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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, 2022**
**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 28, 2022: 54,944,856

**AGIOS PHARMACEUTICALS, INC.**

**FORM 10-Q**

**FOR THE THREE AND NINE MONTHS ENDED SEPTEMBER 30, 2022**

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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, 2022 | December 31, 2021 |
|---|---|---|
| **Assets** | | |
| Current assets: | | |
| Cash and cash equivalents | $ 122,449 | $ 203,126 |
| Marketable securities | 605,231 | 816,892 |
| Accounts receivable, net | 1,818 | — |
| Other receivable | 3,774 | 4,378 |
| Inventory | 5,176 | — |
| Prepaid expenses and other current assets | 46,487 | 39,835 |
| Total current assets | 784,935 | 1,064,231 |
| Marketable securities | 298,352 | 266,375 |
| Operating lease assets | 67,692 | 75,124 |
| Property and equipment, net | 25,438 | 28,923 |
| Financing lease assets | — | 183 |
| Other non-current assets | 3,903 | 2,900 |
| Total assets | $ 1,180,320 | $ 1,437,736 |
| **Liabilities and stockholders' equity** | | |
| Current liabilities: | | |
| Accounts payable | $ 10,415 | $ 16,700 |
| Accrued expenses | 29,756 | 31,967 |
| Operating lease liabilities | 13,342 | 10,828 |
| Financing lease liabilities | 83 | 331 |
| Total current liabilities | 53,596 | 59,826 |
| Operating lease liabilities, net of current portion | 75,499 | 85,659 |
| Other non-current liabilities | 1,055 | 276 |
| Total liabilities | 130,150 | 145,761 |
| Stockholders' equity: | | |
| Preferred stock, $0.001 par value; 25,000,000 shares authorized; no shares issued or outstanding at September 30, 2022 and December 31, 2021 | — | — |
| Common stock, $0.001 par value; 125,000,000 shares authorized; 71,110,442 shares issued and 54,894,031 shares outstanding at September 30, 2022, and 70,550,631 shares issued and 54,334,220 shares outstanding at December 31, 2021 | 71 | 71 |
| Additional paid-in capital | 2,374,755 | 2,334,348 |
| Accumulated other comprehensive loss | (15,083) | (1,198) |
| Treasury stock, at cost (16,216,411 shares at September 30, 2022 and December 31, 2021) | (802,486) | (802,486) |
| Accumulated deficit | (507,087) | (238,760) |
| Total stockholders' equity | 1,050,170 | 1,291,975 |
| Total liabilities and stockholders' equity | $ 1,180,320 | $ 1,437,736 |

*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, 2022 | Three Months Ended September 30, 2021 | Nine Months Ended September 30, 2022 | Nine Months Ended September 30, 2021 |
|---|---|---|---|---|
| Revenues: | | | | |
| Product revenue, net | $ 3,516 | $ — | $ 7,430 | $ — |
| Milestone revenue | — | — | 2,500 | — |
| Total revenue | 3,516 | — | 9,930 | — |
| Operating expenses: | | | | |
| Cost of sales | $ 517 | $ — | $ 1,291 | $ — |
| Research and development | 64,966 | 64,000 | 209,612 | 183,674 |
| Selling, general and administrative | 29,123 | 27,152 | 88,902 | 89,917 |
| Total operating expenses | 94,606 | 91,152 | 299,805 | 273,591 |
| Loss from operations | (91,090) | (91,152) | (289,875) | (273,591) |
| Royalty income from gain on sale of oncology business | 4,443 | 1,996 | 9,851 | 3,996 |
| Interest income, net | 3,818 | 256 | 6,305 | 504 |
| Other income, net | 1,082 | 4,641 | 5,392 | 11,165 |
| Net loss from continuing operations | (81,747) | (84,259) | (268,327) | (257,926) |
| Net (loss) income from discontinued operations, net of tax | — | (4,507) | — | 1,957,268 |
| Net (loss) income | $ (81,747) | $ (88,766) | $ (268,327) | $ 1,699,342 |
| Net loss from continuing operations per share - basic and diluted | $ (1.49) | $ (1.48) | $ (4.90) | $ (4.13) |
| Net (loss) income from discontinued operations per share - basic and diluted | $ — | $ (0.08) | $ — | $ 31.31 |
| Net (loss) income per share - basic and diluted | $ (1.49) | $ (1.56) | $ (4.90) | $ 27.19 |
| Weighted-average number of common shares used in computing net loss per share from continuing operations, net (loss) income from discontinued operations and net (loss) income per share – basic and diluted | 54,844,579 | 57,048,175 | 54,734,301 | 62,503,087 |

*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, | |
|---|---|---|---|---|
| | 2022 | 2021 | 2022 | 2021 |
| Net (loss) income | $ (81,747) | $ (88,766) | $ (268,327) | $ 1,699,342 |
| Other comprehensive loss | | | | |
| Unrealized loss on available-for-sale securities | (4,581) | (54) | (13,885) | (303) |
| Comprehensive (loss) income | $ (86,328) | $ (88,820) | $ (282,212) | $ 1,699,039 |

*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, 2021 | 70,550,631 | $ 71 | $ 2,334,348 | $ (1,198) | $ (238,760) | (16,216,411) | $ (802,486) | $ 1,291,975 |
| Common stock issued under stock incentive plan and ESPP | 442,646 | — | 1,289 | — | — | — | — | 1,289 |
| Stock-based compensation expense | — | — | 15,510 | — | — | — | — | 15,510 |
| Other comprehensive loss | — | — | — | (6,547) | — | — | — | (6,547) |
| Net loss | — | — | — | — | (94,774) | — | — | (94,774) |
| Balance at March 31, 2022 | 70,993,277 | $ 71 | $ 2,351,147 | $ (7,745) | $ (333,534) | (16,216,411) | $ (802,486) | $ 1,207,453 |
| Common stock issued under stock incentive plan and ESPP | 38,515 | — | 15 | — | — | — | — | 15 |
| Stock-based compensation expense | — | — | 11,165 | — | — | — | — | 11,165 |
| Other comprehensive loss | — | — | — | (2,757) | — | — | — | (2,757) |
| Net loss | — | — | — | — | (91,806) | — | — | (91,806) |
| Balance at June 30, 2022 | 71,031,792 | $ 71 | $ 2,362,327 | $ (10,502) | $ (425,340) | (16,216,411) | $ (802,486) | $ 1,124,070 |
| Common stock issued under stock incentive plan and ESPP | 78,650 | — | 1,272 | — | — | — | — | 1,272 |
| Stock-based compensation expense | — | — | 11,156 | — | — | — | — | 11,156 |
| Other comprehensive loss | — | — | — | (4,581) | — | — | — | (4,581) |
| Net loss | — | — | — | — | (81,747) | — | — | (81,747) |
| Balance at September 30, 2022 | 71,110,442 | $ 71 | $ 2,374,755 | $ (15,083) | $ (507,087) | (16,216,411) | $ (802,486) | $ 1,050,170 |

| (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 Cash Flows**
***(Unaudited)***

| (In thousands) | Nine Months Ended September 30, 2022 | 2021 |
|---|---|---|
| **Operating activities** | | |
| Net (loss) income | $ (268,327) | $ 1,699,342 |
| Less: Net income from discontinued operations | — | 1,957,268 |
| Net loss from continuing operations | (268,327) | (257,926) |
| Adjustments to reconcile net loss from continuing operations to net cash used in operating activities: | | |
| Depreciation and amortization | 6,750 | 7,038 |
| Stock-based compensation expense | 37,831 | 41,887 |
| Net amortization of premium (accretion of discount) on marketable securities | 721 | 5,326 |
| Loss on disposal of property and equipment | 29 | 9 |
| Non-cash operating lease expense | 7,432 | 7,129 |
| Changes in operating assets and liabilities: | | |
| Accounts receivable, net | (1,818) | — |
| Inventory | (5,176) | — |
| Other receivables | 604 | (6,990) |
| Prepaid expenses and other current and non-current assets | (7,655) | (19,249) |
| Accounts payable | (4,628) | (3,337) |
| Accrued expenses and other current liabilities | (2,211) | (2,667) |
| Operating lease liabilities | (7,646) | (5,315) |
| Other non-current liabilities | 779 | — |
| Net cash used in operating activities - continuing operations | (243,315) | (234,095) |
| Net cash used in operating activities - discontinued operations | — | (89,132) |
| Net cash used in operating activities | (243,315) | (323,227) |
| **Investing activities** | | |
| Purchases of marketable securities | (782,218) | (951,411) |
| Proceeds from maturities and sales of marketable securities | 947,296 | 492,911 |
| Purchases of property and equipment | (4,768) | (1,239) |
| Net cash provided by (used in) investing activities - continuing operations | 160,310 | (459,739) |
| Net cash provided by investing activities - discontinued operations | — | 1,802,936 |
| Net cash provided by investing activities | 160,310 | 1,343,197 |
| **Financing activities** | | |
| Payments on financing lease obligations | (248) | (773) |
| Purchase of treasury stock | — | (783,438) |
| Net proceeds from stock option exercises and employee stock purchase plan | 2,576 | 37,029 |
| Net cash provided by (used in) financing activities - continuing operations | 2,328 | (747,182) |
| Net cash provided by financing activities - discontinued operations | — | — |
| Net cash provided by (used in) financing activities | 2,328 | (747,182) |
| Net change in cash and cash equivalents | (80,677) | 272,788 |
| Cash and cash equivalents at beginning of the period | 203,126 | 127,436 |
| Cash and cash equivalents at end of the period | $ 122,449 | $ 400,224 |

| | | | | |
|---|---|---|---|---|
| **Supplemental disclosure of non-cash investing and financing transactions** | | | | |
| Additions to property and equipment in accounts payable and accrued expenses | $ | 21 | $ | 486 |
| Financing lease liabilities arising from obtaining financing lease assets | $ | — | $ | 511 |
| Cash taxes paid | $ | 1,940 | $ | 8,916 |

*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 leadership in the field of cellular metabolism, with the goal of creating differentiated, small molecule medicines for rare and genetically defined diseases, or GDDs. With a history of focused study on cellular metabolism, we have a deep and mature understanding of this biology, which is involved in the healthy functioning of nearly every system in the body. We accelerate the impact of our portfolio by cultivating connections with patient communities, healthcare professionals, partners and colleagues to discover, develop and deliver potential therapies for GDDs. We are located in Cambridge, Massachusetts.

The lead product candidate in our GDD portfolio, PYRUKYND® (mitapivat), is an activator of both wild-type and mutant pyruvate kinase, or PK, enzymes for the potential treatment of hemolytic anemias. On February 17, 2022, the U.S. Food and Drug Administration, or FDA, approved PYRUKYND® for the treatment of hemolytic anemia in adults with PK deficiency in the United States. In June 2021, we submitted a marketing authorization application, or MAA, to the European Medicines Agency, or EMA, for the treatment of adults with PK deficiency in the European Union, or EU. In September 2022, the Committee for Medicinal Products for Human Use of the EMA, or CHMP, adopted a positive opinion recommending the granting of a marketing authorization for PYRUKYND®. In October 2022, we submitted a marketing authorization application in Great Britain for PYRUKYND® under the European Commission Decision Reliance Procedure. We expect to receive a decision from both the EU and Great Britain regulatory authorities by the end of 2022. In addition, we are currently evaluating PYRUKYND® in clinical trials for the treatment of thalassemia, sickle cell disease, or SCD, and in pediatric patients with PK deficiency. We are also developing AG-946, a novel PK activator, for the potential treatment of lower-risk myelodysplastic syndrome, hemolytic anemias and other indications.

In addition to the aforementioned development programs, we continue to prioritize investment in advancing our late lead-optimization research. We believe this combination of assets represents an attractive portfolio of programs that aligns with our strategy and core expertise in non-malignant hematology and inborn errors of metabolism, and leaves room for continued growth of our pipeline.

We are subject to risks common to companies in our industry including, but not limited to, uncertainties relating to conducting clinical research and development, the manufacture and supply of products for clinical and commercial use, obtaining and maintaining regulatory approvals and pricing and reimbursement for our products, market acceptance, managing global growth and operating expenses, availability of additional capital, competition, obtaining and enforcing patents, stock price volatility, dependence on collaborative relationships and third-party service providers, dependence on key personnel, potential litigation, product liability claims and government investigations.

### *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, which represented a discontinued operation. 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 $200.0 million in cash, if, prior to January 1, 2027, vorasidenib is granted new drug application, or NDA, approval 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 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 $4.4 million and $2.0 million on U.S. net sales of TIBSOVO® by Servier in the royalty income from gain on sale of oncology business line item within the condensed consolidated statements of operations, for the three months ended September 30, 2022 and 2021, respectively, and $9.9 million and $4.0 million for the nine months ended September 30, 2022 and 2021, respectively.

As discussed below in Note 12, *Subsequent Events*, on October 27, 2022, we sold our rights to the royalty on U.S. net sales of TIBSOVO® to entities affiliated with Sagard Healthcare Partners, or Sagard, for $131.8 million. We retained our rights to the potential milestone payment and royalties from Servier if vorasidenib is approved by the FDA.

***Basis of presentation***

The condensed consolidated balance sheet as of September 30, 2022, the condensed consolidated statements of operations, comprehensive (loss) income and stockholders' equity for the three and nine months ended September 30, 2022 and 2021, and the condensed consolidated statements of cash flows for the nine months ended September 30, 2022 and 2021 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, 2022, our results of operations and stockholders' equity for the three and nine months ended September 30, 2022 and 2021, and cash flows for the nine months ended September 30, 2022 and 2021. 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, 2022 are not necessarily indicative of the results to be expected for the year ending December 31, 2022 or for any other future annual or interim period. The condensed consolidated balance sheet data as of December 31, 2021 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, 2021 that was filed with the Securities and Exchange Commission, or SEC, on February 24, 2022.

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 7.1 million shares of our common stock held by certain subsidiaries of BMS for an aggregate purchase price of $344.5 million, or $48.38 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 could repurchase up to $600.0 million of shares of our common stock.

On October 5, 2021, we terminated our Rule 10b5-1 share repurchase program 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. We have not repurchased any shares of common stock in fiscal year 2022 and as of December 31, 2021 we repurchased approximately 9.1 million shares of common stock for $458.0 million, or $50.35 per share, under the Rule 10b5-1 repurchase plan. As of September 30, 2022, we have not repurchased any shares under the Rule 10b-18 repurchase plan. In total, as of September 30, 2022, we repurchased 16.2 million shares of common stock for $802.5 million, or $49.49 per share, under the Repurchase Program. We have paused our share repurchases for the foreseeable future.

