our current and any future product candidates, including our lead product candidate mitapivat. We have invested a significant portion of our efforts and financial resources in the identification of our product candidates and development of our most advanced programs, including mitapivat, In June 2021, we submitted an NDA to the FDA for mitapivat for the treatment of adults with PK deficiency, which was accepted with priority review and granted a PDUFA action date of February 17, 2022, and a MAA, for mitapivat in adults with PK deficiency to the EMA.

We, and any collaborators, are not permitted to commercialize, market, promote or sell any product candidate in the United States without obtaining marketing approval from the FDA. Foreign regulatory authorities, such as the EMA, impose similar requirements in foreign jurisdictions. Before obtaining marketing approval from regulatory authorities for the sale of our product candidates, we must complete preclinical development and then conduct extensive clinical trials to demonstrate the safety and efficacy of our product candidates in humans.

Clinical testing is expensive, difficult to design and implement, can take many years to complete and is uncertain as to outcome. We cannot guarantee that any clinical trials will be conducted as planned or completed on schedule, if at all. The clinical development of our product candidates is susceptible to the risk of failure inherent at any stage of product development. Moreover, we, or any collaborators, may experience any of a number of possible unforeseen adverse events in connection with clinical trials, many of which are beyond our control, including:

- we, or our collaborators, may fail to demonstrate efficacy in a clinical trial or across a broad population of patients;
- it is possible that even if one or more of our product candidates has a beneficial effect, that effect will not be detected during clinical evaluation as a result of one or more of a variety of factors, including the size, duration, design, measurements, conduct or analysis of our clinical trials. Conversely, as a result of the same factors, our clinical trials may indicate an apparent positive effect of a product candidate that is greater than the actual positive effect, if any. For example, many compounds that initially showed promise in earlier stage testing for treating specific disease indications have later been found to cause side effects that prevented further development of the compound;
- our product candidates may have undesirable side effects or other unexpected characteristics or otherwise expose participants to unacceptable health risks, causing us, our collaborators or our investigators, regulators or institutional review boards or the data safety monitoring board for such trial to halt, delay, interrupt, suspend or terminate the trials or cause us, or any collaborators, to abandon development or limit development of that product candidate 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;
- if our product candidates have undesirable side effects, it could result in a more restrictive label, or it could result in the delay or denial of marketing approval by the FDA or comparable foreign regulatory authorities;
- clinical trials of our product candidates may produce negative or inconclusive results, and we, or our collaborators, may decide, or regulators may require us, to conduct additional clinical trials, including testing in more subjects, or abandon product development programs;
- regulators or institutional review boards may not authorize us, our collaborators or our investigators to commence a clinical trial or conduct a clinical trial at a prospective trial site;

- we or our collaborators may have delays in reaching or fail to reach agreement on acceptable clinical trial contracts or clinical trial protocols with prospective trial sites;
- the number of patients required for clinical trials of our product candidates may be larger than we anticipate; enrollment in these clinical trials, which may be particularly challenging for some of the orphan diseases we target in our GDD programs, may be slower than we anticipate; or participants may drop out of these clinical trials at a higher rate than we anticipate;
- third-party contractors used by us or our collaborators may fail to comply with regulatory requirements or meet their contractual obligations in a timely manner, or at all;
- significant preclinical study or clinical trial delays could shorten any periods during which we, or any collaborators, may have the exclusive right to commercialize our product candidates or allow our competitors, or the competitors of any collaborators, to bring products to market before we, or any collaborators, do;
- the cost of clinical trials of our product candidates may be greater than anticipated; and,
- the supply or quality of our product candidates or other materials necessary to conduct clinical trials of our product candidates may be insufficient or inadequate.

In December 2016, we withdrew our IND for AG-519, our second PKR activator, following verbal notification of a clinical hold from the FDA relating to a previously disclosed case of drug-induced cholestatic hepatitis which occurred in our phase 1 clinical trial of AG-519 in healthy volunteers. Although these decisions and this hepatic adverse event finding do not affect our ongoing clinical trials for mitapivat, our first PKR activator, we cannot provide any assurances that there will not be similar or other treatment-related severe adverse events in our other clinical trials of mitapivat, that our other trials will not be placed on clinical hold in the future, or that patient recruitment for our other trials will not be adversely impacted.

Our failure to successfully begin and complete clinical trials of our product candidates and to demonstrate the efficacy and safety necessary to obtain regulatory approval to market any of our product candidates could result in additional costs to us, or any collaborators, would impair our ability to generate revenue from product sales, regulatory and commercialization milestones and royalties and would significantly harm our business.

We may not be successful in our efforts to identify or discover potential product candidates or to develop medicines of commercial value and we may not achieve our goals included in our strategic vision.

A key element of our strategy is to identify and test compounds that target cellular metabolism and adjacent areas of biology in a variety of different types of GDDs. A significant portion of the research that we are conducting involves new compounds and drug discovery methods, including our proprietary technology. The drug discovery that we are conducting using our proprietary technology may not be successful in identifying compounds in our therapeutic areas. In addition, 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 appropriate biomarkers or potential product candidates; or
- 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 medicines that will receive marketing approval and achieve market acceptance.

Research programs to identify new product candidates require substantial technical, financial and human resources. We may choose to focus our efforts and resources on a potential product candidate that ultimately proves to be unsuccessful.

If we are unable to identify suitable compounds for preclinical and clinical development, or any medicines we develop do not effectively correct metabolic pathways or alter the metabolic state of immune cells, we will not be able to achieve our strategic vision and our specific long-term goals and will not be able generate product revenue in future periods, which likely would result in significant harm to our financial position and adversely impact our stock price.

The COVID-19 pandemic has and may continue to affect our ability to initiate or continue our planned, ongoing and future clinical trials, disrupt regulatory activities, or have other adverse effects on our business and operations. In addition, this pandemic may continue to adversely impact economies worldwide, which could result in adverse effects on our business and operations.

In response to the COVID-19 pandemic, we were required to close our facilities except for a limited number of essential facilities and laboratory staff. We recently opened our Cambridge office to employees who prefer to work onsite all or some of the time, and our field-based employees engage with healthcare providers and other third parties remotely and, where local regulations allow, on a limited in-person basis. Effective November 8, 2021, we will require all employees, regardless of role or work location, to be fully vaccinated against COVID-19, as defined by CDC guidelines, subject to limited exceptions.

We may face disruptions that may affect our ability to initiate and complete clinical trials including disruptions in procuring items that are essential for our research and development activities, including, for example, raw materials used in the manufacturing of our product candidates and laboratory supplies for planned and ongoing clinical trials, in each case, for which there may be shortages because of ongoing efforts to address the outbreak. We have enrolled, and seek to enroll, patients in our clinical trials at sites located both in the United States and internationally. Site initiation, participant recruitment and enrollment, participant dosing, distribution of clinical trial materials, study monitoring and data analysis has been and may continue to be paused or delayed due to changes in hospital or university policies, federal, state or local regulations, prioritization of hospital resources toward pandemic efforts, or other reasons related to the pandemic. We have faced and expect to continue to face difficulties recruiting or retaining patients in our ongoing clinical trials because of the pandemic. Patients enrolled in our clinical trials may be unable or unwilling to visit clinical trial sites which may impact the collection of important clinical trial data and has, and may continue to, necessitate remote data verification. In addition, limitations in the ability to visit sites has affected, and may continue to adversely affect, our enrollment timelines for our clinical trials, and may adversely affect the timing of completion of our clinical trials or our ability to complete clinical trials in a fully compliant manner. Additionally, the potential suspension of clinical trial activity at clinical trial sites may have an adverse impact on our clinical trial plans and timelines.

We have faced and may continue to face disruptions in our ability to prepare and submit applications to regulatory authorities for drug approvals and to build and maintain a commercial infrastructure for our product candidates. We may face manufacturing disruptions or disruptions related to the ability to obtain necessary institutional review board or other necessary site approvals, as well as other delays at clinical trial sites.

The response to the COVID-19 pandemic may redirect resources with respect to regulatory and intellectual property matters in a way that would adversely impact our ability to progress regulatory approvals and protect our intellectual property. In addition, we may face impediments to regulatory meetings and approvals due to measures intended to limit in-person interactions.

The COVID-19 pandemic may continue to significantly impact economies and financial markets worldwide, which could result in adverse effects on our business and operations, impact our ability to raise additional funds through public offerings and impact the volatility of our stock price and trading in our stock. We cannot be certain what the overall impact of the COVID-19 pandemic will be on our business and it has the potential to adversely affect our business, financial condition, results of operations, and prospects.

If we experience delays or difficulties in the enrollment of patients in clinical trials, our receipt of necessary regulatory approvals could be delayed or prevented.

We or our collaborators may not be able to initiate or continue clinical trials for our product candidates if we or they are unable to locate and enroll a sufficient number of eligible patients to participate in these trials as required by the FDA or analogous regulatory authorities outside the United States. Furthermore, enrollment has been and may continue to be particularly challenging in light of the ongoing COVID-19 pandemic and even more so for some of the orphan diseases we target in our GDD programs.

Patient enrollment is also affected by other factors including:

- prevalence and severity of the disease under investigation;
- availability and efficacy of approved medications for the disease under investigation;
- eligibility criteria for the study in question;
- perceived risks and benefits of the product candidate under study;
- efforts to facilitate timely enrollment in clinical trials;
- patient referral practices of physicians;
- the ability to monitor patients adequately during and after treatment; and
- proximity and availability of clinical trial sites for prospective patients.

Utilizing our precision medicine approach, we generally focus our development activities on genetically or biomarker defined patients most likely to respond to our therapies. As a result, the potential patient populations for our clinical trials are narrowed, and we may experience difficulties in identifying and enrolling a sufficient number of patients in our clinical trials.

In addition, some of our competitors may have ongoing or planned clinical trials for product candidates that would treat the same indications as our product candidates, and patients who would otherwise be eligible for our clinical trials may instead enroll in clinical trials of our competitors' product candidates. For example, Rocket Pharma LTD, or Rocket Pharma, is developing a gene therapy targeting PK deficiency; Vertex Pharmaceuticals Incorporated, or Vertex, is developing a gene therapy targeting SCD; IMARA Inc., or IMARA, and Forma Therapeutics Holdings, Inc., or Forma, are developing molecules for the treatment of beta thalassemia and SCD; and Global Blood Therapeutics is developing molecules for the treatment of

SCD. Competition for eligible patients may make it particularly difficult for us to enroll enough patients to complete our clinical trials for our product candidates in a timely and cost-effective manner.

We rely on contract research organization, or CROs, and clinical trial sites to ensure the proper and timely conduct of our clinical trials and while we have agreements governing their committed activities, we have limited influence over their actual performance. Our or our collaborators' inability to enroll a sufficient number of patients for our clinical trials would result in significant delays or may require us to abandon one or more clinical trials altogether. Enrollment delays in our clinical trials may result in increased development costs for our product candidates, which would cause the value of our company to decline and limit our ability to obtain additional financing.

Results of preclinical studies and early clinical trials may not be predictive of results of future clinical trials.

The outcome of preclinical studies and early clinical trials may not be predictive of the success of later clinical trials, and interim results of clinical trials do not necessarily predict success in future clinical trials. Many companies in the pharmaceutical and biotechnology industries have suffered significant setbacks in late-stage clinical trials after achieving positive results in earlier development, and we could face similar setbacks. The design of a clinical trial can determine whether its results will support approval of a product and flaws in the design of a clinical trial may not become apparent until the clinical trial is well advanced. We have limited experience in designing clinical trials and may be unable to design and execute a clinical trial to support marketing approval. In addition, preclinical and clinical data are often susceptible to varying interpretations and analyses. Many companies that believed their product candidates performed satisfactorily in preclinical studies and clinical trials have nonetheless failed to obtain marketing approval for the product candidates. Even if we, or any collaborators, believe that the results of clinical trials for our product candidates warrant marketing approval, the FDA or comparable foreign regulatory authorities may disagree and may not grant marketing approval of our product candidates.

In some instances, there can be significant variability in safety or efficacy results between different clinical trials of the same product candidate due to numerous factors, including changes in trial procedures set forth in protocols, differences in the size and type of the patient populations, changes in and adherence to the dosing regimen and other clinical trial protocols and the rate of dropout among clinical trial participants. If we fail to receive positive results in clinical trials of our product candidates, the development timeline and regulatory approval and commercialization prospects for our most advanced product candidates, and, correspondingly, our business and financial prospects would be negatively impacted.

We may expend our limited resources to pursue a particular product candidate or indication and fail to capitalize on product candidates or indications that may be more profitable or for which there is a greater likelihood of success.

Because we have limited financial and managerial resources, we focus 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 medicines or profitable market opportunities. Our spending on current and future research and development programs and product candidates for specific indications may not yield any commercially viable medicines. 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 successfully develop companion diagnostics for our product candidates, or experience significant delays in doing so, we may not realize the full commercial potential of our therapeutics.

Because we are focused on precision medicine, in which predictive biomarkers will be used to identify the right patients for our drug candidates, we believe that our success will depend, in part, on our ability to develop companion diagnostics, which are assays or tests to identify an appropriate patient population for these drug candidates. There has been limited success to date industry-wide in developing these types of companion diagnostics. To be successful, we need to address a number of scientific, technical and logistical challenges. We have little experience in the development of diagnostics and may not be successful in developing appropriate diagnostics to pair with any of our therapeutic product candidates that receive marketing approval. Companion diagnostics are subject to regulation by the FDA and similar regulatory authorities outside the United States as medical devices and require separate regulatory approval prior to commercialization. Given our limited experience in developing diagnostics, we rely and expect to continue to rely in part or in whole on third parties for their design and manufacture. We also may in the future depend on other third parties for the development of other companion diagnostics for

our therapeutic product candidates. If we or our collaborators are unable to successfully develop companion diagnostics for our therapeutic product candidates, or experience delays in doing so:

- the development of our therapeutic product candidates may be adversely affected if we are unable to appropriately select patients for enrollment in our clinical trials;
- our therapeutic product candidates may not receive marketing approval if safe and effective use of a therapeutic product candidate depends on an *in vitro* diagnostic; and
- we may not realize the full commercial potential of any therapeutics that receive marketing approval if, among other reasons, we are unable to appropriately select patients who are likely to benefit from therapy with our medicines.