As of September 30, 2022, we had cash, cash equivalents and marketable securities of $1.0 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**

***Accounts receivable, net***

Our trade accounts receivable arise from product sales and represent amounts due from specialty distributors and specialty pharmacy providers in the U.S. We monitor the financial performance and creditworthiness of our customers so that we can properly assess and respond to changes in their credit profile. We reserve against these receivables for estimated losses that may arise from a customer's inability to pay. Amounts determined to be uncollectible are charged or written-off against the reserve.

***Inventory***

Inventory is stated at the lower of cost or estimated net realizable value on a first-in, first-out basis. Prior to the regulatory approval of our product candidates, we incur expenses for the manufacture of drug product that could potentially be available to support the commercial launch of those products. Until the date at which regulatory approval has been received or is otherwise considered probable, we record all such costs as research and development expenses. Upon approval of our wholly owned product, PYRUKYND®, by the FDA on February 17, 2022 for the treatment of hemolytic anemia in adults with PK deficiency in the United States, we began to capitalize inventories of PYRUKYND®.

***Revenue recognition***

Under Accounting Standards Codification 606, *Revenue from Contracts with Customers*, or ASC 606, revenue is recognized when the customer obtains control of promised goods or services, in an amount that reflects the consideration that we expect to receive in exchange for those goods or services. To determine revenue recognition for arrangements that have been determined to be within the scope of ASC 606, we perform the following five steps: (i) identify the contract(s) with a customer; (ii) identify the performance obligations in the contract; (iii) determine the transaction price; (iv) allocate the transaction price to the performance obligations in the contract; and (v) recognize revenue when (or as) we satisfy a performance obligation. We only apply the five-step model to contracts when it is probable that we will collect the consideration we are entitled to in exchange for the goods or services we transfer to the customer.

This standard applies to all contracts with customers, except for contracts that are within the scope of other standards, such as leases, insurance, collaboration arrangements and financial instruments.

Once the contract is determined to be within the scope of ASC 606, we assess the goods or services promised within each contract and determine those that are performance obligations, and assess whether each promised good or service is distinct. We will then recognize as revenue the amount of the transaction price that is allocated to the respective performance obligation when (or as) the performance obligation is satisfied.

Product Revenue

We generate product revenue from sales of PYRUKYND® to a limited number of specialty distributors and specialty pharmacy providers, or collectively, the Customers. These Customers subsequently resell PYRUKYND® to pharmacies or dispense directly to patients. In addition to distribution agreements with Customers, we enter into arrangements with healthcare providers and payors that provide for government-mandated and/or privately-negotiated rebates, chargebacks and discounts with respect to the purchase of PYRUKYND®.

The performance obligation related to the sale of PYRUKYND® is satisfied and revenue is recognized when the Customer obtains control of the product, which occurs at a point in time, typically upon delivery to the Customer.

Revenues from product sales are recorded at the net sales price, or transaction price, which includes estimates of variable consideration for which reserves are established and result from contractual adjustments, government rebates, returns and other allowances that are offered within the contracts with our Customers, healthcare providers, payors and other indirect customers relating to the sale of our products.

*Contractual Adjustments*. We generally provide Customers with discounts, including prompt pay discounts, and allowances that are explicitly stated in the contracts and are recorded as a reduction of revenue in the period the related product revenue is recognized. In addition, we receive sales order management, data and distribution services from certain Customers.

Chargebacks and discounts represent the estimated obligations resulting from contractual commitments to sell products to qualified healthcare providers at prices lower than the list prices charged to Customers who directly purchase the product from us. Customers charge us for the difference between what they pay for the product and the ultimate selling price to the qualified healthcare providers. These reserves are estimated using the expected value method, based upon a range of possible outcomes that are probability-weighted for the estimated channel mix and are established in the same period that the related revenue is recognized, resulting in a reduction of product revenue.

*Government Rebates*. Government rebates include Medicare, TriCare, and Medicaid rebates, which we estimate using the expected value method, based upon a range of possible outcomes that are probability-weighted for the estimated payor mix. These reserves are recorded in the same period the related revenue is recognized, resulting in a reduction of product revenue. For Medicare, we also estimate the number of patients in the prescription drug coverage gap for whom we will owe an additional liability under the Medicare Part D program.

*Returns*. We estimate the amount of product sales that may be returned by Customers and record this estimate as a reduction of revenue in the period the related product revenue is recognized. We currently estimate product return liabilities using the expected value method, based on available industry data, including our visibility into the inventory remaining in the distribution channel.

***Cost of sales***

Cost of sales consists primarily of manufacturing costs of PYRUKYND®. Based on our policy to expense costs associated with the manufacturing of our products prior to regulatory approval, certain of the manufacturing costs associated with product shipments of PYRUKYND® recorded during the three and nine months ended September 30, 2022 were expensed prior to February 17, 2022 and, therefore, are not included in costs of sales during the three and nine months ended September 30, 2022.

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, 2021.

***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. 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 and by level on a recurring basis as of September 30, 2022:

| (In thousands) | Level 1 | Level 2 | Level 3 | Total |
|---|---|---|---|---|
| Cash equivalents | $ 39,314 | $ 43,946 | $ — | $ 83,260 |
| Total cash equivalents | 39,314 | 43,946 | — | 83,260 |
| | | | | |
| Marketable securities: | | | | |
| U.S. Treasuries | — | 95,798 | — | 95,798 |
| Government securities | — | 308,256 | — | 308,256 |
| Corporate debt securities | — | 499,529 | — | 499,529 |
| Total marketable securities | — | 903,583 | — | 903,583 |
| Total cash equivalents and marketable securities | $ 39,314 | $ 947,529 | $ — | $ 986,843 |

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, 2022.

There have been no changes to the valuation methods during the nine months ended September 30, 2022, and we had no financial assets or liabilities that were classified as Level 3 at any point during the nine months ended September 30, 2022.

**4. 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 in the condensed consolidated balance sheets and statements of stockholders' equity and a component of total comprehensive loss 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 condensed consolidated balance sheets with a corresponding adjustment to earnings, and noncredit-related impairment is recognized in other comprehensive 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, 2022 or 2021.

Marketable securities at September 30, 2022 consisted of the following:

| (In thousands) | Amortized Cost | Unrealized Gains | Unrealized Losses | Fair Value |
|---|---|---|---|---|
| Current: | | | | |
| U.S. Treasuries | $ 80,730 | $ 15 | $ (777) | $ 79,968 |
| Government securities | 125,827 | — | (2,387) | 123,440 |
| Corporate debt securities | 405,159 | — | (3,336) | 401,823 |
| Total Current | 611,716 | 15 | (6,500) | 605,231 |
| | | | | |
| Non-current: | | | | |
| U.S. Treasuries | 16,381 | — | (551) | 15,830 |
| Government securities | 190,206 | 2 | (5,392) | 184,816 |
| Corporate debt securities | 100,363 | — | (2,657) | 97,706 |
| Total Non-current | 306,950 | 2 | (8,600) | 298,352 |
| Total marketable securities | $ 918,666 | $ 17 | $ (15,100) | $ 903,583 |

Marketable securities at December 31, 2021 consisted of the following:

| (In thousands) | Amortized Cost | Unrealized Gains | Unrealized Losses | Fair Value |
|---|---|---|---|---|
| Current: | | | | |
| U.S. Treasuries | $ 269,109 | $ — | $ (36) | $ 269,073 |
| Government securities | 17,764 | 1 | (10) | 17,755 |
| Corporate debt securities | 530,490 | 3 | (429) | 530,064 |
| Total Current | 817,363 | 4 | (475) | 816,892 |
| | | | | |
| Non-current: | | | | |
| U.S. Treasuries | 40,607 | — | (23) | 40,584 |
| Government securities | 148,820 | — | (470) | 148,350 |
| Corporate debt securities | 77,675 | — | (234) | 77,441 |
| Total Non-current | 267,102 | — | (727) | 266,375 |
| Total marketable securities | $ 1,084,465 | $ 4 | $ (1,202) | $ 1,083,267 |

As of September 30, 2022 and December 31, 2021, 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, 2022 and December 31, 2021, we held 257 and 294 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, 2022 and December 31, 2021 related to these securities. The aggregate fair value of debt securities in an unrealized loss position at September 30, 2022 and December 31, 2021 was $881.6 million and $950.5 million, respectively. There were no individual securities that were in a significant unrealized loss position as of September 30, 2022 and December 31, 2021. 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, 2022 and December 31, 2021.

**5. Inventory**

Inventory, which consists of commercial supply of PYRUKYND®, consisted of the following:

| (In thousands) | September 30, 2022 | December 31, 2021 |
|---|---|---|
| Raw materials | $ — | $ — |
| Work-in-process | 4,397 | — |
| Finished goods | 779 | — |
| Total inventory | $ 5,176 | $ — |

**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 approximately five 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:

| | Three Months Ended September 30, | | Nine Months Ended September 30, | |
|---|---|---|---|---|
| (In thousands) | 2022 | 2021 | 2022 | 2021 |
| Operating lease costs | $ 3,807 | $ 3,807 | $ 11,420 | $ 11,423 |
| Cash paid for amounts included in the measurement of operating lease liabilities | $ 4,420 | $ 3,614 | $ 12,610 | $ 10,773 |

We have not entered into any material short-term leases or financing leases as of September 30, 2022.

In arriving at the operating lease liabilities as of September 30, 2022 and December 31, 2021, we applied the weighted-average incremental borrowing rate of 5.7% for both periods over a weighted-average remaining lease term of 5.4 years and 6.2 years, respectively.

As of September 30, 2022, undiscounted minimum rental commitments under non-cancelable leases, for each of the next five years and total thereafter were as follows:

| (In thousands) | | |
|---|---|---|
| Remaining 2022 | $ | 2,950 |
| 2023 | | 18,126 |
| 2024 | | 18,660 |
| 2025 | | 19,507 |
| 2026 | | 20,151 |
| 2027 | | 20,755 |
| Thereafter | | 3,479 |
| Undiscounted minimum rental commitments | $ | 103,628 |
| Interest | | (14,787) |
| Operating lease liabilities | $ | 88,841 |

We provided our landlord a standby letter of credit of $2.9 million as security for our leases. We are not required to maintain any cash collateral for the standby letter of credit.

In August 2021, we entered into a long-term sublease agreement for 13,000 square feet of the office space at 38 Sidney Street, Cambridge, Massachusetts, with the term of the lease running through December 2024. In April 2022, we entered into a long-term sublease agreement for 27,000 square feet of the office space at 64 Sidney Street, Cambridge, Massachusetts, with the term of the lease running through April 2025. We recorded operating sublease income of $1.0 million and $2.7 million for the three and nine months ended September 30, 2022, respectively, in other income, net in the condensed consolidated statements of operations. We received a security deposit from our sublessee of approximately $1.1 million which is recorded within other non-current assets on our condensed consolidated balance sheet.

As of September 30, 2022, the future minimum lease payments to be received under the long-term sublease agreements were as follows:

| (In thousands) | | |
|---|---|---|
| Remaining 2022 | $ | 1,063 |
| 2023 | | 4,329 |
| 2024 | | 4,459 |
| 2025 | | 1,101 |
| Total | $ | 10,952 |

**7. Accrued Expenses**

Accrued expenses consisted of the following:

| (In thousands) | September 30, 2022 | December 31, 2021 |
|---|---|---|
| Accrued compensation | $ 15,747 | $ 19,818 |
| Accrued research and development costs | 7,716 | 5,980 |
| Accrued professional fees | 2,242 | 2,335 |
| Accrued other | 4,051 | 3,834 |
| Total accrued expenses | $ 29,756 | $ 31,967 |

**8. Product Revenue**

We sell PYRUKYND®, our wholly owned product, to the Customers. The Customers subsequently resell PYRUKYND® to pharmacies or dispense directly to patients. In addition to distribution agreements with Customers, we enter into arrangements with healthcare providers and payors that provide for government-mandated and/or privately-negotiated rebates, chargebacks and discounts with respect to the purchase of PYRUKYND®.

The performance obligation related to the sale of PYRUKYND® is satisfied and revenue is recognized when the Customer obtains control of the product, which occurs at a point in time, typically upon delivery to the Customer.

Product revenue, net, were as follows:

| | Three Months Ended September 30, | | Nine Months Ended September 30, | |
|---|---|---|---|---|
| (In thousands) | 2022 | 2021 | 2022 | 2021 |
| Product revenue, net | $ 3,516 | $ — | $ 7,430 | $ — |

***Reserves for Variable Consideration***

Revenues from product sales are recorded at the net sales price, or transaction price, which includes estimates of variable consideration for which reserves are established and result from contractual adjustments, government rebates, returns and other allowances that are offered within the contracts with our Customers, healthcare providers, payors and other indirect customers relating to the sale of our products.

*Contractual Adjustments*

We generally provide Customers with discounts, including prompt pay discounts, and allowances that are explicitly stated in the contracts and are recorded as a reduction of revenue in the period the related product revenue is recognized. In addition, we receive sales order management, data and distribution services from certain Customers.

Chargebacks and discounts represent the estimated obligations resulting from contractual commitments to sell products to qualified healthcare providers at prices lower than the list prices charged to Customers who directly purchase the product from us. Customers charge us for the difference between what they pay for the product and the ultimate selling price to the qualified healthcare providers. These reserves are estimated using the expected value method, based upon a range of possible outcomes that are probability-weighted for the estimated channel mix and are established in the same period that the related revenue is recognized, resulting in a reduction of product revenue.

*Government Rebates*

Government rebates include Medicare, TriCare, and Medicaid rebates, which we estimate using the expected value method, based upon a range of possible outcomes that are probability-weighted for the estimated payor mix. These reserves are recorded in the same period the related revenue is recognized, resulting in a reduction of product revenue. For Medicare, we also estimate the number of patients in the prescription drug coverage gap for whom we will owe an additional liability under the Medicare Part D program.

*Returns*

We estimate the amount of product sales that may be returned by Customers and record this estimate as a reduction of revenue in the period the related product revenue is recognized. We currently estimate product return liabilities using the expected value method, based on available industry data, including our visibility into the inventory remaining in the distribution channel.