As a result of any of these events, our business would be harmed, possibly materially.

Even if any of our product candidates receives marketing approval, we or others may later discover that the product is less effective than previously believed or causes undesirable side effects that were not previously identified, which could compromise our ability, or that of any collaborators, to market the product.

It is possible that our clinical trials, or those of any collaborators, may indicate an apparent positive effect of a product candidate that is greater than the actual positive effect, if any, or alternatively fail to identify undesirable side effects. If, following approval of a product candidate, we, or others, discover that the product is less effective than previously believed or causes undesirable side effects that were not previously identified, any of the following adverse events could occur:

- regulatory authorities may withdraw their approval of the product or seize the product;
- we, or any collaborators, may be required to recall the product, change the way the product is administered or conduct additional clinical trials;
- additional restrictions may be imposed on the marketing of, or the manufacturing processes for, the particular product;
- we may be subject to fines, injunctions or the imposition of civil or criminal penalties;
- regulatory authorities may require the addition of labeling statements;
- we, or any collaborators, may be required to create a Medication Guide outlining the risks of the previously unidentified side effects for distribution to patients;
- we, or any collaborators, could be sued and held liable for harm caused to patients;
- the product may become less competitive; and
- our reputation may suffer.

Even if any of our product candidates receive marketing approval, they may fail to achieve the degree of market acceptance by physicians, patients, healthcare payors and others in the medical community necessary for commercial success.

Even if any of our product candidates receive marketing approval in the future, they may fail to gain and/or maintain sufficient market acceptance by physicians, patients, healthcare payors and others in the medical community. If our product candidates do not achieve an adequate level of acceptance, we may not generate significant product revenue and we may not become profitable. The degree of market acceptance of our product candidates, if approved for commercial sale, will depend on a number of factors, including:

- efficacy and potential advantages compared to alternative treatments;
- the approval, availability, market acceptance and reimbursement for the companion diagnostic;
- the ability to offer our medicines for sale at competitive prices;
- convenience and ease of administration compared to alternative treatments;
- the willingness of the target patient population to try new therapies and of physicians to prescribe these therapies;
- ensuring uninterrupted product supply;
- the strength of marketing and distribution support;
- sufficient third-party coverage or reimbursement; and
- the prevalence and severity of any side effects.

If we are unable to establish and maintain sales and marketing capabilities or enter into agreements with third parties to sell and market our product candidates, we may not be successful in commercializing our product candidates if and when they are approved.

We have limited experience in the sale, marketing or distribution of pharmaceutical products. To achieve commercial success for approved medicines for which we retain sales and marketing responsibilities, we must either develop a sales and marketing organization or outsource these functions to other third parties. Although we had established sales and marketing capabilities to

support our co-promotion efforts for IDHIFA® and our sales of TIBSOVO® prior to the sale of our oncology business to Servier, we are again in the process of building our sales and marketing infrastructure to sell, or participate in sales activities with any collaborators for, our other product candidates if and when they are approved.

There are risks involved with both establishing our own sales and marketing capabilities and entering into arrangements with third parties to perform these services. For example, recruiting and training a sales force is expensive and time consuming and could delay any product launch. If the commercial launch of a product candidate for which we recruit a sales force and establish marketing capabilities is delayed or does not occur for any reason, we would have prematurely or unnecessarily incurred these 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 commercialize our medicines on our own include:

- our inability to recruit and retain adequate numbers of effective sales and marketing personnel;
- the inability of sales personnel to obtain access to physicians or persuade adequate numbers of physicians to prescribe any future medicines;
- the lack of complementary medicines to be offered by sales personnel, which may put us at a competitive disadvantage relative to companies with more extensive product lines; and
- unforeseen costs and expenses associated with creating an independent sales and marketing organization.

If we enter into arrangements with third parties to perform sales, marketing and distribution services, our product revenue or the profitability of product revenue to us are likely to be lower than if we were to market and sell any medicines that we develop ourselves. In addition, we may not be successful in entering into arrangements with third parties to sell and market our product candidates or may be unable to do so on terms that are favorable to us. We likely will have little control over such third parties, and any of them may fail to devote the necessary resources and attention to sell and market our medicines effectively. If we do not establish sales and marketing capabilities successfully, either on our own or in collaboration with third parties, we will not be successful in commercializing our product candidates.

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

We face competition with respect to our current product candidates, and we and our collaborators will face competition with respect to any product candidates that we or they may seek to develop or commercialize in the future. Potential competitors include major pharmaceutical companies, specialty pharmaceutical companies, biotechnology companies, academic institutions, government agencies and other public and private research organizations that conduct research, seek patent protection and establish collaborative arrangements for research, development, manufacturing and commercialization. There are a number of large pharmaceutical and biotechnology companies that currently market and sell products or are pursuing the development of products for the treatment of the disease indications for which we are developing our product candidates, such as PK deficiency, thalassemia and SCD. For example, Acceleron Pharma Inc. (in collaboration with Bristol-Myers Squibb Company) and bluebird bio, Inc., or bluebird, are each marketing therapies to treat beta thalassemia, Novartis International AG, Emmaus Life Sciences and Global Blood Therapeutics are each marketing therapies to treat SCD, Rocket Pharma is conducting a clinical trial of a gene therapy targeting PK deficiency, and a number of other biotechnology companies have product candidates in clinical development in similar indications as ours.

We are developing product candidates to treat patients with GDDs. There are a variety of treatment options available, including a number of marketed enzyme replacement therapies, for treating patients with GDDs. In addition to currently marketed therapies, there are also a number of products that are either enzyme replacement therapies, gene therapies or PK activators in various stages of clinical development to treat GDDs. These products in development may provide efficacy, safety, convenience and other benefits that are not provided by currently marketed therapies or for which there are no approved treatments. As a result, they may provide significant competition for any of our product candidates for which we obtain marketing approval.

There are also a number of product candidates in preclinical or clinical development by third parties to treat GDDs by targeting similar mechanisms of action as our product candidates. These companies include large pharmaceutical companies, such as Novartis, as well as biotechnology companies of various sizes, such as BioMarin Pharmaceutical Inc., bluebird, Forma, IMARA, PTC Therapeutics, Inc., Rocket Pharma, and Vertex. Our competitors may develop products that are more effective, safer, more convenient or less costly than any that we are developing or that would render our product candidates obsolete or non-competitive. In addition, our competitors may discover biomarkers that more efficiently measure metabolic pathways than our methods, which may give them a competitive advantage in developing potential products. Our competitors may also obtain marketing approval from the FDA or other regulatory authorities for their products more rapidly than we may obtain approval for ours, which could result in our competitors establishing a strong market position before we are able to enter the market.

Many of our competitors have significantly greater financial resources and expertise in research and development, manufacturing, preclinical testing, conducting clinical trials, obtaining regulatory approvals and marketing approved products than we do. 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 clinical 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 necessary for, our programs.

If the FDA does not grant our products, if and when approved, appropriate periods of data exclusivity before approving generic versions of our products, the sales of our products could be adversely affected.

With FDA approval of an NDA, the product covered by the application is specified as a "reference-listed drug" in the FDA's publication, "Approved Drug Products with Therapeutic Equivalence Evaluations," or the Orange Book. Manufacturers may seek approval of generic versions of reference-listed drugs through submission of abbreviated new drug applications, or ANDAs, in the United States. In support of an ANDA, a generic manufacturer need not conduct clinical trials. Rather, the applicant generally must show that its product has the same active ingredient(s), dosage form, strength, route of administration and conditions of use or labeling as the reference-listed drug and that the generic version is bioequivalent to the reference-listed drug, meaning it is absorbed in the body at the same rate and to the same extent. Generic products may be significantly less costly to bring to market than the reference-listed drug and companies that produce generic products are generally able to offer them at lower prices. Thus, following the introduction of a generic drug, a significant percentage of the sales of any reference-listed drug may be typically lost to the generic product.

The FDA may not approve an ANDA for a generic product until any applicable period of non-patent exclusivity for the reference-listed drug has expired. The Federal Food, Drug, and Cosmetic Act, or FDCA, provides a period of five years of non-patent exclusivity for a new drug containing a new chemical entity. Specifically, in cases where such exclusivity has been granted, an ANDA may not be filed with the FDA until the expiration of five years unless the submission is accompanied by a Paragraph IV certification that a patent covering the reference-listed drug is either invalid or will not be infringed by the generic product, in which case the applicant may submit its application four years following approval of the reference-listed drug. The FDCA also provides a period of three years of new clinical investigation data exclusivity in connection with the approval of a supplemental indication for the product for which a clinical trial is essential for approval.

In the event that a generic manufacturer is somehow able to obtain FDA approval without adherence to these periods of data exclusivity, the competition that our approved products may face from generic versions could negatively impact our future revenue, profitability and cash flows and substantially limit our ability to obtain a return on our investments in those product candidates.

Product liability lawsuits against us or any collaborators could cause us or our collaborators to incur substantial liabilities and could limit commercialization of any medicines that we or they may develop.

We and any collaborators face a risk of product liability exposure related to our product candidates in human clinical trials and will face an even greater risk as we or they commercially sell any medicines. If we or any collaborators cannot successfully defend ourselves or themselves against claims that our product candidates or medicines caused injuries, we or they could incur substantial costs and liabilities. Regardless of merit or eventual outcome, liability claims may also result in, among other thing, decreased demand for any product candidates or medicines that we may develop, reputational harm and lost revenue.

Although we maintain product liability insurance coverage, it may not be adequate to cover all liabilities that we may incur.

Our internal computer systems, or those of any third parties with which we contract, may fail or suffer security breaches, which could result in a material disruption of our product development programs.

Despite the implementation of security measures, our internal computer systems and those of third parties with which we contract are vulnerable to damage from computer viruses, worms and other destructive or disruptive software, unauthorized access, natural disasters, 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 information of our employees.

System failures, accidents, cyber incidents or security breaches could cause interruptions in our operations, and could result in a material disruption of our clinical and commercialization activities and business operations, whether due to a loss of our trade secrets or other proprietary information or other similar disruptions, in addition to possibly requiring substantial expenditures of resources to remedy. For example, the loss of clinical trial data from completed or future 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 competitive position could be harmed and our product research, development and commercialization efforts could be delayed. In addition, we may not have adequate insurance coverage to provide compensation for any losses associated with such events.

If a material breach of our security or that of our vendors occurs, the market perception of the effectiveness of our security measures could be harmed, we could lose business and our reputation and credibility could be damaged. We could be required to expend significant amounts of money and other resources to repair or replace information systems or networks. Although we develop and maintain systems and controls designed to prevent these events from occurring, and we have a process to identify and mitigate threats, 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, despite our efforts, the possibility of these events occurring cannot be eliminated entirely.

Compliance with global privacy and data security requirements could result in additional costs and liabilities to us or inhibit our ability to collect and process data globally, and the 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.

The regulatory framework for the collection, use, safeguarding, sharing, transfer and other processing of information worldwide is rapidly evolving and is likely to remain uncertain for the foreseeable future. Globally, virtually every jurisdiction in which we operate has established its own data security and privacy frameworks with which we must comply. For example, the collection, use, disclosure, transfer, or other processing of personal data regarding individuals in the European Union, including personal health data, is subject to EU General Data Protection Regulation, or the GDPR, which applies to all member states of the European Economic Area, or EEA. The GDPR is wide-ranging in scope and imposes numerous requirements on companies that process personal data. The GDPR imposes significant obligations on us with respect to clinical trials conducted in the EEA. In addition, the GDPR also imposes strict rules on the transfer of personal data to countries outside the EU, including the United States and, as a result, increases the scrutiny that clinical trial sites located in the EEA should apply to transfers of personal data from such sites to countries that are considered to lack an adequate level of data protection, such as the United States. The GDPR also permits data protection authorities to require destruction of improperly gathered or used personal information and/or impose substantial fines for violations of GDPR, and it also confers a private right of action on data subjects and consumer associations to lodge complaints with supervisory authorities, seek judicial remedies and obtain compensation for damages resulting from violations of GDPR. In addition, the GDPR provides that EU member states may make their own further laws and regulations limiting the processing of personal data, including genetic, biometric or health data.

Given the breadth and depth of changes in data protection obligations, preparing for and complying with the GDPR's requirements is rigorous and time intensive and requires significant resources and a review of our technologies, systems and practices, as well as those of any third-party collaborators, service providers, contractors or consultants that process or transfer personal data collected in the EU. The GDPR and other changes in laws or regulations associated with the enhanced protection of certain types of sensitive data, such as healthcare data or other personal information from our clinical trials, could require us to change our business practices and put in place additional compliance mechanisms, may interrupt or delay our development, regulatory and commercialization activities and increase our cost of doing business, and could lead to government enforcement actions, private litigation and significant fines and penalties against us and could have a material adverse effect on our business, financial condition or results of operations. Similarly, failure to comply with federal and state laws regarding privacy and security of personal information could expose us to fines and penalties under such laws. 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 reputation and our business.

Similar privacy and data security requirements are either in place or underway in the United States. There are a broad variety of data protection laws that are applicable to our activities, and a wide range of enforcement agencies at both the state and federal levels that can review companies for privacy and data security concerns based on general consumer protection laws. The Federal Trade Commission and state Attorneys General all are aggressive in reviewing privacy and data security protections for consumers. New laws also are being considered at both the state and federal levels. For example, the California Consumer Privacy Act, which went into effect on January 1, 2020, is creating similar risks and obligations as those created by GDPR, though the California Consumer Privacy Act does exempt certain information collected as part of a clinical trial subject to the Federal Policy for the Protection of Human Subjects (the Common Rule). Many other states are considering similar legislation. A broad range of legislative measures also have been introduced at the federal level. Accordingly, failure to comply with

current and any future federal and state laws regarding privacy and security of personal information could expose us to fines and penalties. We also face a threat of consumer class actions related to these laws and the overall protection of personal data. 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 reputation and our business.