The following table summarizes balances and activity in each of the product revenue allowance and reserve categories for the nine months ended September 30, 2022:

| (In thousands) | Contractual Adjustments | Government Rebates | Returns | Total |
|---|---|---|---|---|
| Balance at December 31, 2021 | $ — | $ — | $ — | $ — |
| Current provisions relating to sales in the current year | 298 | 474 | 83 | 855 |
| Adjustments relating to prior years | — | — | — | — |
| Payments/returns relating to sales in the current year | (235) | (119) | — | (354) |
| Payments/returns relating to sales in the prior years | — | — | — | — |
| Balance at September 30, 2022 | $ 63 | $ 355 | $ 83 | $ 501 |

Total revenue-related reserves above, included in our condensed consolidated balance sheets, are summarized as follows:

| (In thousands) | September 30, 2022 | December 31, 2021 |
|---|---|---|
| Reduction of accounts receivable | $ 53 | $ — |
| Component of accrued expenses | 448 | — |
| Total revenue-related reserves | $ 501 | $ — |

The following table presents changes in our contract assets during the nine months ended September 30, 2022:

| (In thousands) | December 31, 2021 | Additions | Deductions | September 30, 2022 |
|---|---|---|---|---|
| Contract assets[1] | | | | |
| Accounts receivable, net | $ — | $ 8,285 | $ (6,467) | $ 1,818 |

(1) Additions to contract assets relate to amounts billed to Customers for product sales and deductions to contract assets primarily relate to collection of receivables during the reporting period.

## 9. 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, 2022, the total number of shares reserved under the 2007 Plan and the 2013 Plan was 12,967,465, and we had 5,268,971 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, 2022:

| | Number of Stock Options | Weighted-Average Exercise Price |
|---|---|---|
| Outstanding at December 31, 2021 | 4,798,826 | $ 58.51 |
| Granted | 1,829,973 | 28.89 |
| Exercised | (5,476) | 13.18 |
| Forfeited/Expired | (714,236) | 63.40 |
| Outstanding at September 30, 2022 | 5,909,087 | $ 48.81 |
| Exercisable at September 30, 2022 | 3,478,806 | $ 57.97 |
| Vested and expected to vest at September 30, 2022 | 5,909,087 | $ 48.81 |

At September 30, 2022, there was approximately $45.3 million of total unrecognized compensation expense related to unvested stock option awards, which we expect to recognize over a weighted-average period of approximately 2.8 years.

*Restricted stock units*

The following table presents RSU activity for the nine months ended September 30, 2022:

| | Number of Stock Units | Weighted-Average Grant Date Fair Value |
|---|---|---|
| Unvested shares at December 31, 2021 | 1,002,924 | $ 51.51 |
| Granted | 856,708 | 31.19 |
| Vested | (395,691) | 53.40 |
| Forfeited | (199,564) | 41.02 |
| Unvested shares at September 30, 2022 | 1,264,377 | $ 38.85 |

As of September 30, 2022, there was approximately $31.6 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, 2022:

| | Number of Stock Units | Weighted-Average Grant Date Fair Value |
|---|---|---|
| Unvested shares at December 31, 2021 | 234,059 | $ 54.28 |
| Granted | 337,243 | 30.33 |
| Vested | (53,777) | 54.28 |
| Forfeited | (35,190) | 45.20 |
| Unvested shares at September 30, 2022 | 482,335 | $ 38.19 |

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

As of September 30, 2022, there was no unrecognized compensation expense related to PSUs with performance-based vesting criteria that are considered probable of achievement, and $18.4 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, 2022:

| | Number of Stock Units | Weighted-Average Grant Date Fair Value |
|---|---|---|
| Unvested shares at December 31, 2021 | 42,695 | $ 41.50 |
| Granted | — | — |
| Unvested shares at September 30, 2022 | 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, 2022, 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 104,867 and 94,888 shares of common stock during the nine months ended September 30, 2022 and 2021, respectively, under the 2013 ESPP. The 2013 ESPP provides participating employees with the opportunity to purchase up to an aggregate of 1,854,545 shares of our common stock. As of September 30, 2022, we had 1,289,780 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) | 2022 | 2021 | 2022 | 2021 |
| Stock options | $ 5,864 | $ 7,214 | $ 17,720 | $ 24,399 |
| Restricted stock units | 5,115 | 4,735 | 16,512 | 16,724 |
| Performance-based stock units | — | — | 2,919 | — |
| Employee stock purchase plan | 177 | 199 | 680 | 764 |
| Total stock-based compensation expense | $ 11,156 | $ 12,148 | $ 37,831 | $ 41,887 |

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

| (In thousands) | Three Months Ended September 30, 2022 | Three Months Ended September 30, 2021 | Nine Months Ended September 30, 2022 | Nine Months Ended September 30, 2021 |
|---|---|---|---|---|
| Research and development expense | $ 4,628 | $ 5,607 | $ 16,207 | $ 19,002 |
| Selling, general and administrative expense | 6,528 | 6,541 | 21,624 | 22,885 |
| Total stock-based compensation expense | $ 11,156 | $ 12,148 | $ 37,831 | $ 41,887 |

**10. 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, 2022 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 net 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 from 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, 2022 | Three and Nine Months Ended September 30, 2021 |
|---|---|---|
| Stock options | 5,909,087 | 5,032,591 |
| Restricted stock units | 1,264,377 | 1,081,482 |
| Performance-based stock units | — | — |
| Employee stock purchase plan shares | 10,503 | 7,470 |
| Total common stock equivalents | 7,183,967 | 6,121,543 |

**11. Income Taxes**

We recorded no provision for income taxes for the three months ended September 30, 2022 and a provision of $3.9 million for the three months ended September 30, 2021, and recorded no provision for income taxes for the nine months ended September 30, 2022 and $16.8 million for the nine months ended September 30, 2021. The tax provision for the nine months ended September 30, 2021 was recorded within discontinued operations as it related 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, 2022 and 2021. Cash taxes paid were $1.9 million and $8.9 million for the nine months ended September 30, 2022 and 2021, respectively.

**12. Subsequent Events**

On October 27, 2022, we entered into an agreement with entities affiliated with Sagard Healthcare Partners, or Sagard, and sold our rights to the royalty on U.S. net sales of TIBSOVO® for $131.8 million. This royalty was part of the consideration for our March 31, 2021 sale of our oncology business to Servier. We received payment from Sagard on October 27, 2022.

## 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 in conjunction with our unaudited condensed consolidated financial statements as of September 30, 2022 and for the three and nine months ended September 30, 2022 and 2021, 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, 2021 filed with the SEC on February 24, 2022. 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, 2021. 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 leadership in the field of cellular metabolism, with the goal of creating differentiated, small molecule medicines for rare and genetically defined diseases, or GDDs. With a history of focused study on cellular metabolism, we have a deep and mature understanding of this biology, which is involved in the healthy functioning of nearly every system in the body. We accelerate the impact of our portfolio by cultivating connections with patient communities, healthcare professionals, partners and colleagues to discover, develop and deliver potential therapies for GDDs.

The lead product candidate in our GDD portfolio, PYRUKYND® (mitapivat), is an activator of both wild-type and mutant pyruvate kinase, or PK, enzymes for the potential treatment of hemolytic anemias. On February 17, 2022, the U.S. Food and Drug Administration, or FDA, approved PYRUKYND® for the treatment of hemolytic anemia in adults with PK deficiency in the United States. In June 2021, we submitted a marketing authorization application, or MAA, to the European Medicines Agency, or EMA, for the treatment of adults with PK deficiency in the European Union, or EU. In September 2022, the Committee for Medicinal Products for Human Use of the EMA, or CHMP, adopted a positive opinion recommending the granting of a marketing authorization for PYRUKYND®. In October 2022, we submitted a marketing authorization application in Great Britain for PYRUKYND® under the European Commission Decision Reliance Procedure. We expect to receive a decision from both the EU and Great Britain regulatory authorities by the end of 2022. In addition, we are currently evaluating PYRUKYND® in clinical trials for the treatment of thalassemia, sickle cell disease, or SCD, and in pediatric patients with PK deficiency. We are also developing AG-946, a novel PK activator, for the potential treatment of lower-risk myelodysplastic syndrome, hemolytic anemias and other indications.

In addition to the aforementioned development programs, we continue to prioritize investment in advancing our late lead-optimization research. We believe this combination of assets represents an attractive portfolio of programs that aligns with our strategy and core expertise in non-malignant hematology and inborn errors of metabolism, and leaves room for continued growth of our pipeline.

#### *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, which represented a discontinued operation. 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 $200.0 million in cash, if, prior to January 1, 2027, vorasidenib is granted new drug application, or NDA, approval 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 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, or Celgene, and following the sale Servier will conduct certain clinical development activities within the IDHIFA® development program.

As discussed above in Note 12, *Subsequent Events*, on October 27 2022, we sold our rights to the royalty on U.S. net sales of TIBSOVO® to entities affiliated with Sagard Healthcare Partners, or Sagard, for $131.8 million. We retained our rights to the potential milestone payment and royalties from Servier if vorasidenib is approved by the FDA.

***Evolution of our Research Organization***

In May 2022, we announced our determination to evolve our approach to exploratory research and drug discovery to focus on our existing late-lead optimization programs and to prioritize in-licensing or acquiring assets for pipeline growth.

We reduced approximately 45 roles focused on exploratory research in connection with the evolution of our research organization, and plan to retain an internal research team focused on roles critical to advancing our current and future late-stage research and early clinical programs. We estimate that this initiative may provide annual average cost savings of approximately $40 million to $50 million associated with research and related expenses between 2023 and 2026.

**Financial Operations Overview**

***Impact of COVID-19 on our Business***

As of September 30, 2022, 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 and we may in the future experience further such disruptions. In addition, we have experienced disruptions to certain clinical and research activities at our contract research organizations, or CROs, due to the recent COVID-19 surges. We have been monitoring our supply chain network for disruptions due to the COVID-19 pandemic, and our third-party manufacturers, other than certain CROs based in China, 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 customers could negatively impact our consolidated financial position, results of operations and 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, preparing for and executing on the commercial launch of PYRUKYND® and, prior to the sale of our oncology business to Servier on March 31, 2021, marketing TIBSOVO® and IDHIFA®. 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 have financed and expect to continue to finance our operations primarily through cash on hand, royalty payments from Servier with respect to U.S. net sales of TIBSOVO® prior to the sale of these royalty rights to Sagard, proceeds from the sale of our rights to the royalty on U.S. net sales of TIBSOVO® to Sagard, a potential milestone payment and royalties from Servier if vorasidenib is approved by the FDA, the actual and potential future sales of PYRUKYND® and, potentially, collaborations, strategic alliances, licensing arrangements and other nondilutive strategic transactions.

We have historically incurred operating losses. Our net loss for the nine months ended September 30, 2022 was $268.3 million and our net income for the nine months ended September 30, 2021 was $1,699.3 million. As of September 30, 2022, we had an

accumulated deficit of $507.1 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. 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: PYRUKYND®, and AG-946; continue to prioritize advancement of our late lead-optimization research; expand and protect our intellectual property portfolio, including by in-licensing or acquiring assets for pipeline growth; and hire additional commercial and development personnel.

***Revenues***

Our wholly owned product, PYRUKYND®, received approval from the FDA on February 17, 2022, for the treatment of hemolytic anemia in adults with PK deficiency in the United States. Upon FDA approval of PYRUKYND® in the United States, we began generating product revenue from sales of PYRUKYND®. We sell PYRUKYND® to a limited number of specialty distributors and specialty pharmacy providers, or collectively, the Customers. These Customers subsequently resell PYRUKYND® to pharmacies or dispense directly to patients. In addition to distribution agreements with Customers, we enter into arrangements with healthcare providers and payors that provide for government-mandated and/or privately-negotiated rebates, chargebacks and discounts with respect to the purchase of PYRUKYND®. For further discussion of our revenue recognition policy, see Note 2, *Summary of Significant Accounting Polices* and Note 8, *Product Revenue*, to the condensed consolidated financial statements in this Form 10-Q.

In the future, we expect to continue to generate revenue from a combination of product sales, royalties on product sales, cost reimbursements, milestone payments, and upfront payments to the extent we enter into future collaborations or licensing agreements.

***Cost of Sales***

Cost of sales consists primarily of manufacturing costs for sales of PYRUKYND®. Based on our policy to expense costs associated with the manufacturing of our products prior to regulatory approval, certain of the manufacturing costs associated with product shipments of PYRUKYND® recorded during the three and nine months ended September 30, 2022 were expensed prior to February 17, 2022, and, therefore, are not included in costs of sales during the three and nine months ended September 30, 2022.

***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 unable to predict the amount of net cash inflows from PYRUKYND® or any of our 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 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 our most advanced programs:

***PYRUKYND® (mitapivat): First-in-Class PK Activator***

We are developing PYRUKYND® for the treatment of PK deficiency and other hemolytic anemias such as thalassemia and SCD. PYRUKYND® is an orally available small molecule and a potent activator of the wild-type and mutated PK enzymes.

In February 2022, the FDA approved PYRUKYND® for the treatment of hemolytic anemia in adults with PK deficiency in the United States. In June 2021, we submitted an MAA to the EMA for the treatment of adults with PK deficiency in the EU. In September 2022, the Committee for Medicinal Products for Human Use of the EMA, or CHMP, adopted a positive opinion recommending the granting of a marketing authorization for PYRUKYND®. In October 2022, we submitted a marketing authorization application in Great Britain for PYRUKYND® under the European Commission Decision Reliance Procedure. We expect to receive a decision on marketing authorization from both the EU and Great Britain regulatory authorities by the end of 2022. We have worldwide development and commercial rights to PYRUKYND® and expect to fund the future development and commercialization costs related to this program. PYRUKYND® has been granted orphan drug designation for the treatment of PK deficiency by the FDA and the EMA. Additionally, PYRUKYND® has received orphan drug designation from the FDA for the treatment of thalassemia and SCD. We have built our commercial infrastructure to support the commercial launch of PYRUKYND® in adult PK deficiency in the United States. If approved, we are committed to providing patient access in the EU and Great Britain. Our current plan is to provide access through a global managed access program, which provides a pathway for eligible adults receiving care in the EU and Great Britain who are diagnosed with PK deficiency to have access to PYRUKYND® free of charge. Beyond the global managed access program, we continue to evaluate options for the commercialization of PYRUKYND® outside of the United States, including through exploring potential partnership opportunities.