Risks Related to Our Dependence on Third Parties

We may depend on collaborations with third parties for the development and commercialization of our product candidates. If those collaborations are not successful, we may not be able to capitalize on the market potential of these product candidates.

We may seek collaborations for the development and commercialization of our product candidates with large and mid-size pharmaceutical companies and biotechnology companies. We face significant competition in seeking appropriate collaborators. Collaborations are complex and time-consuming to negotiate and document. Whether we reach a definitive agreement for a collaboration will depend, among other things, upon our assessment of the collaborator's resources and expertise, the terms and conditions of the proposed collaboration and the proposed collaborator's evaluation of a number of factors. We may not be able to negotiate collaborations on a timely basis, on acceptable terms, or at all. Collaborators may have rights that restrict us from entering into future agreements on certain terms with potential collaborators.

If we enter into any such arrangements with collaborators, we will likely have limited control over the amount and timing of resources that our collaborators dedicate to the development or commercialization of our product candidates. Collaborators may not pursue development and commercialization of our product candidates or may elect not to continue or renew development 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, which may result in a need for additional capital to pursue further development or commercialization of the applicable product candidate. 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 proprietary information or expose us to potential litigation. Disputes may arise between the collaborators and us that result in the delay or termination of the research, development or commercialization of our medicines or product candidates or that result in costly litigation or arbitration that diverts management attention and resources.

Our ability to generate revenue from these arrangements will depend on our collaborators' abilities to successfully perform the functions assigned to them in these arrangements.

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

We do not independently conduct clinical trials of any of our product candidates. We rely and expect to continue to rely on third parties, such as CROs, clinical data management organizations, medical institutions and clinical investigators, to conduct our clinical trials. In addition, we currently rely and expect to continue to rely on third parties to conduct some aspects of our research and preclinical testing. Any of these third parties may terminate their engagements with us, some in the event of an uncured material breach and some at any time. If any of our relationships with these third parties terminate, we may not be able to enter into similar arrangements with alternative third-parties or to do so on commercially reasonable terms. Switching or adding additional third parties involves additional cost and requires management time and focus. As a result, delays may occur in our product development activities. Although we seek to carefully manage our relationships with our CROs, we could encounter such challenges or delays that could have a material adverse impact on our business, financial condition and prospects.

Our reliance on third parties for research and development activities reduces our control over these activities but does not relieve us of our responsibilities. For example, we are responsible for ensuring that each of our studies is conducted in accordance with the applicable protocol and legal, regulatory and scientific standards, and our reliance on third parties does not relieve us of our responsibility to comply with any such standards. We and these third parties are required to comply with current good clinical practices, or cGCP, which are regulations and guidelines enforced by the FDA, the Competent Authorities of the Member States of the European Economic Area and comparable foreign regulatory authorities for all of our product candidates in clinical development. Regulatory authorities enforce these cGCPs through periodic inspections of trial sponsors, principal investigators and trial sites. If we or any of these third parties fail to comply with applicable cGCPs, the clinical data generated in our clinical trials may be deemed unreliable and the FDA, the EMA, or comparable foreign regulatory authorities may require us to perform additional clinical trials before approving our marketing applications. We cannot assure you a given regulatory authority will determine that any of our clinical trials comply with cGCP regulations. We also are required to register

ongoing clinical trials and post the results of completed clinical trials on a U.S. government-sponsored database, clinicaltrials.gov, within certain timeframes. Failure to do so can result in fines, adverse publicity and civil and criminal sanctions.

Furthermore, third parties on whom we rely may also have relationships with other entities, some of which may be our competitors. In addition, these third parties are not our employees, and except for remedies available to us under our agreements with such third parties, we cannot control whether or not they devote sufficient time and resources to our on-going clinical, nonclinical and preclinical programs.

If these third parties do not successfully carry out their contractual duties or obligations or meet expected deadlines, if they need to be replaced or if the quality or accuracy of the clinical data they obtain is compromised, our clinical trials may be extended, delayed or terminated and we may 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 medicines.

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

We contract with third parties for the manufacture of our product candidates for preclinical and clinical testing and we expect to contract with third parties for the manufacture of our product candidates for commercialization.

We do not have any manufacturing facilities. We currently rely, and expect to continue to rely, on third-party manufacturers for the materials and manufacture of our product candidates for preclinical and clinical testing and expect to rely on third-party manufacturers for commercial supply of any product candidate for which we or our collaborators obtain marketing approval.

Although we expect to complete long-term supply agreements for commercial supply of mitapivat with third-party manufacturers ahead of a potential regulatory approval, we may be unable to establish similar long-term supply agreements with third-party manufacturers with respect to our other GDD product candidates or to do so on acceptable terms. Even if we are able to establish agreements with third-party manufacturers, reliance on third-party manufacturers entails additional risks, including:

- reliance on the third party for regulatory compliance, quality assurance, environmental and safety and pharmacovigilance reporting;
- the possible breach of the manufacturing agreement by the third party; and
- the possible termination or nonrenewal of the agreement by the third party at a time that is costly or inconvenient for us.

Third-party manufacturers may not be able to comply with current good manufacturing practices, or cGMP. regulations or similar regulatory requirements on a global basis. Our failure, or the failure of our third-party manufacturers, to comply with applicable regulations could result in sanctions being imposed on us, including fines, injunctions, civil penalties, delays, suspension or withdrawal of approvals, license revocation, seizures or recalls of product candidates or medicines, operating restrictions and criminal prosecutions, any of which could significantly and adversely affect supplies of our medicines and harm our business and results of operations.

We have been monitoring our supply chain network for any disruptions due to the COVID-19 pandemic, and our manufacturers have remained largely unaffected, with any campaign delays experienced to date being limited to a few days in duration. Although global shipping continues to be disrupted due to the pandemic, we have not yet experienced a supply impact. If either we or any third parties on which we rely are adversely impacted by restrictions resulting from the COVID-19 pandemic, our supply chain may be disrupted, limiting our ability to manufacture our product candidates for our clinical trials and research and development operations.

Any performance failure on the part of our existing or future manufacturers could delay clinical development or marketing approval. We do not currently have arrangements in place for redundant supply for drug product. If any one of our current contract manufacturers cannot perform as agreed, we may be required to replace that manufacturer. Although we believe that there are several potential alternative manufacturers who could manufacture our product candidates, we may incur added costs and delays in identifying and qualifying any such replacement.

Our current and anticipated future dependence upon others for the manufacture of our product candidates or medicines may adversely affect our future profit margins and our ability to commercialize any medicines that receive marketing approval on a timely and competitive basis.

Risks Related to Our Intellectual Property

If we are unable to obtain and maintain patent or trade secret protection for our medicines and technology, or if the scope of the patent protection obtained is not sufficiently broad, our competitors could develop and commercialize medicines and technology similar or identical to ours, and our ability to successfully commercialize our medicines and technology may be adversely affected.

Our success depends in large part on our ability to obtain and maintain patent protection in the United States and other countries with respect to our proprietary medicines and technology. We seek to protect our proprietary position by filing patent applications in the United States and abroad related to our novel technologies and medicines that are important to our business. We do not yet have issued patents for all our most advanced product candidates in all markets in which we intend to commercialize but we continue to actively pursue patent protection for our assets around the world.

The patent prosecution process is costly 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 and/or file patent applications on every aspect of our research and development output that is or may be eligible for patent protection. Although we enter into non-disclosure and confidentiality agreements with parties who may have access to patentable aspects of our research and development output, such as our employees, corporate collaborators, outside scientific collaborators, contract research organizations, contract manufacturers, consultants, advisors and other third parties, any of these parties may breach the agreements and disclose such output before a patent application is filed, thereby jeopardizing our ability to seek patent protection. There is also the possibility that loss or theft of data or records may jeopardize the ability to seek patent protection or impede the progress or drafting of patent applications.

We have licensed patent rights, and in the future may license additional patent rights, from third parties. Such licenses may be accompanied by milestone and/or royalty payment obligations. These licensed patent rights may be valuable to our business, and we may not have the right to control the preparation, filing and prosecution of patent applications, or to maintain the patents, covering technology or medicines underlying such licenses. We cannot be certain that these patents and applications will be prosecuted and enforced in a manner consistent with the best interests of our business. If any such licensors fail to maintain such patents, or lose rights to those patents, the rights we have licensed may be reduced or eliminated and our right to develop and commercialize any of our products that are the subject of such licensed rights could be adversely affected. In addition to the foregoing, the risks associated with patent rights that we license from third parties also apply to patent rights we own.

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 that protect our technology or medicines or that effectively prevent others from commercializing competitive technologies and medicines. Changes in either the patent laws or interpretation of the patent laws in the United States and other countries may diminish the value of our patents or narrow the scope of our patent protection. The laws of foreign countries may not protect our rights to the same extent as the laws of the United States. Publications of discoveries in the scientific literature often lag behind the actual discoveries, and patent applications in the United States and other jurisdictions are typically not published until 18 months after filing, or in some cases not at all. Therefore we cannot be certain that we were the first to make the inventions claimed in our owned or licensed 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 United States, the first to make the claimed invention was entitled to the patent, while outside the United States, the first to file a patent application was entitled to the patent. Beginning in March 2013, the United States 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 will be entitled to the patent. We may be subject to a third-party pre-issuance submission of prior art to the U.S. Patent and Trademark Office, or USPTO, or become involved in opposition, derivation, revocation, reexamination, post-grant and 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 technology or products and compete directly with us, without payment to us, or result in our inability to manufacture or commercialize medicines 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 or other third parties from competing with us or otherwise provide us with any competitive

advantage. Our competitors or other third parties may be able to circumvent our patents by developing similar or alternative technologies or products 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 United States and abroad. Such challenges may result in loss of the patent or in one or more patent claims being narrowed or invalidated, which could limit our ability to stop others from using or commercializing similar or identical technology and products, or limit the duration of the patent protection of our technology and medicines. Given the significant amount of time required for the discovery, development, preclinical and clinical testing and regulatory review and approval of new product candidates, patents protecting such candidates might expire before or shortly after such candidates are commercialized. As a result, our intellectual property may not provide us with sufficient rights to exclude others from commercializing products similar or identical to ours. In such circumstances we would be relying primarily on regulatory or marketing exclusivity to exclude others from commercializing a generic version of our products.

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 may infringe our patents and other intellectual property rights. To counter infringement or unauthorized use, we may be required to file infringement claims, which can be expensive and time consuming. In addition, in an infringement proceeding, a court may decide that a patent of ours is invalid or unenforceable, or may refuse to stop the other party from using the technology at issue on the grounds that our patents do not cover the technology in question. An adverse result in any litigation proceeding 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 or our collaborators 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.

The biotechnology and pharmaceutical industries are characterized by extensive litigation regarding patents and other intellectual property rights. Our commercial success depends upon our ability and the ability of our collaborators to develop, manufacture, market and sell our product candidates and use our proprietary technologies without infringing the proprietary rights and intellectual property of third parties. We have in the past and may in the future become party to, or threatened with, adversarial proceedings or litigation regarding intellectual property rights with respect to our medicines and technology, including opposition, derivation, revocation, reexamination, post-grant and inter partes review or interference proceedings before the USPTO or other patent offices around the world. For example, in 2011, The Leonard and Madlyn Abramson Family Cancer Research Institute at the Abramson Cancer Center of the University of Pennsylvania initiated a lawsuit against us, one of our founders, Craig B. Thompson, M.D., and Celgene, alleging misappropriation of intellectual property and, in 2012, the Trustees of the University of Pennsylvania initiated a similar lawsuit against us and Dr. Thompson. Each of these lawsuits was settled in 2012. We are not aware of any other legal proceedings having been filed against us to date. Third parties may assert infringement claims against us based on existing patents or patents that may be granted in the future. If we or one of our collaborators are found to infringe a third party's intellectual property rights, we or they could be required to obtain a license from such third party to continue developing and marketing our medicines and technology. However, we or our collaborators may not be able to obtain any required license on commercially reasonable terms or at all. Even if we or our collaborators were able to obtain a license, it could be non-exclusive, thereby giving our competitors and other third parties access to the same technologies licensed to us. We or our collaborators could be forced, including by court order, to cease developing and commercializing the infringing technology or medicine. In addition, we or our collaborators could be found liable for monetary damages. A finding of infringement could prevent us or our collaborators from commercializing our product candidates or force us to cease some of our business operations, which could materially harm our business. Claims that we or our collaborators 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, consultants or advisors are currently or were previously employed at universities or other biotechnology or pharmaceutical companies, including our competitors or potential competitors. Although we try to ensure that our employees, consultants and advisors 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 individuals have used or disclosed intellectual property, including trade secrets or other proprietary information, of any such individual's current or former employer. Litigation may be necessary to defend against these claims. If we fail in defending any such claims, in addition to paying monetary damages, we may lose valuable

intellectual property rights or personnel. Even if we are successful in defending against such claims, litigation could result in substantial costs and be a distraction to our organization.

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 substantial 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 and more mature and developed intellectual property portfolios. 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.

If we are unable to protect the confidentiality of our confidential information related to our proprietary platforms and technology, our business and competitive position could be harmed.

In addition to seeking patents for some of our technology and medicines, we also rely on maintaining the confidentiality of unpatented know-how, technology and other proprietary information, to maintain our competitive position. For example, we consider the confidential information and know-how related to our cellular metabolism technology platform to be our primary intellectual property assets in this space. Unpatented proprietary technical information and know-how can be difficult to protect.

We seek to protect this proprietary technical information and know-how, in part, by entering into non-disclosure and confidentiality agreements with parties who have access to them, such as our employees, corporate collaborators, outside scientific collaborators, contract research organizations, 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, and we may not be able to obtain adequate remedies for such breaches. Enforcing a claim that a party illegally disclosed or misappropriated proprietary information is difficult, expensive and time-consuming, and the outcome is unpredictable. If any of our proprietary technical information and know-how were to be lawfully obtained or independently developed by a competitor or other third party, we would have no right to prevent them from using that technology or information to compete with us. Moreover, we anticipate that with respect to this platform, at least some of this technical information and know-how will, over time, be disseminated within the industry through independent development, the publication of journal articles describing the methodology, and the movement of personnel skilled in the art from academic to industry scientific positions.

Risks Related to Regulatory Approval of Our Product Candidates and Other Legal Compliance Matters

Even if we complete necessary preclinical studies and clinical trials, the marketing approval process is expensive, time-consuming and uncertain and may prevent us from obtaining approvals for the commercialization of some or all of our product candidates. If we or our collaborators are not able to obtain, or if there are delays in obtaining, required regulatory approvals, we or they will not be able to commercialize, or will be delayed in commercializing, our product candidates, and our ability to generate revenue will be materially impaired.

Our product candidates and the activities associated with their development and commercialization, including their design, testing, manufacture, safety, efficacy, record keeping, labeling, storage, approval, advertising, promotion, sale and distribution, export and import, are subject to comprehensive regulation by the FDA and other regulatory agencies in the United States and by the EMA and comparable regulatory authorities in other countries. With the exception of the FDA approvals of IDHIFA® and TIBSOVO®, the rights of which we have sold to Servier, we and our collaborators have not received approval to market any of our product candidates from regulatory authorities in any jurisdiction.

Securing marketing approval requires the submission of extensive preclinical and clinical data and supporting information to the various regulatory authorities for each therapeutic indication to establish the product candidate’s safety and efficacy. Securing regulatory approval also requires the submission of information about the product manufacturing process to, and inspection of manufacturing facilities by, the relevant regulatory authority. Our product candidates may not be effective, may be only moderately effective or may prove to have undesirable or unintended side effects, toxicities or other characteristics that may preclude our obtaining marketing approval or prevent or limit commercial use.

The FDA, EMA and other foreign regulatory authorities have substantial discretion in the approval process. Accordingly, it is possible that the FDA or EMA may refuse to accept for substantive review any NDA, sNDA or MAA that we submit for our product candidates, or may conclude after review of our data that our marketing application is insufficient to obtain marketing

approval of our product candidates, including with respect to the NDA and MAA for mitapivat that are each currently under review by the FDA and EMA, respectively. If the FDA or EMA does not accept or approve our applications for any of our product candidates, the applicable regulator may require that we conduct additional clinical trials, preclinical studies or manufacturing validation studies and submit that data before reconsidering our applications. Depending on the extent of these or any other FDA- or EMA-required trials or studies, approval of any marketing applications that we submit may be delayed by several years, or may require us to expend more resources than we planned. It is also possible that additional trials or studies, if performed and completed, may not be considered sufficient by the FDA or EMA to approve any marketing applications. We may not be successful in obtaining FDA or EMA approval of our product candidates on a timely basis, or ever. We have limited experience in filing and supporting the applications necessary to gain marketing approvals and expect to rely on third-party contract research organizations to assist us in this process, and failure to obtain marketing approval for our product candidates will prevent us from commercializing the product candidate in the applicable jurisdictions.

Further, the process of obtaining marketing approvals, both in the United States and abroad, is expensive, may take many years if additional clinical trials are required, 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. Changes in marketing approval policies during the development period, changes in or the enactment of additional statutes or regulations, or changes in regulatory review for each submitted product application, may cause delays in the approval or rejection of an application. In addition, varying interpretations of the data obtained from preclinical and clinical testing could delay, limit or prevent marketing approval of a product candidate. Any marketing approval we or our collaborators ultimately obtain may be limited or subject to restrictions or post-approval commitments that render the approved medicine not commercially viable.

In addition, the COVID-19 pandemic may continue to disrupt the U.S. and international healthcare and regulatory systems. These disruptions could materially delay the review of, and/or decision making with respect to, marketing approvals for our product candidates. Any delay in regulatory review or decision making resulting from such disruptions could materially affect the development of our product candidates.

Disruptions at the FDA and other agencies may prolong the time necessary for regulatory submissions to be reviewed and/or new drugs to be 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, have had to furlough critical employees and stop critical activities. If a prolonged government shutdown were to occur, 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.

If we or our collaborators experience delays in obtaining approval or if we or they fail to obtain approval of our product candidates, the commercial prospects for our product candidates may be harmed and our ability to generate revenue will be materially impaired.

Failure to obtain marketing approval in foreign jurisdictions would prevent our medicines from being marketed in such jurisdictions and any of our medicines that are approved for marketing in such jurisdiction will be subject to risk associated with foreign operations.

In order to market and sell our medicines in the EU and many other foreign jurisdictions, we or our collaborators must obtain separate marketing approvals and comply with numerous and varying regulatory requirements. The approval procedure varies among countries and can involve additional testing. The time required to obtain approval may differ substantially from that required to obtain FDA approval. The regulatory approval process outside the United States generally includes all of the risks associated with obtaining FDA approval. In addition, in many countries outside the United States, a product must be approved for reimbursement before the product can be approved for sale in that country. We or our collaborators may not obtain approvals from regulatory authorities outside the United States on a timely basis, if at all. Moreover, approval by the FDA does not ensure approval by regulatory authorities in other countries or jurisdictions, and approval by one regulatory authority outside the United States does not ensure approval by regulatory authorities in other countries or jurisdictions or by the FDA. We may not be able to file for marketing approvals and may not receive necessary approvals to commercialize our medicines in any market.

Additionally, we could face heightened risks with respect to seeking marketing approval in the United Kingdom as a result of the recent withdrawal of the United Kingdom from the EU on December 31, 2020, commonly referred to as Brexit. On December 24, 2020, the United Kingdom and EU entered into a Trade and Cooperation Agreement, which sets out certain procedures for approval and recognition of medical products in each jurisdiction. Any delay in obtaining, or an inability to obtain, any marketing approvals, as a result of Brexit or otherwise, would prevent us from commercializing any product candidates in the United Kingdom and/or the EU and restrict our ability to generate revenue and achieve and sustain profitability. If any of these outcomes occur, we may be forced to restrict or delay efforts to seek regulatory approval in the United Kingdom and/or EU for any product candidates, which could significantly and materially harm our business.

We expect that we will be subject to additional risks in commercializing any of our product candidates that receive marketing approval outside the United States, including tariffs, trade barriers and regulatory requirements; economic weakness, including inflation, or political instability in particular foreign economies and markets; compliance with tax, employment, immigration and labor laws for employees living or traveling abroad; foreign currency fluctuations, which could result in increased operating expenses and reduced revenue, and other obligations incident to doing business in another country; and workforce uncertainty in countries where labor unrest is more common than in the United States.

Fast track designation and/or priority review designation by the FDA may not actually lead to a faster development or regulatory review or approval process, nor does it assure approval of the product candidate by the FDA.

If a product candidate is intended for the treatment of a serious or life-threatening disease or condition and the product candidate demonstrates the potential to address unmet medical needs for this disease or condition, the drug sponsor may apply for FDA fast track designation.

Further, 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. Receiving priority review from the FDA does not guarantee approval within the six-month review cycle or thereafter.

The FDA has broad discretion on whether to grant fast track designation and/or priority review designation to a product candidate, so even if we believe a particular product candidate is eligible for such designation or status, the FDA may decide not to grant it. Even if our product candidates receive fast track designation and/or priority review designation, we may not experience a faster development process, review or approval, if at all, compared to conventional FDA procedures. The FDA may withdraw fast track designation if it believes that the designation is no longer supported by data from our clinical development program.

In August 2021, the FDA accepted our NDA for mitapivat for the treatment of adults with PK deficiency with priority review designation. We may seek fast track designation and/or priority review designation for our other product candidates.

We, or any collaborators, may not be able to obtain orphan drug designation or orphan drug exclusivity for our drug candidates and, even if we do, that exclusivity may not prevent the FDA or the EMA from approving competing drugs.

Regulatory authorities in some jurisdictions, including the United States and Europe, may designate drugs and biologics for relatively small patient populations as orphan drugs. 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, which is generally defined as a patient population of fewer than 200,000 individuals annually in the United States.

Generally, if a product 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 EMA or the FDA from approving another marketing application for the same product for that time period. The applicable period is seven years in the United States and ten years in Europe. The European exclusivity period can be reduced to six years if a product no longer meets the criteria for orphan drug designation or if the product is sufficiently profitable so that market exclusivity is no longer justified. Orphan drug exclusivity may 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 patients with the rare disease or condition. Moreover, even after an orphan drug is approved, the FDA can subsequently approve a different product for the same condition if the FDA concludes 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.

Moreover, even after an orphan drug is approved, the FDA can subsequently approve a different product for the same condition if the FDA concludes 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. The FDA may reevaluate the Orphan Drug Act and its regulations and policies. 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.

Any product or product candidate for which we or our collaborators obtain marketing approval could be subject to restrictions or withdrawal from the market and we may be subject to substantial penalties if we fail to comply with regulatory requirements or if we experience unanticipated problems with our medicines, when and if any of them are approved.

Any product or product candidate for which we or our collaborators obtain marketing approval, along with the manufacturing processes, post-approval clinical data, labeling, advertising and promotional activities for such medicine, will be subject to continual requirements of and review by the FDA and other regulatory authorities. These requirements include submissions of safety and other post-marketing information and reports, registration and listing requirements, cGMP requirements relating to quality control and manufacturing, quality assurance and corresponding maintenance of records and documents, and requirements regarding the distribution of samples to physicians and record keeping. Even if marketing approval of a product

candidate is granted, the approval may be subject to limitations on the indicated uses for which the medicine may be marketed or to the conditions of approval, or contain requirements for costly post-marketing testing and surveillance to monitor the safety or efficacy of the medicine, including the requirement to implement a risk evaluation and mitigation strategy.

The FDA and other agencies, including the Department of Justice, or the DOJ, closely regulate and monitor the post-approval marketing and promotion of products to ensure that they are marketed and distributed only for the approved indications and in accordance with the provisions of the approved labeling. The FDA and DOJ impose stringent restrictions on manufacturers' communications regarding off-label use and if we market our medicines for uses other than their respective approved indications, we may be subject to enforcement action for off-label marketing. Violations of the FDCA and other statutes, including the False Claims Act, relating to the promotion and advertising of prescription drugs may lead to investigations and enforcement actions alleging violations of federal and state health care fraud and abuse laws, as well as state consumer protection laws, which violations may result in the imposition of significant administrative, civil and criminal penalties.

Our relationships with healthcare providers, physicians and third-party payors are subject to applicable anti-kickback, fraud and abuse and other healthcare laws and regulations, which, in the event of a violation, could expose us to criminal sanctions, civil penalties, contractual damages, reputational harm and diminished profits and future earnings.

Healthcare providers, physicians and third-party payors will play a primary role in the recommendation and prescription of any product candidates for which we obtain marketing approval. Our future arrangements with healthcare providers, physicians and third-party payors 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 any medicines for which we obtain marketing approval. Restrictions under applicable federal and state healthcare laws and regulations include the following:

- the federal 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, or in return for, either the referral of an individual for, or the purchase, order or recommendation or arranging of, any good or service, for which payment may be made under a federal healthcare program such as Medicare and Medicaid;
- the federal False Claims Act imposes criminal and civil penalties, including through civil whistleblower or qui tam actions, against individuals or entities for, among other things, knowingly presenting, or causing to be presented, false or fraudulent claims for payment by a federal healthcare program or making a false statement or record material to payment of a false claim or avoiding, decreasing or concealing 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, or HIPAA, imposes criminal and civil liability for executing a scheme to defraud any healthcare benefit program or making false statements relating to healthcare matters;
- HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act and its implementing regulations, also imposes obligations, including mandatory contractual terms, with respect to safeguarding the privacy, security and transmission of individually identifiable health information;
- the federal Physician Payments Sunshine Act requires applicable manufacturers of covered drugs to report payments and other transfers of value to physicians and teaching hospitals; and
- analogous state and foreign laws and regulations, such as state anti-kickback and false claims laws and transparency statutes, may apply to sales or marketing arrangements and claims involving healthcare items or services reimbursed by non-governmental third-party payors, including private insurers.

Some state laws require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government and may require drug manufacturers to report information related to payments and other transfers of value to physicians and other healthcare providers or marketing expenditures. State and foreign laws also govern the privacy and security of health information in some circumstances, many of which differ from each other in significant ways and often are not preempted by HIPAA, thus complicating compliance efforts.

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, imprisonment, exclusion of products 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 healthcare 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.

The provision of benefits or advantages to physicians to induce or encourage the prescription, recommendation, endorsement, purchase, supply, order or use of medicinal products is also prohibited in the EU. The provision of benefits or advantages to physicians is governed by the national anti-bribery laws of EU Member States, such as the U.K. Bribery Act 2010. Infringement of these laws could result in substantial fines and imprisonment.

Payments made to physicians in certain EU Member States must be publicly disclosed. Moreover, agreements with physicians often must be the subject of prior notification and approval by the physician's employer, his or her competent professional organization and/or the regulatory authorities of the individual EU Member States. These requirements are provided in the national laws, industry codes or professional codes of conduct, applicable in the EU Member States. Failure to comply with these requirements could result in reputational risk, public reprimands, administrative penalties, fines or imprisonment.

Even if we or any collaborators are able to commercialize any product candidates, such products may become subject to unfavorable pricing regulations and third-party reimbursement practices, which would harm our business.