We are evaluating PYRUKYND® in the following clinical trials:

- ENERGIZE, a phase 3, double-blind, randomized, placebo-controlled multicenter study evaluating the efficacy and safety of PYRUKYND® as a potential treatment for adults with non-transfusion-dependent α- or β-thalassemia, defined as ≤5 red blood cell, or RBC, units during the 24-week period before randomization and no RBC transfusions ≤8 weeks before providing informed consent or during the screening period. The primary endpoint of the trial is percentage of patients with hemoglobin response, defined as a ≥1.0 g/dL increase in average hemoglobin concentration from Week 12 through Week 24 compared with baseline. Secondary endpoints include markers of hemolysis and ineffective erythropoiesis, as well as patient-reported outcome measures. This trial is enrolling patients, and we expect to enroll a meaningful portion of the patients by the end of 2022.
- ENERGIZE-T, a phase 3, double-blind, randomized, placebo-controlled multicenter study evaluating the efficacy and safety of PYRUKYND® as a potential treatment for adults with transfusion-dependent α- or β-thalassemia, defined as 6 to 20 RBC units transfused and ≤6-week transfusion-free period during the 24-week period before randomization. The primary endpoint of the trial is percentage of patients with transfusion reduction response, defined as a ≥50% reduction in transfused RBC units with a reduction of ≥2 units of transfused RBCs in any consecutive 12-week period through Week 48 compared with baseline. Secondary endpoints include additional transfusion reduction measures and percentage of participants with transfusion-independence. This trial is enrolling patients, and we expect to enroll a meaningful portion of the patients by the end of 2022.
- RISE UP, a phase 2/3 study evaluating the efficacy and safety of PYRUKYND® in SCD patients who are 16 years of age or older, have had between two and 10 sickle cell pain crises in the past 12 months, and have hemoglobin within the range of 5.5 to 10.5 g/dL during screening. The phase 2 portion of the trial, which has initiated, includes a 12-week randomized, placebo-controlled period in which participants will be randomized in a 1:1:1 ratio to receive 50 mg PYRUKYND® twice daily, 100 mg PYRUKYND® twice daily or matched placebo. The primary endpoints are hemoglobin response, defined as ≥1 g/dL increase in average hemoglobin concentration from Week 10 through Week 12 compared to baseline, and safety. These data will be used to establish a clear dosing paradigm for the phase 3 portion. The phase 3 portion includes a 52-week randomized, placebo-controlled period in which participants will be randomized in a 2:1 ratio to receive the recommended PYRUKYND® dose level or placebo. The primary endpoints are hemoglobin response, defined as ≥1 g/dL increase in average hemoglobin from baseline to Week 52, and annualized rate of sickle

cell pain crises. Participants who complete either the phase 2 or phase 3 portion will have the option to move into a 216-week open-label extension period to continue to receive PYRUKYND®. The phase 2 portion of this trial is enrolling patients, and we expect to complete enrollment in the phase 2 portion of the trial by the end of 2022.

- ACTIVATE-kids and ACTIVATE-kidsT, double-blind phase 3 studies evaluating the efficacy and safety of PYRUKYND® as a potential treatment for PK deficiency in not regularly transfused and regularly transfused patents between one and 18 years old, respectively. The primary endpoint of ACTIVATE-kids is percentage of patients with hemoglobin response, defined as ≥1.5 g/dL increase in hemoglobin concentration from baseline that is sustained at two or more scheduled assessments at weeks 12, 16, and 20 during the double-blind period. The primary endpoint of ACTIVATE-kidsT is transfusion reduction response, defined as ≥33% reduction in total RBC transfusion volume from week 9 through week 32 of the double-blind period. Both trials are enrolling patients.
- An extension study evaluating the long-term safety, tolerability and efficacy of treatment with PYRUKYND® in patients from ACTIVATE and ACTIVATE-T, our completed pivotal trials of PYRUKYND® in not regularly transfused and regularly transfused adult patients with PK deficiency.
- An extension study evaluating the long-term safety, tolerability and efficacy of treatment with PYRUKYND® in patients from DRIVE PK, our completed global phase 2, first-in-patient, open-label safety and efficacy clinical trial of PYRUKYND® in adult, not regularly transfused patients with PK deficiency.
- An extension study evaluating the safety, tolerability and efficacy of treatment with PYRUKYND® in patients from our completed phase 2, open-label safety and efficacy clinical trial of PYRUKYND® in adults with non-transfusion-dependent α- and β-thalassemia.
- In collaboration with the National Institutes of Health, or NIH, we are evaluating PYRUKYND® in a phase 1 trial in patients with SCD pursuant to a cooperative research and development agreement. The core trial period has completed. The long-term extension study is ongoing. 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 PYRUKYND® in patients with SCD pursuant to an investigator sponsored trial agreement. The trial has completed enrollment and patient follow-up is ongoing, and a 2-year extension study has been activated for patients who complete the follow-up period.

*AG-946: Novel PK Activator*

We are developing AG-946, a novel PK activator, for the potential treatment of hemolytic anemias and other indications. We are evaluating AG-946, in a phase 1 trial of AG-946 in healthy volunteers and in patients with SCD. The trial has completed the healthy volunteer cohort, and we have initiated the SCD patient cohort of this trial. We initiated a phase 2a study of AG-946 in adults with lower-risk myelodysplastic syndrome, or MDS, in the third quarter of 2022.

In addition to the aforementioned development programs, we are advancing our late lead-optimization research.

***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 ongoing and future commercialization activities related to our GDD portfolio, including the commercialization of PYRUKYND® and any of our other 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.

**Critical Accounting Estimates**

Our critical accounting estimates are those 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 estimates are those relating to revenue recognition, 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 material changes to our existing critical accounting estimates discussed in Part II, Item 7 of our Annual Report on Form 10-K for the year ended December 31, 2021.

**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, 2022 and 2021***

***Revenues***

| (In thousands) | Three Months Ended September 30, 2022 | Three Months Ended September 30, 2021 | Nine Months Ended September 30, 2022 | Nine Months Ended September 30, 2021 |
|---|---|---|---|---|
| Revenues: | | | | |
| Product revenue, net | $ 3,516 | $ — | $ 7,430 | $ — |
| Milestone revenue | — | — | 2,500 | — |
| Total revenue | $ 3,516 | $ — | $ 9,930 | $ — |

*Total Revenue - Three Months Ended September 30, 2022 vs. Three Months Ended September 30, 2021* – The increase in total revenue of $3.5 million for the three months ended September 30, 2022 compared to the three months ended September 30, 2021 was due to product revenue associated with PYRUKYND®, which was approved in February 2022.

*Total Revenue - Nine Months Ended September 30, 2022 vs. Nine Months Ended September 30, 2021* – The increase in total revenue of $9.9 million for the nine months ended September 30, 2022 compared to the nine months ended September 30, 2021 was due to product revenue associated with PYRUKYND®, which was approved in February 2022, and revenue recognized associated with the licensing of intellectual property for our Friedreich's Ataxia preclinical program.

***Total Operating Expenses***

| (In thousands) | Three Months Ended September 30, 2022 | Three Months Ended September 30, 2021 | Nine Months Ended September 30, 2022 | Nine Months Ended September 30, 2021 |
|---|---|---|---|---|
| Operating expenses: | | | | |
| Cost of sales | $ 517 | $ — | $ 1,291 | $ — |
| Research and development | 64,966 | 64,000 | 209,612 | 183,674 |
| Selling, general and administrative | 29,123 | 27,152 | 88,902 | 89,917 |
| Total operating expenses | $ 94,606 | $ 91,152 | $ 299,805 | $ 273,591 |

*Total Operating Expenses - Three Months Ended September 30, 2022 vs. Three Months Ended September 30, 2021* – The increase in total operating expenses of $3.5 million for the three months ended September 30, 2022 compared to the three months ended September 30, 2021 was primarily due to an increase in selling, general and administrative expenses of $2.0 million, driven by an increase in workforce-related expenses.

*Total Operating Expenses - Nine Months Ended September 30, 2022 vs. Nine Months Ended September 30, 2021* – The increase in total operating expenses of $26.2 million for the nine months ended September 30, 2022 compared to the nine months ended September 30, 2021 was primarily due to an increase in research and development expenses of $25.9 million which is described below under Research and Development Expenses, partially offset by a decrease in selling, general and administrative expenses of $1.0 million due to a reduction in workforce-related expenses. Included in selling, general and administrative expenses for the nine months ended September 30, 2021 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, 2022 | Three Months Ended September 30, 2021 | Nine Months Ended September 30, 2022 | Nine Months Ended September 30, 2021 |
|---|---|---|---|---|
| PK activator (PYRUKYND®) | $ 20,906 | $ 20,130 | $ 57,036 | $ 49,543 |
| Novel PK activator (AG-946) | 2,943 | 2,820 | 11,517 | 6,849 |
| Other research and platform programs | 4,945 | 6,109 | 20,669 | 14,684 |
| Total direct research and development expenses | 28,794 | 29,059 | 89,222 | 71,076 |
| Compensation and related expenses | 25,959 | 21,816 | 86,481 | 70,965 |
| Facilities and IT related expenses & other | 10,213 | 9,883 | 32,392 | 33,987 |
| Other expenses - transition services | — | 3,242 | 1,517 | 7,646 |
| Total indirect research and development expenses | 36,172 | 34,941 | 120,390 | 112,598 |
| Total research and development expense | $ 64,966 | $ 64,000 | $ 209,612 | $ 183,674 |

*Total Research and Development Expenses - Three Months Ended September 30, 2022 vs. Three Months Ended September 30, 2021* – Total research and development expenses for the three months ended September 30, 2022 remained relatively consistent with the three months ended September 30, 2021.

*Total Research and Development Expenses - Nine Months Ended September 30, 2022 vs. Nine Months Ended September 30, 2021* – The increase in total research and development expenses of $25.9 million for the nine months ended September 30, 2022 compared to the nine months ended September 30, 2021 was due to an $18.1 million increase in our direct expenses and a $7.8 million increase in our indirect expenses. The increase in direct expenses was due to a $7.5 million increase in PYRUKYND® costs, a $6.0 million increase in other research and platform programs, and a $4.6 million increase in AG-946 costs. The increase in PYRUKYND® costs was primarily due to startup costs for the phase 3 trials of PYRUKYND® in patients with thalassemia, ENERGIZE and ENERGIZE-T, the phase 3 trials of PYRUKYND® in pediatric patients with PK deficiency, ACTIVATE-kids and ACTIVATE-kidsT, and the phase 2/3 trial of PYRUKYND® in patients with SCD, RISE UP, offset by closeouts of the ACTIVATE and ACTIVATE-T studies. The increase in other research and platform programs was primarily driven by planned increased activity associated with our preclinical PAH program as well as planned increased activity on various other exploratory activities. The increase in AG-946 costs was primarily due to start-up costs for the phase 2 trial of AG-946 in patients with lower-risk MDS and increased spend for the phase 1 trial of AG-946 in healthy volunteers and in patients with SCD. The increase in indirect expenses was primarily due to an $15.5 million increase in compensation and related expenses primarily due to increased headcount, as well as certain workforce-related expenses associated with the evolution of our research organization. This increase was partially offset by $6.1 million of additional reimbursable transition related services we provided to Servier in the nine months ended September 30, 2021 compared to the nine months ended September 30, 2022 related to the sale of the oncology business for discovery, clinical development, technical operations, and related activities, which were completed during the three months ended March 31, 2022.

***Other Income and Expense***

| (In thousands) | Three Months Ended September 30, 2022 | Three Months Ended September 30, 2021 | Nine Months Ended September 30, 2022 | Nine Months Ended September 30, 2021 |
|---|---|---|---|---|
| Royalty income from gain on sale of oncology business | $ 4,443 | $ 1,996 | $ 9,851 | $ 3,996 |
| Interest income, net | 3,818 | 256 | 6,305 | 504 |
| Other income, net | 1,082 | 4,641 | 5,392 | 11,165 |

*Other Income and Expense - Three Months Ended September 30, 2022 vs. Three Months Ended September 30, 2021* – The $3.6 million decrease in other income, net in the three months ended September 30, 2022 compared to the three months ended September 30, 2021 primarily related to approximately $4.5 million of reimbursable transition related services and fees for the sale of the oncology business in the three months ended September 30, 2021, partially offset by sublease income of $1.0 million in the three months ended September 30, 2022. The $3.6 million increase in interest income, net in the three months ended September 30, 2022 compared to the three months ended September 30, 2021 was primarily attributable to an increase in interest rates. The $2.4 million increase in royalty income from gain on sale of oncology business related to higher income from royalties on U.S. net sales of TIBSOVO® by Servier in the three months ended September 30, 2022 compared to the three months ended September 30, 2021.

*Other Income and Expense - Nine Months Ended September 30, 2022 vs. Nine Months Ended September 30, 2021* – The $5.9 million increase in royalty income from gain on sale of oncology business related to higher income from royalties on U.S.

net sales of TIBSOVO® by Servier in the nine months ended September 30, 2022 compared to the nine months ended September 30, 2021. The $5.8 million increase in interest income, net in the nine months ended September 30, 2022 compared to the nine months ended September 30, 2021 is primarily attributable to an increase in interest rates. The $5.8 million decrease in other income, net in the nine months ended September 30, 2022 compared to the nine months ended September 30, 2021 primarily related to approximately $11.0 million of reimbursable transition related services and fees for the sale of the oncology business in the nine months ended September 30, 2021 compared to $2.6 million in the nine months ended September 30, 2022, partially offset by sublease income of $2.7 million in the nine months ended September 30, 2022.

***Loss from Operations and Net (Loss) Income***

| | Three Months Ended September 30, | | Nine Months Ended September 30, | |
|---|---|---|---|---|
| (In thousands) | 2022 | 2021 | 2022 | 2021 |
| Net loss from continuing operations | $ (81,747) | $ (84,259) | $ (268,327) | $ (257,926) |
| Net (loss) income from discontinued operations, net of tax | — | (4,507) | — | 1,957,268 |
| Net (loss) income | $ (81,747) | $ (88,766) | $ (268,327) | $ 1,699,342 |

*Loss from Operations and Net (Loss) Income - Three Months Ended September 30, 2022 vs. Three Months Ended September 30, 2021* – The $2.5 million decrease in net loss from continuing operations for the three months ended September 30, 2022 compared to the three months ended September 30, 2021 was primarily driven by the increase in revenue discussed above under Revenues and the increase in interest income, net and royalty income from gain on sale of oncology business discussed above under Other Income and Expense, partially offset by a decrease in other income, net discussed above under Other Income and Expense, higher selling, general and administrative expenses discussed above under Total Operating Expenses and higher research and development expenses discussed above under Research and Development Expenses. The change in net (loss) income from discontinued operations for the three months ended September 30, 2022 compared to the three months ended September 30, 2021 was driven by the sale of our oncology business to Servier.

*Loss from Operations and Net (Loss) Income - Nine Months Ended September 30, 2022 vs. Nine Months Ended September 30, 2021* – The $10.4 million increase in net loss from continuing operations for the nine months ended September 30, 2022 compared to the nine months ended September 30, 2021 was primarily driven by the higher research and development expenses discussed above under Research and Development Expenses and a decrease in other income, net discussed above under Other Income and Expense, partially offset by the increase in revenue in the nine months ended September 30, 2022 discussed above under Revenues and the increase in interest income, net and royalty income from gain on sale of oncology business discussed above under Other Income and Expense. The change in net (loss) income from discontinued operations and net (loss) income for the nine months ended September 30, 2022 compared to the nine months ended September 30, 2021 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 (loss) income from discontinued operations.

**Liquidity and Capital Resources**

***Sources of liquidity***

Since our inception, and through September 30, 2022, we have funded our operations 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 have financed and expect to continue to finance our operations primarily through cash on hand, royalty payments from Servier with respect to U.S. net sales of TIBSOVO® prior to the sale of these royalty rights to Sagard, proceeds from the sale of our rights to the royalty on U.S. net sales of TIBSOVO® to Sagard, a potential milestone payment and royalties from Servier if vorasidenib is approved by the FDA, the actual and potential future sales of PYRUKYND® and, potentially, collaborations, strategic alliances, licensing arrangements and other nondilutive strategic transactions.

On March 31, 2021, we completed the sale of our oncology business to 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 $200.0 million in cash, if, prior to January 1, 2027, vorasidenib is granted NDA approval 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 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, and following the sale Servier is responsible for conducting certain clinical development activities

within the IDHIFA® development program. As discussed above in Note 12, *Subsequent Events*, on October 27, 2022, we sold our rights to the royalty on U.S. net sales of TIBSOVO® to Sagard for $131.8 million. We retained our rights to the potential milestone payment and royalties from Servier if vorasidenib is approved by the FDA.

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 7.1 million shares of our common stock held by certain subsidiaries of BMS for an aggregate purchase price of $344.5 million, or $48.38 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 could repurchase up to $600.0 million of shares of our common stock. 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 not repurchased any shares of common stock in fiscal year 2022 and as of December 31, 2021, we repurchased approximately 9.1 million shares of common stock for $458.0 million, or $50.35 per share, under the Rule 10b5-1 repurchase plan. As of September 30, 2022, we have not repurchased any shares under the Rule 10b-18 repurchase plan. In total, as of September 30, 2022, we repurchased 16.2 million shares of common stock for $802.5 million, or $49.49 per share, 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 cash, cash equivalents and marketable securities of $1.0 billion and the $131.8 million payment received from Sagard on October 27, 2022, we are eligible to receive a $200.0 million milestone payment and royalty payments on U.S. net sales of vorasidenib under our transaction agreement with Servier. Our right to such payments under our transaction agreement with 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 vorasidenib, if approved, 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 vorasidenib.

***Cash flows***

The following table provides information regarding our cash flows for the nine months ended September 30, 2022 and 2021:

| | Nine Months Ended September 30, | |
|---|---|---|
| (In thousands) | **2022** | **2021** |
| Net cash used in operating activities | $ (243,315) | $ (323,227) |
| Net cash provided by investing activities | 160,310 | 1,343,197 |
| Net cash provided by (used in) financing activities | 2,328 | (747,182) |
| Net change in cash and cash equivalents | $ (80,677) | $ 272,788 |

*Net cash used in operating activities.* Cash used in operating activities of $243.3 million during the nine months ended September 30, 2022, of which all was used by continuing operations, was primarily due to operating expenses driven by research and development costs described above under Research and Development Expenses, partially offset by cash received from revenues of $8.8 million and royalties on U.S. net sales of TIBSOVO® of $8.6 million.

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.

*Net cash provided by investing activities*. Cash provided by investing activities of $160.3 million during the nine months ended September 30, 2022, of which all was used by continuing operations, was primarily due to higher proceeds from maturities and sales of marketable securities than purchases of marketable securities.

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.

*Net cash provided by (used in) financing activities*. Cash provided by financing activities of $2.3 million during the nine months ended September 30, 2022, of which all was provided by continuing operations, was primarily the result of the $2.6 million of

proceeds received from stock option exercises and purchases made pursuant to our 2013 Employee Stock Purchase Plan, or 2013 ESPP.

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, 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.

***Funding requirements***

Although our expenses decreased 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 continue the research, development and clinical trials of, seek marketing approvals for, and commercialize our product candidates in our GDD portfolio, including as we commercialize PYRUKYND®. If we obtain marketing approval for PYRUKYND® in other indications outside of the United States or 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, 2022 and the $131.8 million payment received from Sagard on October 27, 2022 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 and timing of future revenue received from commercial sales of PYRUKYND® or any of our product candidates for which we may receive marketing approval;
- the amount of contingent consideration we ultimately receive from Servier;
- the costs and timing of our ongoing commercialization activities, including product manufacturing, sales, marketing and distribution for PYRUKYND® for the treatment of hemolytic anemia in adults with PK deficiency;
- the anticipated cost-savings associated with the evolution of our research organization;
- the scope, progress, results and costs of drug discovery, preclinical development, laboratory testing and clinical trials for our product candidates;
- the costs associated with in-licensing or acquiring assets for pipeline growth;
- 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;
- 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
- operational delays, disruptions and/or increased costs associated with rising global energy prices or energy shortages or rationing.

Until such time, if ever, as we can generate substantial product revenue, we expect to finance our cash needs primarily through cash on hand, proceeds from the sale of our rights to the royalty on U.S. net sales of TIBSOVO® to Sagard, the potential milestone payment and royalties from Servier if vorasidenib is approved by the FDA, the actual and potential sales of PYRUKYND® 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 with respect to vorasidenib 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.

**Contractual Obligations**

During the nine months ended September 30, 2022, there were no material changes to our contractual obligations and commitments described under Management's Discussion and Analysis of Financial Condition and Results of Operations in our Annual Report on Form 10-K for the year ended December 31, 2021.

## 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, 2022 and December 31, 2021, we had cash, cash equivalents and marketable securities of $1.0 billion and $1.3 billion, 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, 2022 and December 31, 2021, 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, 2022, 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 Securities Exchange Act of 1934, or 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, 2022 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

*The following risk factors and other information included in this Quarterly Report on Form 10-Q should be carefully considered. The risks and uncertainties described below are not the only risks and uncertainties we face. Additional risks and uncertainties not presently known to us or that we presently deem less significant may also impair our business operations. Please see page 19 of this Quarterly Report on Form 10-Q for a discussion of some of the forward-looking statements that are qualified by these risk factors. If any of the following risks occur, our business, financial condition, results of operations and future growth prospects could be materially and adversely affected.*

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

***If we do not successfully commercialize PYRUKYND® and other products for which we receive approval, our prospects may be substantially harmed.***

In February 2022, we obtained marketing approval from the FDA for PYRUKYND® (mitapivat) for the treatment of hemolytic anemia in adults with pyruvate kinase (PK) deficiency in the United States. PYRUKYND® is the first product for which we have received marketing approval following the sale of our oncology business to Servier in March 2021 and PYRUKYND® is the first product in our GDD portfolio that has received marketing approval. As of the date of this Quarterly Report on Form 10-Q, we are in the process of commercially launching PYRUKYND®. Our ability to generate meaningful revenue from PYRUKYND® will depend heavily on our successful development and commercialization of the product.

The development and commercialization of PYRUKYND® could be unsuccessful if:

- the medical community and third-party payors do not accept PYRUKYND® as safe, efficacious and cost-effective for the treatment of hemolytic anemia in adults with PK deficiency;
- we fail to maintain the necessary financial resources and expertise to manufacture, market and sell PYRUKYND®;
- we fail to develop, implement and maintain effective marketing, sales and distribution strategies and operations for the development and commercialization of PYRUKYND®;
- we fail to continue to develop, validate and maintain a commercially viable manufacturing process for PYRUKYND® that is compliant with current good manufacturing practices, or cGMP;
- we fail to successfully obtain third party reimbursement and generate commercial demand that results in sales of PYRUKYND®;
- PYRUKYND® or any product candidate that we commercialize, may become subject to unfavorable pricing regulations and third-party reimbursement practices, which would harm our business;
- we encounter any third-party patent interference, derivation, inter partes review, post-grant review, reexamination or patent infringement claims with respect to PYRUKYND®;
- we fail to comply with regulatory and legal requirements applicable to the sale of PYRUKYND®;
- competing drug products are approved for the same indications as PYRUKYND®;
- we fail to approve marketing approval of PYRUKYND® in jurisdictions other than the United States;
- new significant safety risks are identified;
- we fail to gain and/or maintain sufficient market acceptance by physicians, patients, healthcare payors and others in the medical community;
- a significant number of eligible patients with PK deficiency are not prescribed PYRUKYND® and, if they are, such patients do not stay on treatment; or
- PYRUKYND® does not demonstrate acceptable safety and efficacy in current or future clinical trials, or otherwise does not meet applicable regulatory standards for approval in indications other than currently approved indication.

If we experience significant delays or an inability to successfully develop and commercialize PYRUKYND® our business would be materially harmed.

***We depend heavily on the success of our clinical product candidates, including our lead product candidate PYRUKYND® for use in indications other than PK deficiency and in other jurisdictions. 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.***

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 clinical programs, including PYRUKYND®. Our ability to generate meaningful product revenue will depend heavily on the successful clinical development and eventual commercialization of our current and any future product candidates, including PYRUKYND® for use in indications other than PK deficiency and in jurisdictions outside of the United States. In February 2022, the FDA approved PYRUKYND® for the treatment of hemolytic anemia in adults with PK deficiency in the United States. In June 2021, we submitted a MAA to the EMA for the treatment of adults with PK deficiency in the EU and, in September 2022, the Committee for Medical Products for Human Use of the EMA, or CHMP, adopted a positive opinion recommending the granting of a marketing authorization for PYRUKYND®. In October 2022, we submitted a marketing authorization application in Great Britain for PYRUKYND® under the European Commission Decision Reliance Procedure. We expect a decision from both the EU and Great Britain regulatory authorities by the end of 2022.

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 PK 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 PYRUKYND®, our first PK 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 PYRUKYND®, 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 engage in in-licensing transactions or acquisitions that could disrupt our business, cause dilution to our stockholders or reduce our financial resources.***

We may in the future enter into transactions to in-license products, technologies or assets or to acquire other products, technologies, assets or businesses. As part of the evolution of our research organization, we plan to prioritize in-licensing or acquiring assets for future pipeline growth. Because we have not made any acquisitions to date, our ability to do so successfully in the future is unproven. If we do identify suitable candidates or assets for in-licensing transactions or acquisitions, we may not be able to make such transactions on favorable terms, or at all. Any in-licensing transaction or acquisitions we undertake 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 an in-licensing transaction or issue our common stock or other equity securities to the stockholders of the counterparty, which would reduce the percentage ownership of our existing stockholders. We could incur losses resulting from undiscovered liabilities of the acquired business, product or technology 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. Such transactions 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 ensure that following any transaction we would achieve the expected synergies to justify the transactions. We cannot predict the number, timing or size of future transactions or the effect that any such transactions might have on our operating results.

***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, disrupt our ability to maintain a commercial infrastructure for our product 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 began requiring 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. Although we have experienced disruptions to certain clinical and research activities at our contract research organizations, or CROs, due to recent COVID-19 surges, 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 may 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 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 or reduced availability of CRO personnel may have an adverse impact on our clinical trial plans and timelines.

We have been monitoring our supply chain network for disruptions due to the COVID-19 pandemic, and our third-party manufacturers, other than certain CROs based in China, 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.

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 and 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 in the future and a continuation of the pandemic 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, continue or complete 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; Forma Therapeutics Holdings, Inc., or Forma (which was acquired by Novo Nordisk), is developing molecules for the treatment of beta thalassemia and SCD; Global Blood Therapeutics (which was acquired by Pfizer) is developing molecules for the treatment of SCD; Fibrogen, Inc. is developing Roxadustat for the treatment of anemia in MDS patients; Geron Corporation is developing imetelstat for the treatment of low-risk MDS; and Roivant Sciences is developing RVT-2001 (licensed from Eisai Co., Ltd.) for the treatment of transfusion-dependent anemia in patients with lower-risk MDS. Competition for eligible patients may make it particularly difficult for us to enroll a sufficient number of patients to complete our clinical trials for our product candidates in a timely and cost-effective manner.

We rely on 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 later-stage 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 stages of 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. 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. While we obtained marketing approval of PYRUKYND® for the treatment of hemolytic anemia in adults with PK deficiency in the United States, we cannot be certain that we will obtain marketing approval of PYRUKYND® in other indications or other jurisdictions. The results of clinical trials of PYRUKYND® for the treatment of PK deficiency do not predict that PYRUKYND® will be efficacious in our ongoing clinical trials in other indications. 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. In May 2022, we announced our decision to evolve our approach to exploratory research and drug discovery to prioritize investment in advancing our late lead-optimization research, while continuing to progress our registration-enabling clinical programs in thalassemia, SCD and pediatric PK deficiency and our phase 2a trial in lower-risk MDS. 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.

***We or others may later discover that PYRUKYND®, or any of our product candidates that may receive marketing approval in the future, 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, including PYRUKYND®, 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.

***PYRUKYND®, or any of our product candidates that may receive marketing approval in the future, may fail to achieve the degree of market acceptance by physicians, patients, healthcare payors and others in the medical community necessary for commercial success.***

PYRUKYND®, or any of our product candidates that may receive marketing approval in the future, may fail to gain and/or maintain sufficient market acceptance by physicians, patients, healthcare payors and others in the medical community. If PYRUKYND® or any of our product candidates that may receive marketing approval 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 PYRUKYND® and any 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 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 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 PYRUKYND® or our product candidates if 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 have established sales and marketing capabilities to support our commercial launch of PYRUKYND® for the treatment of hemolytic anemia in adults with PK deficiency in the United States, we may need to further build our sales and marketing infrastructure to maintain our ongoing commercialization efforts and to commercialize PYRUKYND® in other indications or outside of the United States or to commercialize any of our other product candidates for which we obtain marketing approval.