The commercial success of our product candidates will depend substantially, both domestically and abroad, on the extent to which the costs of our product candidates will be paid by third-party payors, including government health administration authorities and private health coverage insurers. If coverage and reimbursement is not available, or reimbursement is available only to limited levels, we, or any collaborators, may not be able to successfully commercialize our product candidates. Even if coverage is provided, the approved reimbursement amount may not be high enough to allow us, or any future collaborators, to establish or maintain pricing sufficient to realize a sufficient return on our or their investments. In the United States, no uniform policy of coverage and reimbursement for products exists among third-party payors and coverage and reimbursement for products can differ significantly from payor to payor. As a result, the coverage determination process is often a time-consuming and costly process that will require us to provide scientific and clinical support for the use of our products to each payor separately, with no assurance that coverage and adequate reimbursement will be applied consistently or obtained in the first instance.

There is significant uncertainty related to third-party payor coverage and reimbursement of newly approved drugs. Marketing approvals, pricing and reimbursement for new drug products vary widely from country to country. Some countries require approval of the sale price of a drug before it can be marketed. In many countries, the pricing review period begins after marketing or product licensing approval is granted. In some foreign markets, prescription pharmaceutical pricing remains subject to continuing governmental control even after initial approval is granted. 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 may be required to conduct a clinical trial that compares the cost effectiveness of our product candidates 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 ability to generate revenues and become profitable could be impaired.

As a result, we, or any collaborators, might obtain marketing approval for a product in a particular country, but then be subject to price regulations that delay commercial launch of the product, possibly for lengthy time periods, which may negatively impact the revenue we are able to generate from the sale of the product in that country. Adverse pricing limitations may hinder our ability or the ability of any collaborators to recoup our or their investment in one or more product candidates, even if our product candidates obtain marketing approval.

Patients who are provided medical treatment for their conditions generally rely on third-party payors to reimburse all or part of the costs associated with their treatment. Therefore, our ability, and the ability of any collaborators, to commercialize any of our product candidates will depend in part on the extent to which coverage and reimbursement for these products and related treatments will be available from third-party payors. Third-party payors decide which medications they will cover and establish reimbursement levels. The healthcare industry is acutely focused on cost containment, both in the United States and elsewhere. Government authorities and other third-party payors have attempted to control costs by limiting coverage and the amount of reimbursement for particular medications, which could affect our ability or that of any collaborators to sell our product candidates profitably. These payors may not view our products, if any, as cost-effective, and coverage and reimbursement may not be available to our customers, or those of any collaborators, or may not be sufficient to allow our products, if any, to be marketed on a competitive basis. Cost-control initiatives could cause us, or any collaborators, to decrease the price we, or they, might establish for products, which could result in lower than anticipated product revenue. If the prices for our products, if any, decrease or if governmental and other third-party payors do not provide coverage or adequate reimbursement, our prospects for revenue and profitability will suffer.

In addition, increasingly, third-party payors are requiring higher levels of evidence of the benefits and clinical outcomes of new technologies and are challenging the prices charged. We cannot be sure that coverage will be available for any product candidate that we, or any collaborator, commercialize and, if available, that the reimbursement rates will be adequate. Further, the net reimbursement for drug products may be subject to additional reductions if there are changes to laws that presently restrict imports of drugs from countries where they may be sold at lower prices than in the United States. An inability to

promptly obtain coverage and adequate payment rates from both government-funded and private payors for any of our product candidates for which we, or any collaborator, obtain marketing approval could significantly harm our operating results, our ability to raise capital needed to commercialize products and our overall financial condition.

Current and future healthcare reform legislation may increase the difficulty and cost for us and any collaborators to obtain reimbursement and commercialize our drug candidates.

In the United States and foreign jurisdictions, there have been a number of legislative and regulatory changes and proposed changes regarding the healthcare system that could prevent or delay marketing approval of our product candidates, restrict or regulate post-approval activities and affect our ability, or the ability of any collaborators, to profitably sell any product 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, as amended by the Health Care and Education Affordability Reconciliation Act, or collectively the ACA. In August 2011, the Budget Control Act of 2011, among other things, created measures for spending reductions by Congress. This legislation resulted in aggregate reductions to Medicare payments to providers of up to 2% per fiscal year, which will remain in effect through 2030 under the CARES Act. 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 product candidates for which we may obtain regulatory approval or the frequency with which any such product candidate is prescribed or used.

Since enactment of the ACA, there have been, and continue to be, numerous legal challenges and Congressional actions to repeal and replace provisions of the law. For example, in 2017, 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. On November 10, 2020, the Supreme Court heard oral arguments as to whether the individual mandate portion of the ACA is an essential and inseverable feature of the ACA, and therefore because the mandate was repealed as part of the Tax Cuts and Jobs Act, the remaining provisions of the ACA are invalid as well. On February 10, 2021, the Biden Administration withdrew the federal government’s support for overturning the ACA. On June 17, 2021, the Supreme Court struck down the lower court rulings, finding that the plaintiffs did not have standing to challenge the ACA’s minimum essential coverage provision at issue in the case.

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 revoked these Orders and 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. This Executive Order also directs the U.S. Department of Health and Human Services to create a special enrollment period for the Health Insurance Marketplace in response to the COVID-19 pandemic. We cannot predict how federal agencies will respond to such Executive Orders.

The costs of prescription pharmaceuticals in the United States and foreign jurisdictions are subject to considerable legislative and executive actions and could impact the prices we obtain for our drug products, if and when approved.

The costs of prescription pharmaceuticals have also been the subject of considerable discussion in the United States.

To date, 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 drug pricing, review the relationship between pricing and manufacturer patient programs, reduce the costs of drugs under Medicare and reform government program reimbursement methodologies for products. To those ends, President Trump issued several executive orders intended to lower the costs of prescription drug products. Certain of these orders are reflected in recently promulgated regulations, including an interim final rule implementing President Trump’s most favored nation model, but such final rule is currently subject to a nationwide preliminary injunction. In addition, on August 21, 2021, the Centers for Medicare & Medicaid Services, or CMS, issued a new proposed rule similar to President Trump’s most favored nation model under which Medicare Part B reimbursement for certain drugs would be based on lower prices in other countries. It remains to be seen whether the orders and resulting regulations put in place during the Trump Administration will remain in force. Further, on September 24, 2020, the Trump Administration finalized a rulemaking allowing states or certain other non-federal government entities to submit importation program proposals to the FDA for review and approval. Applicants are required to demonstrate that their importation plans pose no additional risk

to public health and safety and will result in significant cost savings for consumers. The FDA has issued draft guidance that would allow manufacturers to import their own FDA-approved drugs that are authorized for sale in other countries (multi-market approved products).

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 health care authorities 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 health care 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.

We are subject to U.S. and foreign anti-corruption and anti-money laundering laws with respect to our operations and non-compliance with such laws can subject us to criminal and/or civil liability and harm our business.

We are subject to the U.S. Foreign Corrupt Practices Act of 1977, as amended, the U.S. domestic bribery statute contained in 18 U.S.C. § 201, the U.S. Travel Act, the USA PATRIOT Act, and other state and national anti-bribery and anti-money laundering laws in countries in which we conduct activities. Anti-corruption laws are interpreted broadly and prohibit companies and their employees, agents, third-party intermediaries, joint venture partners and collaborators from authorizing, promising, offering, or providing, directly or indirectly, improper payments or benefits to recipients in the public or private sector. We may have direct or indirect interactions with officials and employees of government agencies or government-affiliated hospitals, universities, and other organizations. In addition, we may engage third party intermediaries to promote our clinical research activities abroad and/or to obtain necessary permits, licenses, and other regulatory approvals. We can be held liable for the corrupt or other illegal activities of these third-party intermediaries, our employees, representatives, contractors, partners, and agents, even if we do not explicitly authorize or have actual knowledge of such activities.

Noncompliance with anti-corruption and anti-money laundering laws could subject us to whistleblower complaints, investigations, sanctions, settlements, prosecution, other enforcement actions, disgorgement of profits, significant fines, damages, other civil and criminal penalties or injunctions, suspension and/or debarment from contracting with certain persons, the loss of export privileges, reputational harm, adverse media coverage, and other collateral consequences. If any subpoenas, investigations, or other enforcement actions are launched, or governmental or other sanctions are imposed, or if we do not prevail in any possible civil or criminal litigation, our business, results of operations and financial condition could be materially harmed. In addition, responding to any action will likely result in a materially significant diversion of management's attention and resources and significant defense and compliance costs and other professional fees. In certain cases, enforcement authorities may even cause us to appoint an independent compliance monitor which can result in added costs and administrative burdens.

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 the success of 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 production efforts. Failure to comply with these laws and regulations also may result in substantial fines, penalties or other sanctions.

Risks Related to Employee Matters and Managing Growth

Our future success depends on our ability to retain our key executives and scientific leadership and to attract, retain and motivate qualified personnel.

We are highly dependent on the principal members of our management and scientific teams, each of whom is employed "at will," meaning we or they may terminate the employment relationship 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 these persons could impede the achievement of our research, development and commercialization objectives. We cannot predict the likelihood, timing or effect of future transitions among our executive leadership.

Recruiting and retaining qualified scientific, clinical, manufacturing, regulatory and sales and marketing personnel will also be 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 and universities and research institutions for similar personnel. Our consultants and advisors, including our scientific co-founders, who assist us in formulating our research and development and commercialization strategy 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 also cannot be sure of the effect that the recent sale of our oncology business to Servier will have on our ability to retain and hire key personnel. Our current and prospective employees may feel uncertain about their roles with us now that we are a smaller company focused on GDDs, which may have an adverse effect on our ability to attract or retain key management personnel or other key employees. Furthermore, the ongoing COVID-19 pandemic and our flexible workplace policy allowing employees to work from home may make it difficult for us to maintain our corporate culture.

We expect to continue to experience growth in the number of our employees as we expand our development, regulatory and future sales and marketing capabilities. To manage our 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. Any inability to manage growth could delay the execution of our business plans or disrupt our operations.

Our employees may engage in misconduct or other improper activities, including noncompliance with regulatory standards and requirements, which could have a material adverse effect on our business.

We are exposed to the risk of employee fraud or other misconduct. Misconduct by employees could include intentional failures to comply with FDA regulations, provide accurate information to the FDA, comply with manufacturing standards we have established, comply with federal and state healthcare fraud and abuse laws and regulations, report financial information or data accurately, disclose unauthorized activities to us, or comply with securities laws. Employee misconduct could also involve the improper use of information obtained in the course of clinical trials, including for illegal insider trading activities, which could result in regulatory sanctions and serious harm to our reputation. We have adopted a Code of Business Conduct and Ethics, but it is not always possible to identify and deter employee misconduct, and the precautions we take to detect and prevent this activity 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 or regulations. 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.

We may engage in acquisitions that could disrupt our business, cause dilution to our stockholders or reduce our financial resources.

In the future, we may enter into transactions to acquire other businesses, products or technologies. Because we have not made any acquisitions to date, our ability to do so successfully is unproven. If we do identify suitable candidates, we may not be able to make such acquisitions on favorable terms, or at all. Any acquisitions we make may not strengthen our competitive position, and these transactions may be viewed negatively by customers or investors. We may decide to incur debt in connection with an acquisition or issue our common stock or other equity securities to the stockholders of the acquired company, which would reduce the percentage ownership of our existing stockholders. We could incur losses resulting from undiscovered liabilities of the acquired business that are not covered by the indemnification we may obtain from the seller. In addition, we may not be able to successfully integrate the acquired personnel, technologies and operations into our existing business in an effective, timely and non-disruptive manner. Acquisitions may also divert management attention from day-to-day responsibilities, increase our expenses and reduce our cash available for operations and other uses. We cannot predict the number, timing or size of future acquisitions or the effect that any such transactions might have on our operating results.

Risks Related to Our Common Stock and Other Matters

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 you might otherwise receive a premium for your 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 shareholder rights plan, or so-called “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 is likely to be volatile, which could result in substantial losses for purchasers of our common stock.

The trading price of our common stock has been, and may continue to be, volatile and could be subject to wide fluctuations in response to various factors, some of which are beyond our control. For example, since January 1, 2015 the price of our common stock on the Nasdaq Global Select Market has ranged from $27.77 per share to $138.85 per share. The stock market in general and the market for biopharmaceutical companies in particular have experienced extreme volatility that has often been unrelated to the operating performance of particular companies. While the full extent of the economic impact and the duration of the COVID-19 pandemic may be difficult to assess or predict, it has already caused, and is likely to result in further, significant disruption of global financial markets, which may reduce our ability to access capital either at all or on favorable terms.

The market price for our common stock may be influenced by many factors, including:

- the impacts of the recent sale of our oncology business to Servier on our business;
- the impact of our repurchases of shares of common stock from our stockholders;
- announcements by us or our competitors of significant acquisitions, strategic partnerships, joint ventures, collaborations or capital commitments;
- the timing and results of clinical trials of product candidates, or our competitors’ product candidates;
- regulatory actions with respect to our product candidates or our competitors’ products and product candidates;
- commencement or termination of collaborations for our development programs;
- failure or discontinuation of any of our development programs;
- regulatory or legal developments in the United States and other countries;
- developments or disputes concerning patent applications, issued patents or other proprietary rights;
- the recruitment or departure of key personnel;
- the level of expenses related to any of our product candidates or clinical development programs;
- the results of our efforts to develop additional product candidates;
- actual or anticipated changes in estimates as to financial results or development timelines;
- announcement or expectation of additional financing efforts;

- sales of our common stock by us, our insiders or other stockholders, including shares issuable upon exercise of outstanding stock options and upon vesting of stock units under our stock incentive plans;
- variations in our financial results or results of companies that are perceived to be similar to us;
- whether an active trading market for our shares is sustained;
- changes in estimates, evaluations or recommendations by securities analysts, that cover our stock or the failure by one or more securities analysts to continue to cover our stock;
- changes in the structure of healthcare payment systems;
- the societal and economic impact of public health epidemics, such as the ongoing COVID-19 pandemic and any recession, depression or sustained market event resulting from the pandemic;
- market conditions in the pharmaceutical and biotechnology sectors;
- general economic, industry and market conditions; and
- the other factors described in this “Risk Factors” section.