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 PYRUKYND® or any of our product candidates for which we obtain marketing approval.

***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 PYRUKYND® and our current product candidates, and we will face competition with respect to any product candidates that we 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 or our product candidates, such as PK deficiency, thalassemia, SCD and lower-risk MDS. For example, Merck & Co., Inc. and bluebird bio, Inc., or bluebird, are each marketing therapies to treat beta thalassemia, Novartis International AG, Emmaus Life Sciences and Global Blood Therapeutics (which was acquired by Pfizer) 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.

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 or target indications 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 (which was acquired by Novo Nordisk), PTC Therapeutics, Inc., Rocket Pharma, and Vertex. Our competitors may develop products that are more effective, safer, more convenient or less costly than PYRUKYND® or any product candidates that we are developing or that would render PYRUKYND® or 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 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 or follow-on 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.

A manufacturer may also submit an NDA under section 505(b)(2) of the Federal Food, Drug and Cosmetic Act, or FDCA, that references the FDA's prior approval of the innovator product or preclinical studies and/or clinical trials that were not conducted by, or for, the applicant and for which the applicant has not obtained a right of reference. A 505(b)(2) NDA product, or follow-product, may be for a new or improved version of the original reference listed drug.

The FDA may not approve an ANDA or 505(b)(2) NDA until any applicable period of non-patent exclusivity for the reference-listed drug has expired. The FDCA provides a period of five years of new chemical entity exclusivity for a new drug containing a new active moiety. Specifically, in cases where such exclusivity has been granted, an ANDA or a 505(b)(2) NDA 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 deemed by the FDA as essential for approval.

In the event that a generic or follow-on 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 and follow-on 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.

In addition, if there are patents listed for our drug products in the Orange Book, ANDAs and 505(b)(2) NDAs would be required to include a certification as to each listed patent indicating whether the applicant intends to challenge the patent. We cannot predict which, if any, patents in our current portfolio or patents we may obtain in the future will be eligible for listing in the Orange Book, how any generic or follow-on competitor would address such patents, whether we would sue on any such patents or the outcome of any such suit.

***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 face an even greater risk as we or they commercially sell any medicines, including PYRUKYND®. 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 EU, 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 Financial Position**

***We face new challenges as a smaller, less diversified company following the sale of our oncology business to Servier.***

Following the sale of our oncology business to Servier in March 2021, we have focused our resources and efforts on product and product candidates for the treatment of GDDs. The success of the GDD business is subject to various risks and uncertainties, including the possibility that we may not be able to successfully commercialize PYRUKYND®, which was approved by the FDA in February 2022 for the treatment of hemolytic anemia in adults with PK deficiency in the United States, the possibility of adverse clinical and other developments in respect of PYRUKYND® or our other product candidates of the GDD business, 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 our approved products at the time of sale, TIBSOVO® and IDHIFA®, has resulted in us being a smaller, less diversified company with a more limited business concentrated on products and 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, even with the FDA approval of PYRUKYND®, the diversification of our revenues, costs and cash flows has diminished following the sale of our oncology business. 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.

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

Until such time, if ever, as we can generate substantial product revenue, including from sales of PYRUKYND®, we expect to finance our cash needs primarily through cash on hand, proceeds from the sale of our rights to the royalty on U.S. net sales of TIBSOVO® to entities affiliated with Sagard Healthcare Partners, or Sagard, a potential milestone payment and royalties 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 with respect to vorasidenib 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 when we will achieve cash-flow positivity and 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 and timing of future revenue received from commercial sales of PYRUKYND® and any of our other product candidates for which we may receive marketing approval;
- the amount of contingent consideration we ultimately receive from Servier;

- the costs and timing of our ongoing commercialization activities, including product manufacturing, sales, marketing and distribution, for PYRUKYND® for the treatment of hemolytic anemia in adults with PK deficiency;
- the anticipated cost-savings associated with the evolution of our research organization;
- the scope, progress, results and costs of preclinical development, laboratory testing and clinical trials for our product candidates;
- the costs associated with in-licensing or acquiring assets for pipeline growth;
- 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;
- 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
- operational delays, disruptions and/or increased costs associated with rising global energy prices or energy shortages or rationing.

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

We have a history of incurring operating losses. Our net loss for the nine months ended September 30, 2022 was $268.3 million, and our net income for the nine months ended September 30, 2021 was $1.7 billion. The net income for the nine months ended September 30, 2021 was due to the sale of our oncology business to Servier on March 31, 2021. As of September 30, 2022, we had an accumulated deficit of $507.1 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 of our royalty rights to IDHIFA®, from royalties on sales of IDHIFA®. We have only recently obtained marketing approval for and have begun to commercialize PYRUKYND® for the treatment of hemolytic anemia in adults with PK deficiency in the United States. PYRUKYND® is the first product we have received marketing approval for following the sale of our oncology business, including approved products TIBSOVO® and IDHIFA®, to Servier in March 2021. We have neither obtained marketing approval for PYRUKYND® in any other indications or for any indication outside of the United States nor have we obtained marketing approval for any of our other product candidates, all of which are in preclinical or clinical development stages. In June 2021, we submitted a MAA for PYRUKYND® in adults with PK deficiency to the EMA and, and, in September 2022, the CHMP adopted a positive opinion recommending the granting of a marketing authorization for PYRUKYND®. In October 2022, we submitted a marketing authorization application in Great Britain for PYRUKYND® under the European Commission Decision Reliance Procedure. We expect to receive a decision from both the EU and Great Britain regulatory authorities by year-end.

Prior to the sale of our oncology business to Servier, we 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 have financed and expect to continue to finance our operations primarily through cash on hand, royalty payments from Servier with respect to U.S. net sales of TIBSOVO® prior to the sale of these royalty rights to Sagard, proceeds from the sale of our rights to the royalty on U.S. net sales of TIBSOVO® to Sagard, a potential milestone payment and royalties from Servier if vorasidenib is approved by the FDA, the actual and potential future sales of PYRUKYND® 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:

- commercially launch PYRUKYND® for the treatment of hemolytic anemia in adults with PK deficiency in the United States;
- continue to establish and maintain a sales, marketing and distribution infrastructure to commercialize PYRUKYND® and other product candidates for which we may obtain marketing approval;
- initiate and continue clinical trials for our products and product candidates, including PYRUKYND® in other indications;
- 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;
- require the manufacture of larger quantities of product candidates for clinical development and 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 product candidates, medicines and technologies.

To become and remain profitable, we must develop and successfully 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 agreed to pay to us:

- $200.0 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® (we sold our rights to the royalty to Sagard in October 2022); 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.

Although to date, prior to the sale to Sagard, we have received royalties from Servier on U.S. net sales of TIBSOVO®, we cannot predict what success, if any, Servier may have in the United States with respect to future sales of 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 vorasidenib. The potential royalty payments with respect to vorasidenib 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 report.

***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, COVID-19 relief provisions were included in the Consolidated Appropriations Act, 2021, or CAA, which was enacted on December 27, 2020 and the American Rescue Plan Act of 2021, or ARPA, was enacted on March 11, 2021. All

contain numerous tax provisions. Regulatory guidance under the Tax Act, the FFCR Act, the CARES Act, the CAA and the ARPA 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 possible that Congress will enact additional legislation in connection with the COVID-19 pandemic. Furthermore, as a result of the changes in the U.S. presidential administration and control of the U.S. Senate, it is possible that additional tax legislation will be enacted. Such legislation 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, the CAA or the ARPA.

**Risks Related to Our Dependence on Third Parties**

***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. We are exposed to risk of fraud or other misconduct by such third parties.

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.

If either we or any third parties on which we rely are adversely impacted by rising global energy costs or energy shortages or rationing, delays may occur in our product development activities, which delays could have a material adverse impact on our business, financial condition and prospects.

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 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 for commercial supply of PYRUKYND® and any product candidate for which we or our collaborators obtain marketing approval.

Although we have entered into long-term supply agreements for commercial supply of PYRUKYND® with third-party manufacturers, 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 cGMPs, 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, other than certain CROs based in China, 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 and/or by rising global energy costs or energy shortages or rationing, our supply chain may be disrupted, limiting our ability to manufacture our product candidates for our clinical trials and research and development operations and our product for commercialization.

Any performance failure on the part of our existing or future manufacturers could delay clinical development, marketing approval or our commercialization efforts. 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 or 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.

***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.

**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 and 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 and 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 approval of PYRUKYND®, for the treatment of hemolytic anemia in adults with PK deficiency in the United States, we have not received approval to market any of our current 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 MAA for PYRUKYND® that is currently under review by the EMA. 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. Should the FDA determine that an inspection is necessary for approval of a regulatory submission and an inspection cannot be completed during the review cycle due to restrictions on travel due to COVID-19, and the FDA does not determine a remote interactive evaluation to be adequate, the FDA has stated that it generally intends to issue a complete response letter or defer action on the regulatory submission until an inspection can be completed.

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 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, and the United Kingdom and EU continue to work on the rules for implementation. Since the regulatory framework for pharmaceutical products in the United Kingdom covering the quality, safety, and efficacy of pharmaceutical products, clinical trials, marketing authorization, commercial sales, and distribution of pharmaceutical products is derived from EU directives and regulations, the consequences of Brexit and the impact the future regulatory regime that applies to products and the approval of product candidates in the United Kingdom remains unclear. 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, 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. In addition, we do not have experience commercializing products outside of the United States and such efforts may depend on our ability to find a suitable collaborator.

***Fast track designation and/or priority review designation by the FDA or PRIME designation in the EU 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 or the EMA.***

We may seek fast track designation, priority review designation and/or PRIME designation for our product candidates.

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 addition, in the EU, the PRIME designation program focuses on product candidates that target conditions for which there exists no satisfactory method of treatment in the EU or product candidates that may offer a major therapeutic advantage over existing treatments. The benefits of a PRIME designation include, among other things, the potential to qualify product for accelerated review, meaning reduction in the review time for an opinion on approvability to be issued earlier in the application process. PRIME designation enables an applicant to request parallel EMA scientific advice and health technology assessment advice to facilitate timely market access. Even if our product candidates receive PRIME designation, we may not experience a faster development process, review or approval compared to conventional EMA procedures and it does not assure or increase the likelihood of the EMA's grant of a marketing authorization.

***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.

In addition, 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 and Congress 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. Depending on what changes the FDA may make to its orphan drug regulations and policies, our business could be adversely impacted.

***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 PYRUKYND® and 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 PYRUKYND® and any other 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 other covered recipients; 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.

***PYRUKYND® or any product candidate that we commercialize may become subject to unfavorable pricing regulations and third-party reimbursement practices, which would harm our business.***

The commercial success of PYRUKYND® or of any 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 PYRUKYND® or 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 PYRUKYND® or 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 PYRUKYND® or 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 PYRUKYND® or any product candidate that we, or any collaborator, may 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 PYRUKYND® or any of our product candidates for which we, or any collaborator, may 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 PYRUKYND® or any other 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 2031. However, pursuant to the CARES Act and subsequent legislation, these Medicare sequester reductions were suspended through the end of March 2022 and from April 2022 through June 2022, a 1% cut was in effect, with the full 2% cut having resumed thereafter. The American Taxpayer Relief Act of 2012, among other things, reduced Medicare payments to several providers and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. These laws may result in additional reductions in Medicare and other healthcare funding and otherwise affect the prices we may obtain for any of our 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 prices 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 prices 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 pharmaceutical pricing, review the relationship between pricing and manufacturer patient programs, reduce the costs of drugs under Medicare and Medicaid. To those ends, President Trump issued several executive orders intended to lower the costs of prescription products. Certain provisions of these orders have been reflected in promulgated regulations, including an interim final rule implementing a most favored nation model for prices, which would tie Medicare Part B payments for certain physician-administered pharmaceuticals to the lowest price paid in other economically advanced countries. Such final rule has been subject to a nationwide preliminary injunction, and, on December 29, 2021, Centers for Medicare & Medicaid Services, or CMS, issued a final rule to rescind it. With the issuance of this rule, CMS stated it will explore all options to incorporate value into payments for Medicare Part B drugs and improve beneficiaries' access to evidence-based care.

In addition, in October 2020, the United States Department of Health and Human Services, or HHS, and the FDA published a final rule allowing states and other entities to develop a Section 804 Importation Program, or SIP, to import certain prescription drugs from Canada into the United States. The final rule is currently the subject of ongoing litigation, but at least six states (Vermont, Colorado, Florida, Maine, New Mexico and New Hampshire) have passed laws allowing for the importation of drugs from Canada with the intent of developing SIPs for review and approval by the FDA. Further, on November 20, 2020, HHS finalized a regulation removing safe harbor protection for price reductions from pharmaceutical manufacturers to plan sponsors under Part D, either directly or through pharmacy benefit managers, unless the price reduction is required by law. The implementation of the rule has been delayed by the Biden administration from January 1, 2022 to January 1, 2023 in response to ongoing litigation. The rule also creates a new safe harbor for price reductions reflected at the point-of-sale, as well as a new safe harbor for certain fixed fee arrangements between pharmacy benefit managers and manufacturers, the implementation of which has been delayed until January 1, 2026, by the Infrastructure Investment and Jobs Act.

More recently, with passage of the Inflation Reduction Act in August 2022, Congress authorized Medicare beginning in 2026 to negotiate lower prices for certain costly single-source drug and biologic products that do not have competing generics or biosimilars. This provision is limited in terms of the number of pharmaceuticals whose prices can be negotiated in any given year and it only applies to drug products that have been approved for at least 9 years and biologics that have been licensed for 13 years. Drugs and biologics that have been approved for a single rare disease or condition are categorically excluded from price negotiation. Further, the new legislation provides that if pharmaceutical companies raise prices in Medicare faster than the rate of inflation, they must pay rebates back to the government for the difference. The new law also caps Medicare out-of-pocket drug costs at an estimated $4,000 a year in 2024 and, thereafter beginning in 2025, at $2,000 a year.

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 or product candidates or additional pricing pressures.