In the past, following periods of volatility in the market price of a company's securities, securities class-action litigation often has been instituted against that company. Such litigation, if instituted against us, could cause us to incur substantial costs to defend such claims and divert managements' attention and resources, which could seriously harm our business, financial condition, results of operations and prospects.

We also cannot guarantee that an active trading market for our shares will be sustained. An inactive trading market for our common stock may impair our ability to raise capital to continue to fund our operations by selling shares and may impair our ability to acquire other companies or technologies by using our shares as consideration.

Our financial condition and operating results also may fluctuate from quarter to quarter and year to year due to a variety of factors, many of which are beyond our control. Accordingly, you should not rely upon the results of any quarterly or annual periods as indications of future operating performance.

Our executive officers, directors and principal stockholders maintain the ability to significantly influence all matters submitted to stockholders for approval.

As of September 30, 2021, our executive officers, directors and principal stockholders, in the aggregate, beneficially owned shares representing a significant percentage of our capital stock. As a result, if these stockholders were to choose to act together, they would be able to significantly influence all matters submitted to our stockholders for approval, as well as our management and affairs. For example, these persons could significantly influence the election of directors and approval of any merger, consolidation or sale of all or substantially all of our assets. This concentration of voting power could delay or prevent an acquisition of our company on terms that other stockholders may desire.

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

Under Section 382 of the Code and corresponding provisions of state law, if a company undergoes an “ownership change,” generally defined as a greater than 50% change (by value) in its equity ownership by certain stockholders over a three-year period, the company’s ability to use its pre-change net operating loss carryforwards and other pre-change tax attributes (such as research tax credits) to offset its post-change taxable income may be limited. Our prior equity offerings and other changes in our stock ownership, some of which are outside of our control, may have resulted or could in the future result in an ownership change. We completed a review of our changes in ownership through December 31, 2019, and determined that we did not have a qualified ownership change since our last review as of December 31, 2018. Future ownership changes under Section 382 may limit the amount of net operating loss and tax credit carryforwards that we could potentially utilize to reduce future tax liabilities.

There is also a risk that due to regulatory changes, such as suspensions on the use of net operating losses, or other unforeseen reasons, our existing net operating losses could expire or otherwise become unavailable to offset future income tax liabilities. The Tax Act, 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. In addition, state net operating losses generated in one state cannot be used to offset income generated in another state. For these reasons we may be unable to use a material portion of our net operating losses and other tax attributes.

Our effective tax rate may fluctuate, and we may incur obligations in tax jurisdictions in excess of accrued amounts.

We are subject to taxation in numerous U.S. states and territories. As a result, our effective tax rate is derived from a combination of applicable tax rates in the various places that we operate. In preparing our financial statements, we estimate the amount of tax that will become payable in each of such places. Nevertheless, our effective tax rate may be different from previous periods or our current expectations due to numerous factors, including as a result of changes in the mix of our

profitability from state to state, the results of examinations and audits of our tax filings, our inability to secure or sustain acceptable agreements with tax authorities, changes in accounting for income taxes and changes in tax laws. Any of these factors may result in tax obligations in excess of amounts accrued in our financial statements.

We incur costs as a result of operating as a public company, and our management is required to devote substantial time to compliance initiatives and corporate governance practices.

We have incurred and will continue to incur significant legal, accounting and other expenses as a public company. The Sarbanes-Oxley Act of 2002, the Dodd-Frank Wall Street Reform and Consumer Protection Act, the listing requirements of The Nasdaq Global Select Market and other applicable securities rules and regulations impose various requirements on public companies, including establishment and maintenance of effective disclosure and financial controls and corporate governance practices. Stockholder activism, the current political environment and the current high level of government intervention and regulatory reform may lead to substantial new regulations. Our management and other personnel devote, and will need to continue to devote, a substantial amount of time to these compliance initiatives. Moreover, these rules and regulations increase our legal and financial compliance costs and make some activities more time-consuming and costly.

There can be no assurance that we will repurchase shares of our common stock or that we will repurchase shares at favorable prices.

On March 25, 2021, we announced that our board of directors authorized the Repurchase Program for the repurchase of up to $1.2 billion of our outstanding shares of common stock. On March 31, 2021, in connection with the Repurchase Program, we entered into a definitive share repurchase agreement with BMS to repurchase 7,121,658 shares of our common stock held by certain subsidiaries of BMS for an aggregate purchase price of $344.5 million, or $48.3785 per share. This repurchase was completed on April 5, 2021. Further, on April 2, 2021, in connection with the Repurchase Program, we entered into a Rule 10b5-1 repurchase plan to which we repurchased approximately 8.7 million shares of common stock for $438.9 million, or $50.57 per share, under the plan. In total, as of September 30, 2021, we have repurchased 15.8 million shares of common stock for $783.4 million under the Repurchase Program. On October 5, 2021, we terminated our Rule 10b5-1 share repurchase program and on October 13, 2021 entered into a Rule 10b-18 repurchase plan that allows us to conduct open market repurchases over time up to our remaining authorization.

The amount and timing of share repurchases are subject to capital availability, our cash balances and future capital requirements and our determination that share repurchases are in the best interest of our stockholders and are in compliance with all respective laws and our applicable agreements. We have paused our share repurchases and for the foreseeable future, we expect that our capital allocation will be prioritized towards opportunities to accelerate programs in our development pipeline and/or pursue potential complementary business development opportunities. A reduction in repurchases under, or the completion of, our Repurchase Program could have a negative effect on our stock price. We can provide no assurance that we will repurchase shares at favorable prices, if at all.

Because we do not anticipate paying any cash dividends on our capital stock in the foreseeable future, capital appreciation, if any, will be the sole source of gain for our stockholders.

We have never declared or paid cash dividends on our capital stock. We currently intend to retain all of our future earnings, if any, to finance the growth and development of our business. As a result, capital appreciation, if any, of our common stock will be the sole source of gain for our stockholders for the foreseeable future.

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

Purchases of Equity Securities by the Issuer and Affiliated Purchasers

On March 25, 2021, we announced that our board of directors authorized a share repurchase program to purchase up to $1.2 billion of our outstanding shares of common stock, or the Repurchase Program. Under the Repurchase Program, we are authorized to repurchase shares through open market purchases, privately-negotiated block sales and through Rule 10b5-1 repurchase plans. The Repurchase Program has no expiration date.

On March 31, 2021, in connection with the Repurchase Program, we entered into a definitive share repurchase agreement with BMS to repurchase 7,121,658 shares of our common stock held by certain subsidiaries of BMS for an aggregate purchase price of $344.5 million, or $48.3785 per share. This repurchase was completed on April 5, 2021. On April 2, 2021, in connection with the Repurchase Program, we entered into a Rule 10b5-1 repurchase plan to repurchase up to $600 million of shares of our common stock of the $1.2 billion shares authorized. As of September 30, 2021, we have repurchased approximately 8.7 million shares of common stock for $438.9 million, or $50.57 per share, under the plan. In total, as of September 30, 2021, we have repurchased 15.8 million shares of common stock for $783.4 million, or $49.58 per share, under the Repurchase Program.

On October 5, 2021, we terminated our Rule 10b5-1 share repurchase plan and on October 13, 2021 we entered into a Rule 10b-18 repurchase plan that allows us to conduct open market repurchases over time up to our remaining authorization under the Repurchase Program.

The amount and timing of share repurchases are subject to capital availability, our cash balances and future capital requirements and our determination that share repurchases are in the best interest of our stockholders and are in compliance with all respective laws and our applicable agreements. We have paused our share repurchases and for the foreseeable future, we expect that our capital allocation will be prioritized towards opportunities to accelerate programs in our development pipeline and/or pursue potential complementary business development opportunities.

The table below summarizes the repurchases made under our Repurchase Program during the three months ended September 30, 2021:

	Issuer Purchases of Equity Securities			
Period	**Total Number of Shares Purchased(1)**	**Average Price Paid per Share**	**Total Number of Shares Purchased as Part of Publicly Announced Plans or Programs (1)**	**Approximate Dollar Value of Shares that May Yet Be Purchased Under the Plans or Programs (in millions)**
July 1, 2021 through July 31, 2021	1,808,409	$ 53.20	1,808,409	$ 574.8
August 1, 2021 through August 31, 2021	2,719,340	$ 44.97	2,719,340	$ 452.5
September 1, 2021 through September 30, 2021	778,435	$ 46.12	778,435	$ 416.6
Total	5,306,184	$ 47.94	5,306,184	

(1) All shares repurchased by us during the three months ended September 30, 2021 were repurchased pursuant to the Repurchase Program, as described above.

Item 6. Exhibits

Exhibit Number	Description of Exhibit	Incorporated by Reference				Filed Herewith
		Form	File Number	Date of Filing	Exhibit Number	
3.1	Restated Certificate of Incorporation	8-K	001-36014	July 30, 2013	3.1	
3.2	Second Amended and Restated By-Laws	8-K	001-36014	December 19, 2018	3.1	
10.1#	Letter Agreement, dated as of July 27, 2021, between the Registrant and Chris Bowden, M.D.					X
10.2	Sublease Agreement, dated July 27, 2021, between the Registrant and Prime Medicine, Inc. (38 Sidney Street)					X
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					X
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.					X
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.					X
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.					X
101.INS	XBRL Instance Document - the instance document does not appear in the Interactive Data File because its XBRL tags are not embedded within the Inline XBRL document					X
101.SCH	XBRL Taxonomy Extension Schema Document					X
101.CAL	XBRL Taxonomy Calculation Linkbase Document					X
101.DEF	XBRL Taxonomy Extension Definition Linkbase Document					X
101.LAB	XBRL Taxonomy Label Linkbase Document					X
101.PRE	XBRL Taxonomy Presentation Linkbase Document					X
104	Cover Page Interactive Data File (formatted as Inline XBRL and contained in Exhibit 101.INS)					X

# Indicates management contract or compensatory plan or arrangement

* This certification will not be deemed “filed” for purposes of Section 18 of the Securities Exchange Act of 1934, as amended, or the Exchange Act, or otherwise subject to the liability of that section. Such certification will not be deemed to be incorporated by reference into any filing under the Securities Act of 1933, as amended, or the Exchange Act, except to the extent specifically incorporated by reference into such filing.

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned thereunto duly authorized.

AGIOS PHARMACEUTICALS, INC.

November 3, 2021 By: /s/ Jacqualyn A. Fouse

Jacqualyn A. Fouse, Ph.D.
Chief Executive Officer
(principal executive officer)

November 3, 2021 By: /s/ Jonathan Biller

Jonathan Biller
Chief Financial Officer and Head of Legal and Corporate Affairs
(principal financial officer)

July 27, 2021

Subject: Role change

Dear Chris,

Per our discussion, effective September1, 2021, you will begin your 6-week company paid sabbatical. At this time, you will transition from your Chief Medical Officer role to a Strategic Advisor and will no longer be an executive officer of the company. Effective October 16, 2021, you will transition from a full-time employee to a part-time employee with an expected work week of 20 hours / week (50% FTE). With this adjustment, your new base salarywill be $265,273.50 annually. You will continue to report to Jackie Fouse, Chief Executive Officer, in this capacity.

For the 2021performance year, you will be eligible to receive your annual bonus at your full-time salary at the Executive level, adjusted for company performance, to be paid out in March 2022 but you will not receive a merit increase or annual equity award in February 2022. Additionally, you will not be eligible to participate in the 2022 performance year-including merit increase, annual equity award and annual bonus.

Your existing equity will continue to vestand you will remain eligible for all employee benefits while you remain an employee of the company (anticipated through 12/31/2022).

This letter is not intended to create or constitute an employment agreement or contract between you and Agios Pharmaceuticals. It is also important for you to understand that Massachusetts is an “at will” employment state. This means that you will have the right to terminate your employment relationship with Agios Pharmaceuticals at any time for any reason. Similarly, Agios Pharmaceuticals will have the right to terminate its employment relationship with you at any time for any reason, except as prohibited by law.

Thank you for all the excellent contributions made in your role as CMO and for the supportyou will continue to provide in your new Strategic Advisor role.

Best regards,

/s/ Melissa McLaughlin
Chief People Officer
Agios Pharmaceuticals, Inc.

Signature:

/s/ Chris Bowden	July 29, 2021
Chris Bowden	Date

SUBLEASE AGREEMENT

THIS SUBLEASE AGREEMENT (the "**Sublease**") is made as of the 27th day of July, 2021, by and between **Agios Pharmaceuticals, Inc.**, a Delaware corporation ("**Sublandlord**") and **Prime Medicine, Inc.**, a Delaware corporation ("**Subtenant**").

RECITALS:

WHEREAS, **Thirty-Eight Sidney Street Limited LLC**, a Delaware limited liability company, as landlord ("**Landlord**"), and Sublandlord, as tenant, are parties to that certain lease agreement dated April 11, 2019 (the "**Prime Lease**") pursuant to which Landlord has leased to Sublandlord certain premises containing approximately 12,995 rentable square feet of space (the "**Premises**") on the third (3rd) floor of the building more commonly known as 38 Sidney Street, Cambridge, Massachusetts (the "**Building**"). A redacted copy of the Prime Lease is attached hereto as Exhibit A.

WHEREAS, Sublandlord desires to sublease to Subtenant and Subtenant desires to sublease from Sublandlord the Premises in accordance with the provisions of this Sublease.

NOW THEREFORE, in consideration of the premises, the rents, and the mutual covenants herein contained, and other good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, the parties agree as follows:

1. Sublease of Premises. Sublandlord does hereby sublease to Subtenant, and Subtenant does hereby sublease from Sublandlord, for the Term (as hereinafter defined) and upon the conditions hereafter provided, the Premises, as depicted on Exhibit B-1 to the Prime Lease located in the Building. The Building is a part of the University Park at MIT as depicted on Exhibit B-2 to the Prime Lease. The Premises being sublet to Subtenant by Sublandlord under this Sublease are the same premises being leased by Sublandlord from Landlord under the Prime Lease.

2. Term. The Term of this Sublease shall commence on the later of (i) August 1, 2021 and (ii) the full execution and delivery of Landlord's consent to this Sublease (the "**Commencement Date**") and shall expire on December 31, 2024 (the "**Term**"), unless otherwise terminated as hereinafter provided. Subtenant will have access to the Premises on the date which is fifteen (15) days prior to the Commencement Date for the purpose of installation of fixtures, telecommunications and other items as it relates to getting the Premises ready for occupancy only. Prior to such access, Subtenant shall deliver evidence of insurance as required by this Sublease. All provisions of this Sublease shall apply during such period of early access except the obligation to pay Base Monthly Rent and Additional Rent. No delay in Subtenant completing its installation work will delay the Commencement Date.

3. Rent.

a. Beginning on the Commencement Date (the "**Rent Commencement Date**"), Subtenant shall pay to Sublandlord, in lawful money of the United States, base annual rent (the "**Base Rent**") during the first year of the Term in the amount of One Million One Hundred Four Thousand Five Hundred Seventy Five and 00/100 Dollars ($1,104,575.00),

payable in equal monthly installments of Ninety Two Thousand Forty Seven and 92/100 ($92,047.92) which are payable on the first (1st) day of each calendar month during the Term, without notice or demand and without abatement, set-off or deduction (except that Subtenant shall pay the first monthly installment on the execution hereof), which Base Rent shall be adjusted on each anniversary of the Commencement Date (unless the Commencement Date is other than the first day of a month, in which event the Base Annual Rent shall be adjusted on the anniversary of the first day of the calendar month following the Commencement Date) as follows:

Period	Base Annual Rent	Base Monthly Rent
Aug. 1, 2021 – July 31, 2022	$ 1,104,575.00	$ 92,047.92
Aug. 1, 2022 – July 31, 2023	$ 1,137,712.25	$ 94,809.35
Aug. 1, 2023 – July 31, 2024	$ 1,171,843.62	$ 97,653.63
Aug. 1, 2024 – Dec. 31, 2024*	$ 1,206,998.93	$ 100,583.24

*partial sublease year

b. Subtenant shall also be responsible for any and all charges, fees or expenses payable under the Prime Lease that are attributable to Subtenant's use or occupancy of the Premises, including: (i) Subtenant's Proportionate Share (as hereinafter defined) of the increase in Real Estate Taxes (as such term is defined in Section 3.2(b) of the Prime Lease) incurred with respect to the current year over and above the amount of Real Estate Taxes incurred with respect to the Base Year (as hereinafter defined); (ii) Subtenant's Proportionate Share of the increase in Operating Expenses (as such term is defined in Section 3.3(b) of the Prime Lease) incurred with respect to the current year over and above the amount of Operating Expenses incurred with respect to the Base Year; (iii) any additional rent payable on account of Subtenant's use of excess heating, ventilation and air conditioning and electricity, but in no event shall Subtenant use more electricity in the Subleased Premises than that which the feeders, risers, panels and other electricity supply equipment serving the Premises are capable of safely supplying; (iv) amounts payable to Landlord or Sublandlord for separately sub-metered utilities and services pursuant to Section 3.4 of the Prime Lease; and (v) any additional rent payable on account of any services provided by Landlord or Sublandlord to Subtenant or otherwise attributable to the use or occupancy of the Premises (collectively, "**Additional Rent**"). Additional Rent shall be paid within ten (10) days of Tenant's receipt of Landlord's invoice therefor.

c. During the Term, the Subtenant shall pay directly to the provider charges for all separately metered utilities serving the Premises, including gas and electric, and shall pay to Sublandlord as Additional Rent its pro rata share of water, sewer and other services and utilities which shall be prorated to reflect Subtenant's proportional usage based upon Subtenant's proportional occupancy of the Building.

d. "**Subtenant's Proportionate Share**" shall mean 10 and 60/100 (10.6%) percent, which is calculated by dividing the square footage of the space (12,995 SF) by the square footage of the total rentable floor area of the Building (122,554 SF).

e. "**Base Year**" with respect to Real Estate Taxes shall mean the fiscal year ending June 30, 2022, and with respect to Operating Expenses, shall mean the calendar year of 2021.

4. Extension Option. On the conditions (which conditions Sublandlord may waive in its sole discretion by written notice to Tenant) that both at the time Subtenant exercises the Extension Option (as defined below) or at any time thereafter until the commencement of the corresponding Extension Term (as defined below) (i) there exists no event of default hereunder, (ii) this Sublease is still in full force and effect, and (iii) Sublandlord shall have determined in its sole discretion, and shall have advised Subtenant of such determination within fifteen (15) days of receipt of Subtenant's Extension Notice (as hereinafter defined), to make the Premises available to Subtenant for lease for the Extension Term, Subtenant may extend the term of the Sublease (the "**Extension Option**"), upon all the same terms, conditions, covenants and agreements herein contained, for one (1) period of six (6) months (the "**Extension Term**") by delivering written notice of its exercise of the Extension Option no later than nine (9) months prior to the expiration of the Term (the "**Extension Notice**"). The Base Rent for such Extension Term shall be at the prevailing fair market rate for comparable space for a 5-year term in the Mid-Cambridge submarket, as such fair market rate is determined by Sublandlord in its sole but reasonable discretion.

5. Condition of Premises. Sublandlord shall deliver the Premises to Subtenant in it's "as is, where is" condition provided that the Premises shall be appropriately demised and with all required base building systems, including, but not limited to, HVAC, electrical, life safety and plumbing systems in good working condition and suitable for the permitted use hereunder. Sublandlord shall be responsible for maintaining all base building systems, including, but not limited to, HVAC, electrical, life safety and plumbing systems. Subtenant's taking possession of the Premises shall be conclusive evidence as against Subtenant that the Premises were in good order and satisfactory condition when Subtenant took possession. No promise of Sublandlord to alter, remodel or improve the Premises and no representation respecting the condition of the Premises or the Building have been made to Subtenant. Additionally, throughout the Term, Subtenant shall have the right to use the existing furniture and IT/AV equipment in the Premises; such existing furniture and IT/AV equipment is listed herein in Exhibit B (the "**Existing Furniture and Equipment**"); such use is included as part of Base Rent. Subtenant shall have no obligation to remove the Existing Furniture and Equipment at the end of the Term.

6. Use. Subtenant will use and occupy the Premises solely for general office use purposes and any ancillary uses related thereto and for no other purpose except as may be permitted by applicable law.

7. Security Deposit/Letter of Credit. As a material inducement for Sublandlord to enter into this Sublease, Subtenant shall deliver on the date hereof an irrevocable, unconditional standby letter of credit issued by Subtenant's financial institution for the benefit of Sublandlord in the face amount of Two Hundred Seventy Six Thousand One Hundred Forty Three and 76/100 ($276,143.76) Dollars (the "**Letter of Credit**"), receipt whereof is hereby acknowledged by Sublandlord. Subtenant shall cause the Letter of Credit to be renewed annually and shall provide to Sublandlord written confirmation of such renewal at least thirty (30) days prior to its expiration. Sublandlord may submit to the issuer of any Letter of Credit hereunder from time to time draws for payment as Sublandlord deems necessary in order to cure or otherwise remedy

any Subtenant default. Within ten (10) days after submission of any request for payment by Sublandlord under any Letter of Credit (a "**Draw**"), Subtenant shall deliver to Sublandlord a written amendment of such Letter of Credit restoring the amount available to be drawn thereunder by Sublandlord to the same level existing immediately prior to the Draw or otherwise as required hereunder.

8. Parking. Commencing on the Rent Commencement Date and continuing through the Term, Subtenant shall be entitled to use and shall pay for 1.5 parking passes per 1,000 square feet (which shall initially be equal to twenty (20) parking passes) in accordance with Section 2.4 of the Prime Lease. For each such parking pass, Subtenant shall pay the higher rate of either (i) $325.00 per month or (ii) the current monthly parking rate charged by Landlord in accordance with Section 2.4 of the Prime Lease.

9. Default Under and/or Termination of the Prime Lease.

a. If for any reason the term of the Prime Lease is terminated prior to the anticipated expiration date of this Sublease, this Sublease shall thereupon terminate, and Sublandlord shall not be liable to Subtenant by reason thereof for damages or otherwise (except those arising out of Sublandlord's failure to remit rent to Landlord if rent hereunder is actually received by Sublandlord from Subtenant, Sublandlord's default hereunder) and Sublandlord shall return to Subtenant rent paid in advance by Subtenant, if any, prorated as of the date of the termination of the Prime Lease.

b. If Landlord elects to take over the right, title and interest of Sublandlord in accordance with the Prime Lease, it is understood and agreed that Landlord shall not (i) be liable for any previous act or omission of Sublandlord under this Sublease, (ii) be subject to any offset which theretofore accrued to Subtenant against Sublandlord, and (iii) be bound by any previous modification of this Sublease to which it has not consented, or by any previous prepayment of more than one month's rent. In such event, Subtenant shall also, promptly upon Landlord's request, execute and deliver all instruments necessary or appropriate to confirm such attornment and recognition.

c. From and after the date of any default by Sublandlord resulting in a termination, reentry or dispossession under the Prime Lease, until the date that this Sublease is terminated in accordance with this Section 7, Subtenant shall pay all Base Annual Rent, Additional Rent and any other sums due by Subtenant under the Sublease directly to Landlord and Subtenant shall continue to perform all of its obligations hereunder.

10. Notice of Default. Sublandlord hereby agrees to provide to Subtenant, within ten (10) business days after receipt thereof, a copy of any notice of default under the Prime Lease which Sublandlord receives from Landlord. Subtenant shall have the option of curing any monetary default which is not being contested by Sublandlord by forwarding to Sublandlord sufficient funds to cure such default. Sublandlord hereby agrees to immediately remit such sums to Landlord.

11. Subordination to and Incorporation of Terms of Prime Lease.

a. This Sublease is in all respects subject and subordinate to any mortgage, deed, deed of trust, ground lease or other instrument now or hereafter encumbering the Building or the land on which it is located, to the terms and conditions of the Prime Lease and to the matters to which the Prime Lease, including any amendments thereto, is or shall be subordinate. The terms, provisions, covenants, stipulations, conditions, rights, obligations, remedies and agreements of the Prime Lease are incorporated into this Sublease by reference and made a part hereof as if herein set forth at length, and shall, as between Sublandlord and Subtenant (as if they were the landlord and the tenant, respectively, under the Prime Lease and as if the Premises were the Premises demised under the Prime Lease), constitute the terms of this Sublease, except to the extent that they do not relate to the Premises or are inapplicable to, or modified or eliminated by, the terms of this Sublease. Sublandlord and Subtenant each agree to observe and be bound by each and every covenant, condition and provision of the Prime Lease insofar as any such covenant, condition or provision affects the Premises or Subtenant's use thereof. Subtenant acknowledges that it has reviewed and is familiar with the Prime Lease. In confirmation of the subordination provided for in this paragraph, Subtenant shall, within ten (10) days after Sublandlord's reasonable request, execute any requested or appropriate certificate or other document.

b. To the extent that Sublandlord is entitled under the Prime Lease to any abatement of rent as a result of damage or casualty to the Premises, then Subtenant shall have the right to an abatement of rent hereunder in an amount equal to the total rent required hereunder multiplied by a fraction equal to the number of square feet in the Premises rendered unusable divided by the number of square feet in the Premises rendered unusable.

c. Subtenant hereby assumes and agrees to perform faithfully and be bound by, with respect to the Premises, all of Sublandlord’s obligations, covenants, agreements and liabilities under the Prime Lease and all terms, conditions, provisions and restrictions contained in the Prime Lease except the following provisions of the Prime Lease:

(i) Section 2.6 – Extension Option;
(ii) Section 2.7 – One-Time Right of First Offer;
(iii) Section 3.1 – Annual Fixed Rent;
(iv) Section 3.7 – Net Lease; and
(v) Exhibit E – Work Letter.

The reference in this Sublease to any particular section or article of the Prime Lease shall not in any way be deemed or construed to derogate from the general incorporation by reference of the entire Prime Lease (except as aforesaid) into this Sublease.

d. Subtenant shall not do anything which could result in a default under the Prime Lease or permit the Prime Lease to be cancelled or terminated.

e. It is expressly understood and agreed that Sublandlord does not assume and shall not have any of the obligations or liabilities of Landlord under the Prime Lease and that Sublandlord is not making the representations or warranties, if any, made by Landlord in the Prime Lease. With respect to work, services, repairs and restoration or the performance of other obligations required of Landlord under the Prime Lease, Sublandlord’s sole obligation with respect thereto shall be to request the same, upon written request from Subtenant, and to use

reasonable efforts to obtain the same from Landlord, which efforts shall not require initiating any litigation. Sublandlord shall not be liable in damages, nor shall rent abate hereunder, for or on account of any failure by Landlord to perform the obligations and duties imposed on it under the Prime Lease.

f. Whenever Subtenant desires to do any act or thing that requires the consent or approval of the Landlord pursuant to the Prime Lease, (i) Subtenant shall not do such act or thing without first having obtained the consent or approval of both Landlord and Sublandlord (and Sublandlord's right to withhold consent or approval shall be independent of Landlord's right), and (ii) in no event shall Sublandlord be required to give its consent or approval prior to Landlord doing so, unless required by Landlord.