In the EU, similar political, economic and regulatory developments may affect our ability to profitably commercialize our product candidates, if approved.

***We are subject to U.S. and foreign export control, import, sanctions, 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 export control and import laws and regulations, including the U.S. Export Administration Regulations, U.S. Customs regulations, various economic and trade sanctions regulations administered by the U.S. Treasury Department's Office of Foreign Assets Control, 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 such 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. 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. Our recent initiative to reduce up to 50 roles focused on exploratory research in connection with the evolution of our research organization could harm our ability to attract and retain qualified scientific, clinical, manufacturing, sales and marketing personnel who are critical to our business.

In the future we may experience growth in the number of our development, regulatory and sales and marketing personnel. To manage any 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 or regulations in other jurisdictions, provide accurate information to the FDA or other regulatory authorities, 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 or interactions with the FDA or other regulatory authorities, 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.

**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 closing price of our common stock on the Nasdaq Global Select Market has ranged from $17.06 per share to $135.01 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 or recent increases in inflation rates (particularly as it relates to clinical- or manufacturing-related costs) may be difficult to assess or predict, such impacts have already caused, and are 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:

- our success in launching and commercializing PYRUKYND®;
- the decision to focus our efforts on our GDD business following the sale of our oncology business to Servier;
- the evolution of our research organization;
- 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 or 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 products, product candidates or development programs;
- the results of our efforts to develop additional product candidates and products;
- 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;
- 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, 2022, 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, 2021, and determined that we did not have a qualified ownership change since our last review as of December 31, 2020. 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. In April 2021, in connection with the Repurchase Program, we repurchased from BMS 7.1 million shares of our common stock held by certain subsidiaries of BMS for an aggregate purchase price of $344.5 million, or $48.38 per share. Further, in April 2021, in connection with the Repurchase Program, we entered into a Rule 10b5-1 repurchase plan pursuant to which we repurchased approximately 9.1 million shares of common stock for $458.0 million, or $50.35 per share, under the plan. In total, as of December 31, 2021, we repurchased 16.2 million shares of common stock for $802.5 million under the Repurchase Program. In October 2021, we terminated our Rule 10b5-1 share repurchase program and entered into a Rule 10b-18 repurchase plan that allows us to conduct open market repurchases over time up to our remaining authorization. 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 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. 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 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 July 8, 2022, by and between the Company and Brian Goff | 10-Q | 001-36014 | August 4, 2022 | 10.2 | |
| 10.2# | Form of Inducement Stock Option Agreement for Brian Goff | 10-Q | 001-36014 | August 4, 2022 | 10.3 | |
| 10.3# | Form of Inducement Restricted Stock Unit Agreement for Brian Goff | 10-Q | 001-36014 | August 4, 2022 | 10.4 | |
| 10.4# | Form of Inducement Performance Stock Unit Agreement for Brian Goff | 10-Q | 001-36014 | August 4, 2022 | 10.5 | |
| 10.5# | Letter Agreement, dated September 16, 2022, by and between the Company and Cecilia Jones | | | | | X |
| 10.6# | Form of Inducement Stock Option Agreement for Cecilia Jones | S-8 | 333- 267624 | September 26, 2022 | 99.1 | |
| 10.7# | Form of Restricted Stock Unit Agreement for Cecilia Jones | S-8 | 333- 267624 | September 26, 2022 | 99.2 | |
| 10.8+# | Form of Inducement Performance Stock Unit Agreement for Cecilia Jones | S-8 | 333- 267624 | September 26, 2022 | 99.3 | |
| 10.9# | Amended and Restated Severance Benefits Plan | 8-K | 001-36014 | October 7, 2022 | 10.1 | |
| 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 |

* 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.

# Indicates management contract or compensatory plan or arrangement.

+Portions of this exhibit have been omitted pursuant to Item 601(b)(10)(iv) of Regulation S-K.

**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, 2022 By: /s/ Brian Goff

Brian Goff
Chief Executive Officer
(principal executive officer)

November 3, 2022 By: /s/ Cecilia Jones

Cecilia Jones
Chief Financial Officer
(principal financial officer)

Exhibit 10.5

**EMPLOYMENT AGREEMENT**

This Employment Agreement (the "Agreement") is made as of September 15, 2022 by and between Agios Pharmaceuticals, Inc. (the "Company"), and M. Cecilia Jones (the "Executive") (together, the "Parties").

RECITALS

WHEREAS the Company desires to employ the Executive as its Chief Financial Officer; and

WHEREAS, the Executive has agreed to accept such employment on the terms and conditions set forth in this Agreement.

NOW, THEREFORE, in consideration of the foregoing and of the respective covenants and agreements of the Parties herein contained, the Parties hereto agree as follows:

1. *Employment Period*. The Executive's employment shall commence on September 26, 2022 (the "Effective Date") and shall continue until terminated in accordance with this Agreement (such period, the "Employment Period"). During the Employment Period, the Executive shall be an at-will employee of the Company and the Executive's employment shall be freely terminable by either the Executive or the Company, for any reason, at any time, by giving notice as described in Section 10 of this Agreement and subject to the terms of Section 4(f) of this Agreement.

2. *Position*. During the Employment Period, the Executive shall serve as the Company's Chief Financial Officer. The Executive's principal place of providing services to the Company will be at the Company's Cambridge, Massachusetts offices; provided; however, that the Executive shall be eligible to participate in any flexible work schedule arrangement then available to the Company's employees. During the Employment Period, the Executive will also engage in business travel as required by the Executive's job duties. Immediately upon the termination of the Executive's employment for any reason, the Executive must resign from any office held in the Company. If the Executive does not do so, the Company is hereby irrevocably authorized to appoint a person in the Executive's name to sign and deliver any required letter(s) of resignation to the Company.

3. *Scope of Employment*.

(a) During the Employment Period, the Executive shall be responsible for the performance of those duties consistent with the Executive's position as an employee and Chief Financial Officer in comparable publicly-traded biotechnology companies, in addition to such other duties as may from time to time be reasonably assigned to the Executive. The Executive shall report to the Company's Chief Executive Officer and shall perform and discharge faithfully, diligently, and to the best of the Executive's ability, the Executive's duties and responsibilities hereunder.

(b) The Executive agrees to devote the Executive's full business time, best efforts, skill, knowledge, attention and energies to the advancement of the business and interests of the Company and to the performance of the Executive's duties and responsibilities as an employee of the Company; provided that the Executive may (i) engage in charitable, educational, religious, civic and similar types of activities, and (ii) serve on the board of directors of one (1)

for-profit business enterprise, provided that in each case such service is approved by the Company prior to commencement thereof in the Company's sole discretion, and only to the extent that such activities are not competitive with the business of the Company and do not individually or in the aggregate inhibit, interfere with, or prohibit the timely performance of the Executive's duties hereunder, and do not create a potential business or fiduciary conflict.

(c) The Executive agrees to abide by the rules, regulations, instructions, personnel practices, and policies of the Company, as well as any applicable codes of ethics or business conduct, and any changes therein that may be adopted from time to time by the Company.

(d) The Executive represents and warrants to the Company that the Executive is under no obligations or commitments, whether contractual or otherwise, that are inconsistent with the Executive's obligations under this Agreement. In connection with the Executive's employment hereunder, the Executive shall not use or disclose any trade secrets or other proprietary information or intellectual property in which the Executive or any other person or entity has any right, title or interest, and the Executive's employment with the Company will not infringe or violate the rights of any other person or entity. The Executive represents and warrants to the Company that the Executive has returned all property and confidential information belonging to any prior employer.

4. *Compensation*. As full compensation for all services rendered by the Executive to the Company during the Employment Period, the Company will provide to the Executive the following:

(e) *Base Salary*. The Executive shall receive a base salary at the annualized rate of $475,000.08 (the "Base Salary"). The Executive's Base Salary shall be paid in equal installments in accordance with the Company's regularly established payroll procedures. The Executive's Base Salary will be reviewed annually by the Company in accordance with normal business practice.

(f) *Annual Discretionary Bonus*. Following the end of each calendar year during the Employment Period, the Executive will be eligible to receive a discretionary annual performance and retention bonus in a target amount of at least 45% of the Executive's Base Salary for the applicable calendar year (the "Target Bonus"), based upon the Board's assessment, in its sole discretion, of the Company's achievement of its performance goals for the applicable calendar year and the Board's and the Executive's manager's assessment of the Executive's achievement of the Executive's performance goals for the applicable calendar year (with such goals to be established by the Executive's manager after consultation with the Executive). No annual bonus or minimum amount thereof is guaranteed, and, except as provided below, the Executive must be an employee in good standing on the date that annual bonuses are paid out in order to be eligible for and to earn any annual bonus, as it also serves as an incentive to remain employed by the Company. The amount of any bonus paid with respect to the 2022 calendar year will be equal to 50% of the bonus the Executive would have received had the Executive been employed with the Company for the full calendar year. Any annual bonus shall be paid to the Executive no later than March 15 of the year following the year with respect to which such bonus is earned. In the event the Executive's employment terminates on or after the last day of the applicable calendar year for any reason other than termination by the Company for Cause or resignation by the Executive without Good Reason and prior to payment of the annual bonus, the Executive shall be deemed to be an employee in good standing on the date such annual bonuses are paid.

(g) *Equity Awards*.

(i)As a material inducement to the Executive entering into employment with the Company and agreeing to the non-competition provision set forth in the Restrictive Covenant Agreement (as defined below):

1. Effective as of the Effective Date or the first business day next following the Effective Date, if the Effective Date falls on a weekend or holiday (the "Grant Date"), the Executive will be granted a stock option to purchase shares of the Company's common stock (the "Option") with a Black-Scholes value (as calculated on the Grant Date using the same methodology that the Company then uses to calculate the value of stock awards for purposes of the Company's financial statements) of $1.875 million, based on the closing price of the Company's common stock on the Nasdaq Global Select Market on the Grant Date (the "Closing Price"). The Option shall be issued outside the Company's 2013 Stock Incentive Plan, as an "inducement grant" within the meaning of Nasdaq Listing Rule 5635(c)(4), will be a non-qualified stock option for United States tax purposes and will be subject to all of the terms set forth in a written agreement covering the Option in the form attached hereto as Exhibit A.

2. Effective as of the Grant Date, the Executive will be granted a number of restricted stock units (the "RSUs"), which the number shall be determined by dividing $625,000 by the Closing Price. The RSUs shall be issued outside the Company's 2013 Stock Incentive Plan, as an "inducement grant" within the meaning of Nasdaq Listing Rule 5635(c)(4), and will be subject to all of the terms set forth in a written agreement covering the RSUs in the form attached hereto as Exhibit B.

3. Effective as of the Grant Date, the Executive will be granted a number of performance share units (the "PSUs") for a number of shares of Common Stock, which number shall be determined by dividing $300,000 by the Closing Price. Each PSU shall entitle the Executive to receive one share of the Company's common stock for each PSU that vests. The PSUs shall be issued outside the Company's 2013 Stock Incentive Plan, as an "inducement grant" within the meaning of Nasdaq Listing Rule 5635(c)(4), and will be subject to all of the terms set forth in a written agreement covering the PSUs attached hereto as Exhibit C.

(ii) The Company will file with the Securities and Exchange Commission, no later than the Effective Date, a Registration Statement on Form S-8 for purposes of registering under the Securities Act of 1933, as amended, all shares of Company common stock that may be issuable under the Option, the RSUs and the PSUs.

(iii) The Executive will be eligible to receive annual equity grants beginning in 2023 consistent with the Company's normal business practice, with any such equity

grants being in the sole discretion of the Board (or the Compensation & People Committee) and, to the extent such grants are made, being on such terms and subject to such conditions as the Board (or the Compensation & People Committee) shall determine in its sole discretion. The amount of any annual equity grant made with respect to the 2022 calendar year will be equal to 50% of the grant the Executive would have received had the Executive been employed with the Company for the full calendar year.

(a) *Paid Time Off*. The Executive shall be eligible for vacation time in accordance with the Company's vacation policy. The Company also provides employees with paid holidays annually in accordance with the Company's holiday schedule.

(b) *Benefits*. The Executive may participate in any and all benefit programs that the Company establishes and makes available to its employees from time to time, provided the Executive is eligible under (and subject to all provisions of) the plan documents governing those programs. The benefit programs made available by the Company, and the rules, terms and conditions for participation in such benefit programs, may be changed by the Company at any time without advance notice (other than as required by such programs or under law). The Executive also shall be eligible to receive annual equity awards, at the discretion of the Executive's manager and the Board.

(c) *Severance.* The Company maintains a Severance Benefits Plan, effective April 22, 2016 (the "Plan"), pursuant to which the Executive will be a Covered Employee eligible to receive Severance Pay and severance benefits in the event of a Covered Termination (each as defined in the Plan). The Executive's participation in the Plan shall be governed by the provisions of the Plan as in effect on the date hereof, as modified by the provisions of Exhibit D attached hereto. For avoidance of doubt, any amendment, modification or termination of the Plan made after the date hereof shall be treated as amendment of this Agreement and, as such, shall be effective as to Executive only upon execution of a written instrument by both the Company and Executive pursuant to Section 14 below.

(d) *Withholdings*. All compensation payable to the Executive shall be subject to applicable taxes and withholdings.

(h) *Indemnification*.. Effective as of the Effective Date, the Executive and the Company shall enter into the Indemnification Agreement attached hereto as Exhibit E.

5. *Sign-on Payment*. The Executive will receive a one-time payment of $175,000. This payment will be made as part of the normal semi-monthly payroll after 30 days of employment. If the Executive leaves the Company within 18 months after the Effective Date (other than in connection with a Covered Termination), the Executive will be required to repay the full amount of this payment. Such payment will be subject to legally required tax withholdings. For purposes of this Agreement, Covered Termination shall mean a "Covered Termination" of the Executive's services as determined under the Plan (as modified by this Agreement).

6. *Expenses*. The Executive will be reimbursed for the Executive's actual, necessary and reasonable business expenses pursuant to Company policy, subject to the provisions of Exhibit F attached hereto.

7. *Restrictive Covenant Agreement*. As a condition of the Executive's employment with the Company and eligibility to receive the equity set forth in Section 4(c) above, the

Executive will be required to execute the Employee Non-Competition, Non-Solicitation, Confidentiality and Assignment Agreement previously provided to the Executive, another copy of which is provided contemporaneously with this Agreement (the "Restrictive Covenant Agreement"). The Executive acknowledges that the Executive's eligibility to receive the equity set forth above is contingent upon the Executive's agreement to the non-competition provision set forth in the Restrictive Covenant Agreement, and that such consideration was mutually agreed upon by the Executive and the Company and is fair and reasonable in exchange for the Executive's compliance with such non-competition obligation.