12. Signage. Sublandlord, at its sole cost and expense, shall request that Landlord provide to Subtenant Building standard signage on all tenant directories at the Building as well as at the entrance to the Premises. All signage to be installed at the Premises shall be subject to the approval of Landlord and subject to the terms of the Prime Lease.

13. Building Rules and Regulations. Subtenant shall comply with all rules and regulations of the Building.

14. Alterations. Notwithstanding anything to the contrary contained in the Prime Lease, Subtenant shall not make any improvements, alterations or changes to the Premises whatsoever, including without limitation, structural or non-structural changes, without the prior written consent of Sublandlord and Landlord and in accordance with the terms of the Prime Lease. Subtenant will not suffer or permit to attach nor will it do any act or make any contract that may create the foundation of any mechanic's or other lien for work, labor, services or materials, or otherwise, and whenever any such lien shall be filed or shall attach Subtenant will, within ten (10) days thereafter, secure a cancellation thereof by paying the same or in such other manner prescribed by law.

15. Insurance. Subtenant shall maintain insurance of the kinds and in the amounts required to be maintained by Sublandlord under the Prime Lease and in accordance with all other requirements therein. All policies of liability insurance shall name as additional insureds the Landlord and Sublandlord and their respective officers, directors or partners, as the case may be, and the respective agents and employees of each of them. Subtenant shall deliver certificates evidencing such insurance with delivery of the first month's rent. Before taking occupancy of the Premises, Subtenant shall provide Sublandlord with proof of such insurance.

16. Assignment and Further Sublease. Provided that both on the date on which Subtenant notifies Sublandlord of its desire to enter into an assignment and on the date on which such assignment is to take effect, Subtenant is not in default of any of its obligations hereunder, during the term of the Sublease, Subtenant shall have the right to sub-sublease all or portion of the Premises subject to (i) Sublandlord written consent, which shall not be unreasonably withheld or delayed, (ii) Landlord's written consent, which shall be subject to and in accordance with the Prime Lease (including the right to terminate the Lease, and, accordingly the Sublease) and (iii) payment of any fee which is required by the Landlord. Subtenant will remain liable for all obligations under the Sublease. Assignment rights shall be pursuant the Prime Lease. Subtenant shall provide such financial and other information regarding the

proposed assignee as requested by Sublandlord and/or Landlord. In the event that Sublandlord and Landlord consent to any assignment or sublease of the Premises, as a condition of such consent, Subtenant shall pay to Sublandlord fifty percent (50%) of any rent, sum or other consideration to be paid or given in connection with any assignment or sublet (after first deducting Subtenant's reasonable actual costs to sub-sublet the Premises), either initially or over time, in excess of Base Rent and Additional Rent hereunder, as if such amount were originally called for by the terms of this Sublease as Additional Rent. Subtenant shall furnish Sublandlord with a sworn statement, certified by an independent certified public accountant, setting forth in detail the computation of any such excess rent (which computation shall be based upon generally accepted accounting principles, including an amortization of Subtenant's actual costs in such assignment or sublease (e.g., the cost of commissions, improvement allowance and any other reasonable actual out-of-pocket transaction cost)), and Sublandlord, or its representatives, shall have access to the books, records and papers of Subtenant in relation thereto, and to make copies thereof.

17. Access. Subtenant shall be afforded access to the Premises 24 hours a day, 7 days a week, and 365 days a year, and on all dates and at all times permitted by applicable government rules and regulations, and in accordance with the terms of the Prime Lease, excluding emergency events, which may cause the Building to limit access to tenants.

18. Surrender. Upon expiration of the Term or other termination of this Sublease, Subtenant shall quit and surrender to Sublandlord the Premises and remove all of its furniture, furnishings, personal property and equipment in order to leave the Premises, broom clean and in as good order, repair and condition as they were on the date the Term of this Sublease commenced, ordinary wear and tear excepted. The obligations of Subtenant to perform this covenant shall survive the expiration or other termination of this Sublease.

19. Default; Remedies.

a. Sublandlord reserves the right to terminate this Sublease and Subtenant's occupancy of the Premises in the event that (i) Subtenant fails to make any Base Rent payment, Additional Rent or any other monetary amount due under this Sublease within five (5) business days of its due date, or (ii) Subtenant fails to observe and perform any of its obligations under this Sublease within ten business (10) days after written notice thereof from Sublandlord, except to the extent such default cannot be cured within said ten business (10) day period, in which event Subtenant shall have such additional time as may be necessary to cure such default so long as Subtenant has commenced cure within such ten business (10) day period and is diligently and continuously pursuing the remedies necessary to cure such default within thirty (30) days after notice thereof. The acceptance of any late payments of Base Rent shall not be deemed a waiver of Sublandlord's rights under this section. In the event it becomes necessary for Sublandlord to enforce its rights against Subtenant by legal action Subtenant shall pay all of Sublandlord's reasonable legal costs and expenses in connection therewith including reasonable legal fees provided that Sublandlord is the prevailing party in such action.

b. In case of any such termination, Subtenant shall pay to and indemnify Sublandlord each month against all loss of rent and all costs, expenses, or obligations which Sublandlord may incur by reason of any such termination between the time of termination and the end of the Term, or, at such election of Sublandlord, exercised at the time of the termination

or at any time thereafter, Subtenant shall pay to Sublandlord as damages, in a lump sum, the then present value of the aggregate amount of rent and other payments provided herein to be paid by Subtenant to Sublandlord through the time when the Term of this Sublease would have expired but for the default by Subtenant. It is understood and agreed that at the time of the termination or at any time thereafter that Subtenant shall be liable for any expenses incurred by Sublandlord in connection with obtaining possession of the Premises, with removing from the Premises property of Subtenant and persons claiming under Subtenant (including warehouse charges), with putting the Premises into condition for delivery to Landlord or reletting and with any reletting, including without limitation, attorneys' fees and brokers' fees, and that any monies collected from any reletting shall be applied first to the foregoing expenses and then to the payment of rent and all other payments due from Subtenant to Sublandlord.

20. Indemnification. Subtenant shall indemnify and hold harmless Sublandlord from and against any and all losses, claims, damages, liabilities, actions, costs and expenses (including reasonable attorneys' fees) incurred by Sublandlord arising out of or related to this Sublease or Subtenant's use and occupancy of the Premises, unless caused by the intentional acts or gross negligence of Sublandlord. This indemnification shall survive termination of this Sublease.

21. Notices. Any notice required or permitted to be given hereunder shall be in writing and may be given by certified mail, return receipt requested, personal delivery, Federal Express or other delivery service. If notice is given by certified mail, return receipt requested, notice shall be deemed given three (3) days after the notice is deposited with the U.S. Mail, postage prepaid, addressed to Subtenant or to Sublandlord at the address set forth below. If notice is given by personal delivery, Federal Express or other delivery service, notice shall be deemed given on the date the notice is actually received by Sublandlord or Subtenant. Either party may by notice to the other specify a different address for notice purposes.

If to Sublandlord: Agios Pharmaceuticals, Inc.
88 Sidney Street
Cambridge, MA 02139

With a copy to: Eckert, Seamans, Cherin & Mellott, LLC
Two International Place, 16th Floor
Boston, MA 02110
Attention: Stuart A. Offner, Esq.

If to Subtenant: Prime Medicine, Inc.
21 Erie Street
Cambridge, MA 02139
Attn: Keith Gottesdiener

If Sublandlord receives any notice from Landlord which affects Subtenant or the Premises, Sublandlord shall provide Subtenant with a copy thereof.

22. Hold Over. If Subtenant holds over after the expiration of the Term or earlier termination thereof, such tenancy shall be a tenancy at sufferance, and shall not constitute a renewal hereof or an extension for any further term, and in such case Base Rent shall be

payable at a monthly rate equal to (a) 150% of Base Rent and Additional Rent applicable during the last rental period of the Term for any holding over during the first ninety (90) days following expiration of the Term or earlier termination thereof, and (b) 175% of Base Rent and Additional Rent applicable during the last rental period of the Term for any holding over subsequent to the holding over period of subsection 22(a). Such tenancy shall be subject to every other applicable term, covenant and agreement contained herein. For purposes of this paragraph holding over shall include (i) Subtenant's remaining in the Premises after the expiration or earlier termination of the Term, and/or (ii) failing to deliver the Premises in the condition required in this Sublease or the Prime Lease. Nothing contained in this paragraph shall be construed as consent by Sublandlord to any holding over by Subtenant, and Sublandlord expressly reserves the right to require Subtenant to surrender possession of the Premises to Landlord as provided in the Sublease and Prime Lease upon the expiration or other termination of this Sublease. If Subtenant holds over without Sublandlord's express written consent, and tenders payment of rent for any period beyond the expiration of the Term by way of check (whether directly to Sublandlord, its agents, or to a lock box) or wire transfer, Subtenant acknowledges and agrees that the cashing of such check or acceptance of such wire shall be considered inadvertent and not be construed as creating a month-to-month tenancy. The provisions of this paragraph shall not be deemed to limit or constitute a waiver of any other rights or remedies of Sublandlord provided herein or at law. If Subtenant fails to surrender the Premises upon the termination or expiration of this Sublease, in addition to any other liabilities to Sublandlord accruing therefrom, Subtenant shall protect, defend, indemnify and hold Sublandlord harmless from all loss, costs (including reasonable attorneys' fees) and liability resulting from such failure, including, without limiting the generality of the foregoing, any claims made by Landlord or any succeeding tenant founded upon such failure to surrender and any lost profits to Sublandlord resulting therefrom.

23. Brokerage Commissions. Each party hereby represents and warrants to the other that it has had no dealings with any real estate broker or agent in connection with this Sublease, excepting only CBRE, which shall be paid in accordance with an existing agreement with Sublandlord, and that it knows of no other real estate broker or agent who is or might be entitled to a commission in connection with this Sublease. Each party agrees to protect, defend, indemnify and hold the other harmless from and against any and all claims inconsistent with the foregoing representations and warranties for any brokerage, finder's or similar fee or commission in connection with this Sublease, if such claims are based on or relate to any act of the indemnifying party which is contrary to the foregoing representations and warranties.

24. Waiver of Jury Trial. THE PARTIES HEREBY WAIVE THEIR RESPECTIVE RIGHTS TO TRIAL BY JURY IN ANY ACTION OR PROCEEDING INVOLVING THE PREMISES, BUILDING OR ARISING OUT OF THIS SUBLEASE OR THE PRIME LEASE.

25. Modification. This Sublease may only be modified by written agreement signed by Sublandlord and Subtenant.

26. Counterparts. This Sublease may be executed in counterparts, each of which shall be an original and all of which, when assembled, shall constitute but one document.

27. Governing Law. The terms and provisions of this Sublease shall be governed by the laws of the Commonwealth of Massachusetts.

28. Consent. It is expressly understood and agreed that this Sublease, and the parties' rights and obligations hereunder, are contingent upon the Landlord's written consent of this Sublease. If Landlord's consent shall not have been obtained within thirty (30) days after the date of this Sublease, Sublandlord and Subtenant shall each have the right to terminate this Sublease by providing the other with its written election to do so before (but not after) Landlord's consent is obtained (the "**Termination Notice**"). In the event of such a termination, neither party shall have any further rights or obligations hereunder.

[SIGNATURES APPEAR ON FOLLOWING PAGE.]

IN WITNESS WHEREOF, the Sublandlord and Subtenant have each executed this Sublease effective as of the date first above written.

SUBLANDLORD:

Agios Pharmaceuticals, Inc.,
a Delaware corporation

By: /s/ Jonathan Biller
Name: Jonathan Biller
Title: CFO, Head of Legal and Corporate Affairs

SUBTENANT:

Prime Medicine, Inc.,
a Delaware corporation

By: /s/ Keith Gottesdiener
Name: Keith Gottesdiener
Title: Chief Executive Office

Landlord hereby consents to this Sublease:

LANDLORD:

Thirty-Eight Sidney Street Limited LLC,
a Delaware limited liability company

By: _____
Name:
Title:

Exhibit “A”

Prime Lease

Exhibit "B"

Existing Furniture and Equipment

Exhibit 31.1

CERTIFICATION

I, Jacqualyn A. Fouse, certify that:

1. I have reviewed this Quarterly Report on Form 10-Q of Agios Pharmaceuticals, 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.

Date: November 3, 2021

/s/ Jacqualyn A. Fouse, Ph.D.

Jacqualyn A. Fouse, Ph.D.
Chief Executive Officer
(principal executive officer)

Exhibit 31.2

CERTIFICATION

I, Jonathan Biller, certify that:

1. I have reviewed this Quarterly Report on Form 10-Q of Agios Pharmaceuticals, 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.

Date: November 3, 2021

/s/ Jonathan Biller

Jonathan Biller
Chief Financial Officer and Head of Legal and Corporate Affairs
(principal financial officer)

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 Agios Pharmaceuticals, Inc. (the "Company") for the fiscal quarter ended September 30, 2021, as filed with the Securities and Exchange Commission on the date hereof (the "Report"), the undersigned, Jacqualyn A. Fouse, Chief Executive Officer of the Company, hereby certifies, pursuant to 18 U.S.C. Section 1350, that, to her knowledge on the date hereof:

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.

Date: November 3, 2021

/s/ Jacqualyn A. Fouse, Ph.D.
Jacqualyn A. Fouse, Ph.D.
Chief Executive Officer
(principal executive officer)

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 Agios Pharmaceuticals, Inc. (the "Company") for the fiscal quarter ended September 30, 2021, as filed with the Securities and Exchange Commission on the date hereof (the "Report"), the undersigned, Jonathan Biller, Chief Financial Officer of the Company, hereby certifies, pursuant to 18 U.S.C. Section 1350, that, to his knowledge on the date hereof:

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.

Date: November 3, 2021

/s/ Jonathan Biller
Jonathan Biller
Chief Financial Officer and Head of Legal and Corporate Affairs
(principal financial officer)