8. *Absence of Restrictions*. The Executive represents and warrants that the Executive is not bound by any employment contracts, restrictive covenants or other restrictions that prevent the Executive from entering into employment with, or carrying out the Executive's responsibilities for, the Company, or which are in any way inconsistent with any of the terms of this Agreement. The Executive has disclosed to Company an agreement with the Executive's former employer containing certain contractual obligations between the Executive and such former employer.

9. *Additional Employment Conditions.* The Executive's employment is contingent upon the Executive's compliance with the Company's mandatory COVID-19 vaccination policy; provided, however, if the Executive requests an exemption from this policy because of a medical condition or sincerely held religious belief, the Company will consider such request for an exemption to the extent required by applicable law. The Executive's employment with the Company is also contingent upon the Executive's successful completion of a background investigation, as well as on the Executive's providing to the Company, within three (3) days of the Effective Date, documentation proving the Executive's identity and eligibility to work in the United States, as required by the Immigration Reform and Control Act of 1986.

10. *Notice*. Any notice delivered under this Agreement shall be deemed duly delivered (a) three (3) business days after it is sent by registered or certified mail, return receipt requested, postage prepaid, (b) one (1) business day after it is sent for next-business day delivery via a reputable nationwide overnight courier service, (c) immediately when sent by electronic mail or confirmed facsimile if sent during normal business hours of the recipient, and if not, then on the next business day, or (d) immediately upon hand delivery, in each case to the address of the recipient set forth below.

To the Executive:

At the address set forth in the Executive's personnel file

To Company:

Agios Pharmaceuticals, Inc.
88 Sidney Street
Cambridge, MA 02139
Attn: Chief People Officer

Either Party may change the address to which notices are to be delivered by giving notice of such change to the other Party in the manner set forth in this Section 10.

11. *Applicable Law and Forum*. This Agreement shall be governed by and construed in accordance with the laws of the Commonwealth of Massachusetts (without reference to the

conflict of laws provisions thereof). Any action, suit or other legal proceeding arising under or relating to any provision of this Agreement shall be commenced only in a court of the Commonwealth of Massachusetts (or, if appropriate, a federal court located within Massachusetts), and the Company and the Executive each consents to the jurisdiction of such a court. The Company and the Executive each hereby irrevocably waives any right to a trial by jury in any action, suit or other legal proceeding arising under or relating to any provision of this Agreement.

12. *Successors and Assigns*. This Agreement shall be binding upon and inure to the benefit of both Parties and their respective successors and assigns, including any corporation with which or into which the Company may be merged or which may succeed to its assets or business; provided, however, that the obligations of the Executive are personal and shall not be assigned by the Executive.

13. *Acknowledgment*. The Executive acknowledges that the Executive has the right to consult with counsel prior to signing this Agreement and states and represents that the Executive has had an opportunity to fully discuss and review the terms of this Agreement with counsel and, if the Executive has not done so, has voluntarily declined to seek such counsel. The Executive further states and represents that the Executive has carefully read this Agreement, understands the contents herein, freely and voluntarily assents to all of the terms and conditions hereof, and signs the Executive's name of the Executive's own free act.

14. *No Oral Modification, Waiver, Cancellation or Discharge*. This Agreement may be amended or modified only by a written instrument executed by both the Company and the Executive. No delay or omission by the Company in exercising any right under this Agreement shall operate as a waiver of that or any other right. A waiver or consent given by the Company on any one occasion shall be effective only in that instance and shall not be construed as a bar to or waiver of any right on any other occasion.

15. *Captions and Pronouns*. The captions of the sections of this Agreement are for convenience of reference only and in no way define, limit or affect the scope or substance of any section of this Agreement. Whenever the context may require, any pronouns used in this Agreement shall include the corresponding masculine, feminine or neuter forms, and the singular forms of nouns and pronouns shall include the plural, and vice versa.

16. *Interpretation*. The Parties agree that this Agreement will be construed without regard to any presumption or rule requiring construction or interpretation against the drafting Party. References in this Agreement to "include" or "including" should be read as though they said "without limitation" or equivalent forms. References in this Agreement to the "Board" shall include any authorized committee thereof.

17. *Severability*. Each provision of this Agreement must be interpreted in such manner as to be effective and valid under applicable law, but if any provision of this Agreement is held to be prohibited by or invalid under applicable law, such provision will be ineffective only to the extent of such prohibition or invalidity, without invalidating the remainder of such provision or the remaining provisions of this Agreement. Moreover, if a court of competent jurisdiction determines any of the provisions contained in this Agreement to be unenforceable because the provision is excessively broad in scope, whether as to duration, activity, geographic application, subject or otherwise, it will be construed by limiting or reducing it to the extent legally permitted, so as to be enforceable to the extent compatible with then applicable law to achieve the intent of the Parties.

18. *Entire Agreement*. This Agreement constitutes the entire agreement between the Parties and supersedes all prior agreements and understandings, whether written or oral, relating to the subject matter of this Agreement.

IN WITNESS WHEREOF, the Parties hereto have executed this Agreement as of the day and year set forth above.

Agios Pharmaceuticals, Inc.

By: /s/ Brian Goff

Name: Brian Goff

Title: Chief Executive Officer

THE EXECUTIVE:

/s/ Cecilia Jones
M. Cecilia Jones

**EXHIBIT A**

**Form of Inducement Option Agreement**

Incorporated by reference to Exhibit 99.1 of the Company's Registration Statement on Form S-8 filed with the Securities and Exchange Commission on September 26, 2022.

**EXHIBIT B**

**Form of Inducement RSU Agreement**

Incorporated by reference to Exhibit 99.2 of the Company's Registration Statement on Form S-8 filed with the Securities and Exchange Commission on September 26, 2022.

**EXHIBIT C**

**Form of Inducement PSU Agreement**

Incorporated by reference to Exhibit 99.3 of the Company's Registration Statement on Form S-8 filed with the Securities and Exchange Commission on September 26, 2022.

**EXHIBIT D**

**Modifications to Severance Benefits Plan**

The definitions and other provisions set forth below shall apply to the Executive's participation in the Severance Benefits Plan.

1. The following definitions are modified to read:

(f) "Cause" for termination shall mean: (a) a finding by the Board, in its reasonable discretion, that (i) the Executive committed an intentional act or acted with gross negligence that has materially injured the business of the Company, or (ii) the Executive has refused or failed to follow lawful directions of the Board; or (iii) the Executive has willfully neglected his or her duties for the Company; (b) the conviction of the Executive, or the entry of a pleading of guilty or nolo contendere by the Executive to any crime involving moral turpitude or any felony; or (c) a material breach of any agreement between the Executive and the Company; provided, however, that no event or condition described in clauses (a) or (c) shall constitute Cause unless the Board gives the Executive written notice of the grounds for termination and provides the Executive 15 days to correct (if susceptible to correction, as determined in the sole discretion of the Board) such grounds, and the Executive fails to make such correction.

(g) "Change of Control" shall mean the:

(a) acquisition by an individual, entity or group (within the meaning of Section 13(d)(3) or 14(d)(2) of the Securities Exchange Act of 1934, or the "Exchange Act") (a "Person") of beneficial ownership of any capital stock of the Company if, after such acquisition, such Person beneficially owns (within the meaning of Rule 13d-3 under the Exchange Act) 50% or more of either (x) the then-outstanding shares of Common Stock (the "Outstanding Company Common Stock") or (y) the combined voting power of the then-outstanding securities of the Company entitled to vote generally in the election of directors (the "Outstanding Company Voting Securities"); provided, however, that for purposes of this subsection (a), the following acquisitions shall not constitute a Change in Control Event: (1) any acquisition directly from the Company or (2) any acquisition by any entity pursuant to a Business Combination (as defined below) which complies with clauses (x) and (y) of subsection (c) of this definition; or

(b) a change in the composition of the Board that results in the Continuing Directors (as defined below) no longer constituting a majority of the Board (or, if applicable, the Board of Directors of a successor corporation to the Company), where the term "Continuing Director" means at any date a member of the Board (x) who was a member of the Board on the date of the initial adoption of Severance Benefits Plan or (y) who was nominated or elected subsequent to such date by at least a majority of the directors who were Continuing Directors at the time of such nomination or election or whose election to the Board was recommended or endorsed by at least a majority of the directors who were Continuing Directors at the time of such nomination or election; provided, however, that there shall be excluded from this clause (y) any individual whose initial assumption of office occurred as a result of an actual or threatened election contest with respect to the election or removal of directors or other actual or threatened solicitation of proxies or consents, by or on behalf of a person other than the Board; or

(c) the consummation of a merger, consolidation, reorganization, recapitalization or share exchange involving the Company or a sale or other disposition of all or substantially all of the assets of the Company (a "Business Combination"), unless, immediately following such Business Combination, each of the following two conditions is satisfied: (x) all or substantially all of the individuals and entities who were the beneficial owners of the Outstanding Company Common Stock and Outstanding Company Voting Securities immediately prior to such Business Combination beneficially own, directly or indirectly, more than 50% of the then-outstanding shares of common stock and the combined voting power of the then-outstanding securities entitled to vote generally in the election of directors, respectively, of the resulting or acquiring corporation in such Business Combination (which shall include, without limitation, a corporation which as a result of such transaction owns the Company or substantially all of the Company's assets either directly or through one or more subsidiaries) (such resulting or acquiring corporation is referred to herein as the "Acquiring Corporation") in substantially the same proportions as their ownership of the Outstanding Company Common Stock and Outstanding Company Voting Securities, respectively, immediately prior to such Business Combination and (y) no Person (excluding any employee benefit plan (or related trust) maintained or sponsored by the Company or by the Acquiring Corporation) beneficially owns, directly or indirectly, 50% or more of the then-outstanding shares of common stock of the Acquiring Corporation, or of the combined voting power of the then-outstanding securities of such corporation entitled to vote generally in the election of directors (except to the extent that such ownership existed prior to the Business Combination); or

(d) the liquidation or dissolution of the Company.

Notwithstanding the foregoing, no event shall constitute a Change in Control Event unless such event also constitutes a "change in control event" within the meaning of Treasury Regulation Section 1.409A-3(i)(5)(i).

(q) "Good Reason" shall mean the occurrence of any of the following events without the Executive's prior written consent: (a) a material diminution in Executive's base compensation; (b) a material diminution in the Executive's authority, duties or responsibilities (this determination will include an analysis of whether the Executive maintains at least the same level, scope, and type of duties and responsibilities with respect to the management, strategy, operations, and business of the Company); (c) a material change in geographic location at which the Executive performs services (if the Executive's new one-way commute is more than thirty five (35) miles greater than the Executive's one-way commute prior to the change in the Executive's principal work location, regardless of whether the Executive receives an offer of relocation benefits, such change shall be deemed material hereunder); or (d) a material breach by the Company of this Agreement or any other agreement to which the Company and the Executive are parties; provided, however, that no such event or condition shall constitute Good Reason unless (x) the Executive gives the Company a written notice of termination for Good Reason not more than 30 days after the initial existence of the condition, (y) the grounds for termination (if susceptible to correction) are not corrected by the Company within 30 days of its receipt of such notice, and (z) the Executive's termination of employment occurs within two months following the Company's receipt of such notice.

2. Section 6, Release; Timing of Severance Benefits, is modified by adding a sentence at the end thereof to read:

The Release shall not (a) require Participant to release claims or rights (i) to Severance Pay or severance benefits under this Plan, (ii) under any equity award or any employee benefit plan, or (iii) to indemnification or insurance coverage, or (b) impose restrictive covenants or other obligations on the Participant broader than those set forth in the Restrictive Covenant Agreement executed by the Participant as a condition of the Participant's employment with the Company.

3. Section 9 is modified to provide that, subject to the Participant's execution and the effectiveness of the Release, in the event of a conflict between the Plan and an equity award agreement with respect to the treatment of such equity award upon a Covered Termination, whichever provision is more favorable to Participant shall apply.

**EXHIBIT E**

**Indemnification Agreement**

Incorporated by reference to Exhibit 10.8 of the Company's Annual Report on Form 10-K for the year ended December 31, 2021 filed with the Securities and Exchange Commission.

**EXHIBIT F**

**Payments Subject to Section 409A**

All reimbursements and in-kind benefits provided under the Agreement shall be made or provided in accordance with the requirements of Section 409A of the Internal Revenue Code of 1986, as amended ("Section 409A") to the extent that such reimbursements or in-kind benefits are subject to Section 409A, including, where applicable, the requirements that (i) any reimbursement is for expenses incurred during the Executive's lifetime (or during a shorter period of time specified in the Agreement), (ii) the amount of expenses eligible for reimbursement during a calendar year may not affect the expenses eligible for reimbursement in any other calendar year, (iii) the reimbursement of an eligible expense will be made on or before the last day of the calendar year following the year in which the expense is incurred and (iv) the right to reimbursement is not subject to set off or liquidation or exchange for any other benefit.

The Company makes no representation or warranty and shall have no liability to the Executive or to any other person if any of the provisions of the Agreement (including this Exhibit F) are determined to constitute deferred compensation subject to Section 409A but that do not satisfy an exemption from, or the conditions of, that section.

The Agreement is intended to comply with, or be exempt from, Section 409A and shall be interpreted accordingly.

[Remainder of page intentionally left blank]

**Exhibit 31.1**

**CERTIFICATION**

I, Brian Goff, 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, 2022

/s/ Brian Goff

Brian Goff
Chief Executive Officer
(principal executive officer)

**Exhibit 31.2**

**CERTIFICATION**

I, Cecilia Jones, 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, 2022

/s/ Cecilia Jones

Cecilia Jones
Chief Financial Officer
(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, 2022, as filed with the Securities and Exchange Commission on the date hereof (the "Report"), the undersigned, Brian Goff, 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, 2022

/s/ Brian Goff
Brian Goff
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, 2022, as filed with the Securities and Exchange Commission on the date hereof (the "Report"), the undersigned, Cecilia Jones, 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, 2022

/s/ Cecilia Jones
Cecilia Jones
Chief Financial Officer
(principal financial officer)